Center for Biological Sequence Analysis - DTU Orbit (28/12/2017)

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Organisation profile

The Center for Biological Sequence Analysis at the Technical University of Denmark was formed in 1993, and conducts basic research in the field of bioinformatics and systems biology. The group of +90 scientists, working in ten specialist research groups, has a highly multi-disciplinary profile (molecular biologists, biochemists, medical doctors, physicists and computer scientists) with a ratio of 2:1 of bio-to-nonbio backgrounds. CBS represents one of the large bioinformatics groups in academia in Europe.

Bioinformatics is the term used to refer to the combination of methods in biology, computation, and information management, which are necessary to advance research relating to all aspects of living systems - from individual molecules, cells, and organs to entire organisms.

Today, research in molecular biology, biotechnology and pharmacology depends on information technology all the way from experiment to the publication of the results. Comprehensive public databases of DNA- and protein sequences, macromolecular structure, gene and protein expression levels, pathway organization and cell signalling, have been established to optimise scientific exploitation of the explosion of data within biology. Unlike many other groups in the field of biomolecular informatics, Center for Biological Sequence Analysis directs its research primarily towards topics related to the elucidation of the functional aspects of complex biological mechanisms.

Among contemporary bioinformatics concerns are reliable computational interpretation of a wide range of experimental data, and the detailed understanding of the molecular apparatus behind cellular mechanisms of sequence information. By exploiting available experimental data and evidence in the design of algorithms, sequence correlations and other features of biological significance can be inferred. In addition to the computational research the center also has experimental efforts in gene expression analysis using DNA chips and data generation in relation to the physical and structural properties of DNA.

In the last decade, the Center for Biological Sequence Analysis has produced a large number of computational methods, which are offered to others via WWW servers.
Based on bioinformatics efforts started in the late 1980s, the activity was established formally as a center in 1993 by a grant from the Danish National Research Foundation.

Today, CBS is - in addition to a contribution from the Technical University of Denmark - funded by a multitude of sources including:

The Danish Research Councils
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Publications:

**Exposure of tropoelastin to peroxynitrous acid gives high yields of nitrated tyrosine residues, di-tyrosine cross-links and altered protein structure and function**

Elastin is an abundant extracellular matrix protein in elastic tissues, including the lungs, skin and arteries, and comprises 30–57% of the aorta by dry mass. The monomeric precursor, tropoelastin (TE), undergoes complex processing during elastogenesis to form mature elastic fibres. Peroxynitrous acid (ONOOH), a potent oxidising and nitrating agent, is formed in vivo from superoxide and nitric oxide radicals. Considerable evidence supports ONOOH formation in the inflamed artery wall, and a role for this species in the development of human atherosclerotic lesions, with ONOOH-damaged extracellular matrix implicated in lesion rupture. We demonstrate that TE is highly sensitive to ONOOH, with this resulting in extensive dimerization, fragmentation and nitration of Tyr residues to give 3-nitrotyrosine (3-nitroTyr). This occurs with equimolar or greater levels of oxidant and increases in a dose-dependent manner. Quantification of Tyr loss and 3-nitroTyr formation indicates extensive Tyr modification with up to two modified Tyr per protein molecule, and up to 8% conversion of initial ONOOH to 3-nitroTyr. These effects were modulated by bicarbonate, an alternative target for ONOOH. Inter- and intra-protein di-tyrosine cross-links have been characterized by mass spectrometry. Examination of human atherosclerotic lesions shows colocalization of 3-nitroTyr with elastin epitopes, consistent with TE or elastin modification in vivo, and also an association of 3-nitroTyr containing proteins and elastin with lipid deposits. These data suggest that exposure of TE to ONOOH gives marked chemical and structural changes to TE and altered matrix assembly, and that such damage accumulates in human arterial tissue during the development of atherosclerosis.

**General information**

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Analysis of 62 hybrid assembled human Y chromosomes exposes rapid structural changes and high rates of gene conversion

The human Y-chromosome does not recombine across its male-specific part and is therefore an excellent marker of human migrations. It also plays an important role in male fertility. However, its evolution is difficult to fully understand because of repetitive sequences, inverted repeats and the potentially large role of gene conversion. Here we perform an evolutionary analysis of 62 Y-chromosomes of Danish descent sequenced using a wide range of library insert sizes and high coverage, thus allowing large regions of these chromosomes to be well assembled. These include 17 father-son pairs, which we use to validate variation calling. Using a recent method that can integrate variants based on both mapping and de novo assembly, we genotype 10898 SNVs and 2903 indels (max length of 27241 bp) in our sample and show by father-son concordance and experimental validation that the non-recurrent SNP and indel variation on the Y chromosome tree is called very accurately. This includes variation called in a 0.9 Mb centromeric heterochromatic region, which is by far the most variable in the Y chromosome. Among the variation is also longer sequence-stretches not present in the reference genome but shared with the chimpanzee Y chromosome. We analyzed 2.7 Mb of large inverted repeats (palindromes) for variation patterns among the two palindrome arms and identified 603 mutation and 416 gene conversions events. We find clear evidence for GC-biased gene conversion in the palindromes (and a balancing AT mutation bias), but irrespective of this, also a strong bias towards gene conversion towards the ancestral state, suggesting that palindromic gene conversion may alleviate Muller’s ratchet. Finally, we also find a large number of large-scale gene duplications and deletions in the palindromic regions (at least 24) and find that such events can consist of complex combinations of simultaneous insertions and deletions of long stretches of the Y chromosome.
Identification of epitopes targeted by antibodies (B cell epitopes) is of critical importance for the development of many diagnostic and therapeutic tools. For clinical usage, such epitopes must be extensively characterized in order to validate specificity and to document potential cross-reactivity. B cell epitopes are typically classified as either linear epitopes, i.e. short consecutive segments from the protein sequence or conformational epitopes adapted through native protein folding. Recent advances in high-density peptide microarrays enable high-throughput, high-resolution identification and characterization of linear B cell epitopes. Using exhaustive amino acid substitution analysis of peptides originating from target antigens, these microarrays can be used to address the specificity of polyclonal antibodies raised against such antigens containing hundreds of epitopes. However, the interpretation of the data provided in such large-scale screenings is far from trivial and in most cases it requires advanced computational and statistical skills. Here, we present an online application for automated identification of linear B cell epitopes, allowing the non-expert user to analyse peptide microarray data. The application takes as input quantitative peptide data of fully or partially substituted overlapping peptides from a given antigen sequence and identifies epitope residues (residues that are significantly affected by substitutions) and visualize the selectivity towards each residue by sequence logo plots. Demonstrating utility, the application was used to identify and address the antibody specificity of 18 linear epitope regions in Human Serum Albumin (HSA), using peptide microarray data consisting of fully substituted peptides spanning the entire sequence of HSA and incubated with polyclonal rabbit anti-HSA (and mouse anti-rabbit-Cy3). The application is made available at: www.cbs.dtu.dk/services/ArrayPitope.
A scored human protein-protein interaction network to catalyze genomic interpretation

Genome-scale human protein-protein interaction networks are critical to understanding cell biology and interpreting genomic data, but challenging to produce experimentally. Through data integration and quality control, we provide a scored human protein-protein interaction network (InWeb_InBioMap, or InWeb_IM) with severalfold more interactions (>500,000) and better functional biological relevance than comparable resources. We illustrate that InWeb_InBioMap enables functional interpretation of >4,700 cancer genomes and genes involved in autism.
Breadth of T cell responses after immunization with adenovirus vectors encoding ancestral antigens or polyvalent papillomavirus antigens

Oncogenic human papillomaviruses (HPVs) are in most cases eliminated by intervention of T cells. As many other pathogens, these oncogenic HPVs belong to an ancient and diverse virus family. Therefore, we found it relevant to investigate the potential and limitations of inducing a broad response - either by inducing cross-reactive T cells or by administering a polyvalent vaccine. To test these strategies, we designed 3 ancestral and 2 circulating sequences based on the two domains of the E1 and E2 proteins of papillomaviruses (PVs) that exhibit the highest degree of conservation in comparison to the other PV proteins. The PV sequences were fused to a T cell adjuvant, the murine invariant chain and encoded in a recombinant adenoviral vector which was administered to naïve outbred mice. By measuring T cell responses induced by these different vaccines and towards peptide pools representing 3 circulating strains and a putative ancestor of oncogenic HPVs, we showed that the ancestral vaccine antigen has to be approximately 90% identical to the circulating PVs before a marked drop of ~90% mean CD8+ T cell responses ensues. Interestingly, the combination of two or three type-specific PV vaccines did not induce a significant decrease of the CD8+ T cell response to the individual targeted PV types. Polyvalent HPV vaccine based on the E1 and E2 proteins seem to be capable of triggering responses towards more than one type of PV while the cross-reactivity of ancestral vaccine seems insufficient in consideration of the sequence diversity between HPV types.

General information
Chromosome copy number variation in telomerized human bone marrow stromal cells; insights for monitoring safe ex-vivo expansion of adult stem cells

Adult human bone marrow stromal cells (hBMSC) cultured for cell therapy require evaluation of potency and stability for safe use. Chromosomal aberrations upsetting genomic integrity in such cells have been contrastingly described as "Limited" or "Significant". Previously reported stepwise acquisition of a spontaneous neoplastic phenotype during three-year continuous culture of telomerized cells (hBMSC-TERT20) didn't alter a diploid karyotype measured by spectral karyotype analysis (SKY). Such screening may not adequately monitor abnormal and potentially tumorigenic hBMSC in clinical scenarios. We here used array comparative genomic hybridization (aCGH) to more stringently compare non-tumorigenic parental hBMSC-TERT strains with their tumorigenic subcloned populations. Confirmation of a known chromosome 9p21 microdeletion at locus CDKN2A/B, showed it also impinged upon the adjacent MTAP gene. Compared to reference diploid human fibroblast genomic DNA, the non-tumorigenic hBMSC-TERT4 cells had a copy number variation (CNV) in at least 14 independent loci. The pre-tumorigenic hBMSC-TERT20 cell strain had further CNV including 1q44 gain enhancing SMYD3 expression and 11q13.1 loss downregulating MUS81 expression. Bioinformatic analysis of gene products reflecting 11p15.5 CNV gain in tumorigenic hBMSC-TERT20 cells highlighted networks implicated in tumorigenic progression involving cell cycle control and mis-match repair. We provide novel biomarkers for prospective risk assessment of expanded stem cell cultures.
Chromosome-wise Protein Interaction Patterns and Their Impact on Functional Implications of Large-Scale Genomic Aberrations

Gene copy-number changes influence phenotypes through gene-dosage alteration and subsequent changes of protein complex stoichiometry. Human trisomies where gene copy numbers are increased uniformly over entire chromosomes provide generic cases for studying these relationships. In most trisomies, gene and protein level alterations have fatal consequences. We used genome-wide protein-protein interaction data to identify chromosome-specific patterns of protein interactions. We found that some chromosomes encode proteins that interact infrequently with each other, chromosome 21 in particular. We combined the protein interaction data with transcriptome data from human brain tissue to investigate how this pattern of global interactions may affect cellular function. We identified highly connected proteins that also had coordinated gene expression. These proteins were associated with important neurological functions affecting the characteristic phenotypes for Down syndrome and have previously been validated in mouse knockout experiments. Our approach is general and applicable to other gene-dosage changes, such as arm-level amplifications in cancer.

Distinct roles for the IIId2 sub-domain in pestivirus and picornavirus internal ribosome entry sites

Viral internal ribosomes entry site (IRES) elements coordinate the recruitment of the host translation machinery to direct the initiation of viral protein synthesis. Within hepatitis C virus (HCV)-like IRES elements, the sub-domain IIId(1) is crucial for recruiting the 40S ribosomal subunit. However, some HCV-like IRES elements possess an additional sub-domain, termed IIId2, whose function remains unclear. Herein, we show that IIId2 sub-domains from divergent viruses have different functions. The IIId2 sub-domain present in Seneca valley virus (SVV), a picornavirus, is dispensable for IRES activity, while the IIId2 sub-domains of two pestiviruses, classical swine fever virus (CSFV) and border disease virus (BDV), are required for 80S ribosomes assembly and IRES activity. Unlike in SVV, the deletion of IIId2 from the CSFV and BDV IRES elements impairs initiation of translation by inhibiting the assembly of 80S ribosomes. Consequently, this negatively affects the replication of CSFV and BDV. Finally, we show that the SVV IIId2 sub-domain is required for
efficient viral RNA synthesis and growth of SVV, but not for IRES function. This study sheds light on the molecular evolution of viruses by clearly demonstrating that conserved RNA structures, within distantly related RNA viruses, have acquired different roles in the virus life cycles.

**General information**

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Diversity, Prevalence, and Longitudinal Occurrence of Type II Toxin-Antitoxin Systems of Pseudomonas aeruginosa Infecting Cystic Fibrosis Lungs

Type II toxin-antitoxin (TA) systems are most commonly composed of two genes encoding a stable toxin, which harms the cell, and an unstable antitoxin that can inactivate it. TA systems were initially characterized as selfish elements, but have recently gained attention for regulating general stress responses responsible for pathogen virulence, formation of drug-tolerant persister cells and biofilms—all implicated in causing recalcitrant chronic infections. We use a bioinformatics approach to explore the distribution and evolution of type II TA loci of the opportunistic pathogen, Pseudomonas aeruginosa, across longitudinally sampled isolates from cystic fibrosis lungs. We identify their location in the genome, mutations, and gain/loss during infection to elucidate their function(s) in stabilizing selfish elements and pathogenesis. We found (1) 26 distinct TA systems, where all isolates harbor four in their core genome and a variable number of the remaining 22 on genomic islands; (2) limited mutations in core genome TA loci, suggesting they are not under negative selection; (3) no evidence for horizontal transmission of elements with TA systems between clone types within patients, despite their ability to mobilize; (4) no gain and limited loss of TA-bearing genomic islands, and of those elements partially lost, the remnant regions carry the TA systems supporting their role in genomic stabilization; (5) no significant correlation between frequency of TA systems and strain ability to establish as chronic infection, but those with a particular TA, are more successful in establishing a chronic infection.
Dynamic Rearrangement of Cell States Detected by Systematic Screening of Sequential Anticancer Treatments

Signaling networks are nonlinear and complex, involving a large ensemble of dynamic interaction states that fluctuate in space and time. However, therapeutic strategies, such as combination chemotherapy, rarely consider the timing of drug perturbations. If we are to advance drug discovery for complex diseases, it will be essential to develop methods capable of identifying dynamic cellular responses to clinically relevant perturbations. Here, we present a Bayesian dose-response framework and the screening of an oncological drug matrix, comprising 10,000 drug combinations in melanoma and pancreatic cancer cell lines, from which we predict sequentially effective drug combinations. Approximately 23% of the tested combinations showed high-confidence sequential effects (either synergistic or antagonistic), demonstrating that cellular perturbations of many drug combinations have temporal aspects, which are currently both underutilized and poorly understood.

Bibliographical note
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Evolutionary analysis of whole-genome sequences confirms inter-farm transmission of Aleutian mink disease virus

Aleutian mink disease virus (AMDV) is a frequently encountered pathogen associated with mink farming. Previous phylogenetic analyses of AMDV have been based on shorter and more conserved parts of the genome, e.g. the partial NS1 gene. Such fragments are suitable for detection but are less useful for elucidating transmission pathways while sequencing entire viral genomes provides additional informative sites and often results in better-resolved phylogenies. We explore how whole-genome sequencing can benefit investigations of AMDV transmission by reconstructing the relationships between AMDV field samples from a Danish outbreak. We show that whole-genome phylogenies are much better resolved than those based on the partial NS1 gene sequences extracted from the same alignment. Well-resolved phylogenies contain more information about the underlying transmission trees and are useful for understanding the spread of a pathogen. In the main case investigated here, the transmission path suggested by the tree structure was supported by epidemiological data. The use of molecular clock models further improved tree resolution and provided time estimates for the viral ancestors consistent with the proposed direction of spread. It was however impossible to infer transmission pathways from the partial NS1 gene tree, since all samples from the case farms branched out from a single internal node. A sliding window analysis showed that there were no shorter genomic regions providing the same phylogenetic resolution as the entire genome. Altogether, these results suggest that phylogenetic analyses based on whole-genome sequencing taking into account sampling dates and epidemiological data is a promising set of tools for clarifying AMDV transmission.
FurIOS: a web-based tool for identification of Vibrionaceae species using the fur gene

Gene based methods for identification of species from the Vibrionaceae family have been developed during the last decades to address the limitations of the commonly used 16S rRNA gene phylogeny. Recently, we found that the ferric-uptake regulator gene (fur) can be used as a single identification marker providing species discrimination, consistent with multi-locus sequencing analyses and whole genome phylogenies. To allow for broader and easy use of this marker, we have developed an online prediction service that allows the identification of Vibrionaceae species based on their fur-sequence. The input is a DNA sequence that can be uploaded on the web service; the output is a table containing the strain identifier, e-value, and percentage of identity for each of the matches with rows colored in green for hits with high probability of being the same species. The service is available on the web at: http://www.cbs.dtu.dk/services/furIOS-1.0/. The fur-sequences can be derived either from genome sequences or from PCR-amplification of the genomic region encoding the fur gene. We have used 191 strains identified as Vibrionaceae based on 16S rRNA gene sequence to test the PCR method and the web service on a large dataset. We were able to classify 171 of 191 strains at the species level and 20 strains remained unclassified. Furthermore, the fur phylogenetics and subsequent in silico DNA-DNA hybridization demonstrated that two strains (ATCC 33789 and ZS-139) previously identified as Vibrio splendidus are more closely related to V. tasmaniensis and V. cyclitrophicus, respectively. FurIOS is an easy-to-use online service that allows the identification of bacteria from the Vibrionaceae family at the species level using the fur gene as a single marker. Its simplistic design and straightforward pipeline makes it suitable for any research environment, from academia to industry.

Introduction

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Genome Sequence of Talaromyces atroroseus, Which Produces Red Colorants for the Food Industry

Talaromyces atroroseus is a known producer of Monascus colorants suitable for the food industry. Furthermore, genetic tools have been established that facilitate elucidation and engineering of its biosynthetic pathways. Here, we report the draft genome of a potential fungal cell factory, T. atroroseus IBT 11181 (CBS 123796).

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Hierarchical Sets: Analyzing Pangenome Structure through Scalable Set Visualizations

The increase in available microbial genome sequences has resulted in an increase in the size of the pangenomes being analyzed. Current pangenome visualizations are not intended for the pangenome sizes possible today and new approaches are necessary in order to convert the increase in available information to increase in knowledge. As the pangenome data structure is essentially a collection of sets we explore the potential for scalable set visualization as a tool for pangenome analysis. We present a new hierarchical clustering algorithm based on set arithmetics that optimizes the intersection sizes along the branches. The intersection and union sizes along the hierarchy are visualized using a composite dendrogram and icicle plot, which, in pangenome context, shows the evolution of pangenome and core size along the evolutionary hierarchy. Outlying elements, i.e. elements whose presence pattern do not correspond with the hierarchy, can be visualized using hierarchical edge bundles. When applied to pangenome data this plot shows putative horizontal gene transfers between the genomes and can highlight relationships between genomes that is not represented by the hierarchy. We illustrate the utility of hierarchical sets by applying it to a pangenome based on 113 Escherichia and Shigella genomes and find it provides a powerful addition to pangenome analysis. The described clustering algorithm and visualizations are implemented in the hierarchicalSets R package available from CRAN (https://cran.r-project.org/web/packages/hierarchicalSets) CONTACT: Thomas Lin Pedersen (thomasp85@gmail.com) Supplementary information Supplementary data are available at Bioinformatics online.
Light Sensitivity of Lactococcus lactis Thioredoxin Reductase

The thioredoxin system has evolved in all kingdoms of life acting as a key antioxidant system in the defense against oxidative stress. The thioredoxin system utilizes reducing equivalents from NADPH to reduce protein disulfide targets. The reducing equivalents are shuttled via a flavin and redox active dithiol motif in thioredoxin reductase (TrxR) to reduce the small ubiquitous thioredoxin (Trx). Trx in turn regulates the protein dithiol/disulfide balance by reduction of protein disulfide targets in e.g. ribonucleotide reductase, peroxiredoxins and methionine sulfoxide reductase. The glutathione system is an alternative thiol-based antioxidant system, but the glutathione biosynthesis system is not present in all organisms.

This thesis focuses on the TrxR from the lactic acid bacteria (LAB) model organism Lactococcus lactis ssp. cremoris MG1363, a strain that is glutathione- and catalasenegative, thus expected to rely mainly on the Trx system for thiol-disulfide control. L. lactis is an important industrial microorganism used as starter culture in the dairy production of cheese, buttermilk etc. and known to be sensitive to oxidative stress. The L. lactis TrxR (LitTrxR) is a homodimeric flavoenzyme with each monomer consisting of a FAD- and a NADPH domain. In this type of low molecular weight (LMW) TrxR the NADPH domain rotates 66° relative to the FAD domain in order to complete a catalytic cycle. The TrxR thus exists in two conformations, referred to as FO- and FR-conformation. In the FRconformation NADPH reduces the FAD co-enzyme, followed by rotation to the FOconformation in which FADH2 reduces the disulfide in the redox active motif of TrxR. The
human TrxR belongs to the high molecular weight (HMW) TrxR involving a selenosulfide pair and functions in a different way than the LMW TrxR, which potentially makes LMW TrxR a therapeutic target.

LITrXr has been shown to be photo-inactivated by visible light exposure (λmax = 460 nm), which has not been reported in other TrxR and the feature was not observed using the E. coli homolog (EcTrxR) as control. The inactivation coincides with a shift in the absorbance spectrum of the tightly bound FAD co-enzyme and oxidation of the methyl group of the isoalloxazine ring, as determined by MS. The extracted FAD from photo-inactivated LITrXr also displayed a positive result in a dinitrophenylhydrazine (DNPH) test, indicating the presence of a carbonyl group, i.e. an aldehyde. LITrXr reduces O2 in the presence of NADPH faster than the EcTrxR and the photo-inactivation is lowered at semi-anaerobic conditions and in the presence of iodine a well-known quencher of photoexcited triplet state flavin.

The present PhD study was initiated in order to identify the underlying functional and structural mechanisms behind this light sensitivity. Crystal structures of photo-inactivated LITrXr revealed oxidative damages over the course of light exposure. An increased electron density was observed around the carbon-7α of the isoalloxazine ring and to a minor degree around the carbon-8α. The Tyr237 in the vicinity of the flavin was shown to develop increased electron density at C3 position (ortho to the hydroxyl group) as a function of light exposure and was verified by MS to be associated with a +16 Da mass shift, consistent with formation of 3,4-dihydroxyphenylalanine (DOPA). A novel FAD si-face open space was identified in all structures of LITrXr and predicted to accommodate O2, thus acting as an oxygen pocket. This model explains how the protein-bound FAD can function as a de facto photosensitizer, generating reactive oxygen species (ROS) upon light exposure. Reaction mechanisms accounting for the observed oxidations on FAD and Tyr237 were proposed with the photo-excited isoalloxazine ring generating a superoxide radical (O2–•) at the si-face oxygen pocket. The one-electron deficient isoalloxazine cation can then oxidize Tyr237, which upon deprotonation forms a Tyr phenoxyl radical, a target of superoxide at the C3 position, accounting for the DOPA formation. The superoxide radicals can in addition react with the deprotonated form of carbon-7α of the isoalloxazine, which via a Russel mechanism accounts for the observed aldehyde formation. Another distinct feature of LITrXr is that it crystallizes mainly in FR-conformation, both with and without NADP+ co-crystallization. LITrXr was only obtained in FO-conformation in reduced environment during the crystallization in the presence of DTT and absence of NADP+. Interestingly, a mixed FO-FR conformation of the homodimer was also obtained in the presence of phosphate, indicating that the two monomers might function asynchronically. The oxygen pocket is arising from the Met43 bending way from the si-face towards Pro15. Three methionines, Met18, Met43 and Met67 are bending towards the residue of Pro15 constituting (what in this work is referred to as) a methionine-proline motif.

Identification of key residue surrounding the oxygen pocket makes it possible to predict TrxR from other organisms harboring the FAD si-face oxygen pocket, including organisms such as Bacillus subtilis (BsTrxR) and pathogens such as Staphylococcus aureus (SaTrxR), Streptococcus pyogenes and Bacillus anthracis. A comparative photo-inactivation of TrxR from L. lactis, S. aureus and B. subtilis reveals that SaTrxR and BsTrxR are much less sensitive to light-inactivation than LITrXr, though SaTrxR exhibited a similar rate of O2 reduction in the presence of NADPH as LITrXr. Light exposure of L. lactis cell extract showed a prominent drop in TrxR activity and after 12 h about 35% of the LlTrxR remained. Preliminary experiments of light exposed living L. lactis cells kept at 4°C, indicate that light exposure is in fact lethal, under the applied conditions. Cell extracts from the same 17 h in vivo irradiated cells showed ~14% remaining TrxR activity. The applied conditions. Cell extracts from the same 17 h in vivo irradiated cells showed ~14% remaining TrxR activity. The applied conditions. Cell extracts from the same 17 h in vivo irradiated cells showed ~14% remaining TrxR activity.

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Identification of key residue surrounding the oxygen pocket makes it possible to predict TrxR from other organisms harboring the FAD si-face oxygen pocket, including organisms such as Bacillus subtilis (BsTrxR) and pathogens such as Staphylococcus aureus (SaTrxR), Streptococcus pyogenes and Bacillus anthracis. A comparative photo-inactivation of TrxR from L. lactis, S. aureus and B. subtilis reveals that SaTrxR and BsTrxR are much less sensitive to light-inactivation than LITrXr, though SaTrxR exhibited a similar rate of O2 reduction in the presence of NADPH as LITrXr. Light exposure of L. lactis cell extract showed a prominent drop in TrxR activity and after 12 h about 35% of the LlTrxR remained. Preliminary experiments of light exposed living L. lactis cells kept at 4°C, indicate that light exposure is in fact lethal, under the applied conditions. Cell extracts from the same 17 h in vivo irradiated cells showed ~14% remaining TrxR activity. The present investigation shows that TrxR light sensitivity might be a widespread phenomenon among bacteria, particular within the phylum of Firmicutes. This feature can potentially be exploited in clinical light therapy, e.g. in targeted blue light therapy of selected drugresistant pathogenic bacteria.
NC/Nga, flaky-tail, Flg-mutated, ovalbumin-challenged, oxazolone-challenged, and IL-23-injected mice. Gene expression data of AD, psoriasis, and contact dermatitis were obtained from previous patient cohorts. Criteria of fold-change/FCH≥2 and false discovery rate/FDR≤0.05 were used for gene arrays. IL-23-injected, NC/Nga, and oxazolone-challenged mice show the largest homology with our human meta-analysis derived AD (MADAD) transcriptome (37%, 18%, 17%, respectively). Similar to human AD, robust Th1, Th2, and also Th17 activation are seen in IL-23-injected and NC/Nga mice, with similar, but weaker, inflammation in ovalbumin-challenged mice. Oxazolone-challenged mice show a Th1-centered reaction and flaky-tail mice demonstrate a strong Th17 polarization. Flg-mutated mice display FLG down-regulation without significant inflammation. No single murine model fully captures all aspects of the AD profile; instead, each model reflects different immune or barrier disease aspects. Overall, among the six murine models, IL-23-injected mice best simulate human AD; still, the translational focus of the investigation should determine which model is most applicable. When testing new drugs for atopic dermatitis, murine models might be used to study barrier or immune features, but human trials are needed to determine effects on actual disease profile.

**General information**

**State:** Published

**Organisations:** Regulatory Genomics, Department of Systems Biology, Center for Biological Sequence Analysis, Rockefeller University, Icahn School of Medicine at Mount Sinai (ISMMS), LEO Pharma AS, University of Copenhagen, Graduate School of Medicine Kyoto University

**Authors:** Ewald, D. A. (Intern), Noda, S. (Ekstern), Oliva, M. (Ekstern), Litman, T. (Ekstern), Nakajima, S. (Ekstern), Li, X. (Ekstern), Xu, H. (Ekstern), Scheipers, P. (Ekstern), Svitacheva, N. (Ekstern), Labuda, T. (Ekstern), Krueger, J. G. (Ekstern), Suárez-Fariñas, M. (Ekstern), Kabashima, K. (Ekstern), Guttman-Yassky, E. (Ekstern)

**Pages:** 562-571

**Publication date:** 2017

**Main Research Area:** Technical/natural sciences
Meta-Analysis of Genome-Wide Association Studies for Abdominal Aortic Aneurysm Identifies Four New Disease-Specific Risk Loci

Abdominal aortic aneurysm (AAA) is a complex disease with both genetic and environmental risk factors. Together, 6 previously identified risk loci only explain a small proportion of the heritability of AAA. To identify additional AAA risk loci using data from all available genome-wide association studies (GWAS). Through a meta-analysis of 6 GWAS datasets and a validation study totalling 10,204 cases and 107,766 controls we identified 4 new AAA risk loci: 1q32.3 (SMYD2), 13q12.11 (LINC00540), 20q13.12 (near PCIF1/MMP9/ZNF335), and 21q22.2 (ERG). In various database searches we observed no new associations between the lead AAA SNPs and coronary artery disease, blood pressure, lipids or diabetes. Network analyses identified ERG, IL6R and LDLR as modifiers of MMP9, with a direct interaction between ERG and MMP9. The 4 new risk loci for AAA appear to be specific for AAA compared with other cardiovascular diseases and related traits suggesting that traditional cardiovascular risk factor management may only have limited value in preventing the progression of aneurysmal disease.

General information

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Integrative Systems Biology, University of Otago, University of Stellenbosch, deCODE/Amgen, University Medical Centre Utrecht, University of Florence, Polish Academy of Sciences, University of Leicester, The Sigfried and Janet Weis Center for Research, Odense Universitetshospital
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Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 8.14
BFI (2015): BFI-level 2
Scopus rating (2015): CiteScore 7.71
Metabolic Syndrome, Insulin Resistance and Cognitive Dysfunction: Does your metabolic profile affect your brain?

Dementia and type 2 diabetes are both characterized by long prodromal phases challenging the study of potential risk factors and their temporal relation. The progressive relation between metabolic syndrome, insulin resistance, and dementia has recently been questioned, wherefore the aim of this study was to assess the potential association between these precursors of type 2 diabetes and cognitive dysfunction. Using data from the Prospective Epidemiological Risk Factor study (n=2,103), a prospective study of elderly women in Denmark, we found that impaired fasting plasma glucose was associated with 44% (9%-91%) larger probability of developing cognitive dysfunction. In addition subjects above the HOMA-IR threshold (HOMA-IR > 2.6) had 47% (9%-99%) larger odds of cognitive dysfunction. The associations could indicate that a significant proportion of dementia cases in women is likely to be preventable by effective prevention and control of the insulin homeostasis.
MGmapper: Reference based mapping and taxonomy annotation of metagenomics sequence reads

An increasing amount of species and gene identification studies rely on the use of next generation sequence analysis of either single isolate or metagenomics samples. Several methods are available to perform taxonomic annotations and a previous metagenomics benchmark study has shown that a vast number of false positive species annotations are a problem unless thresholds or post-processing are applied to differentiate between correct and false annotations. MGmapper is a package to process raw next generation sequence data and perform reference based sequence assignment, followed by a post-processing analysis to produce reliable taxonomy annotation at species and strain level resolution. An in-vitro bacterial mock community sample comprised of 8 genuses, 11 species and 12 strains was previously used to benchmark metagenomics classification methods. After applying a post-processing filter, we obtained 100% correct taxonomy assignments at species and genus level. A sensitivity and precision at 75% was obtained for strain level annotations. A comparison between MGmapper and Kraken at species level, shows MGmapper assigns taxonomy at species level using 84.8% of the sequence reads, compared to 70.5% for Kraken and both methods identified
all species with no false positives. Extensive read count statistics are provided in plain text and excel sheets for both rejected and accepted taxonomy annotations. The use of custom databases is possible for the command-line version of MGmapper, and the complete pipeline is freely available as a bitbucked package (https://bitbucket.org/genomic epidemiology/mg mapper). A web-version (https://cge.cbs.dtu.dk/services/MGmapper) provides the basic functionality for analysis of small fastq datasets.

General information
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Organisations: Department of Bio and Health Informatics, Metagenomics, National Food Institute, Research Group for Genomic Epidemiology, Genomic Epidemiology, Department of Systems Biology, Center for Biological Sequence Analysis
Authors: Petersen, T. N. (Intern), Lukjancenko, O. (Intern), Thomsen, M. C. F. (Intern), Sperotto, M. M. (Intern), Lund, O. (Intern), Aarestrup, F. M. (Intern), Sicheritz-Pontén, T. (Intern)
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Volume: 12
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Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.11 SJR 1.201 SNIP 1.092
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.414 SNIP 1.131 CiteScore 3.32
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.545 SNIP 1.141 CiteScore 3.54
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.74 SNIP 1.147 CiteScore 3.94
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.945 SNIP 1.142 CiteScore 4.15
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 2.369 SNIP 1.23 CiteScore 4.58
ISI indexed (2011): ISI indexed no
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 2.631 SNIP 1.161
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 2.473 SNIP 0.985
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 2.323 SNIP 0.96
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 1.289 SNIP 0.525
Web of Science (2006): Indexed yes
miRandola 2017: a curated knowledge base of non-invasive biomarkers

miRandola (http://mirandola.iit.cnr.it/) is a database of extracellular non-coding RNAs (ncRNAs) that was initially published in 2012, foreseeing the relevance of ncRNAs as non-invasive biomarkers. An increasing amount of experimental evidence shows that ncRNAs are frequently dysregulated in diseases. Further, ncRNAs have been discovered in different extracellular forms, such as exosomes, which circulate in human body fluids. Thus, miRandola 2017 is an effort to update and collect the accumulating information on extracellular ncRNAs that is spread across scientific publications and different databases. Data are manually curated from 314 articles that describe miRNAs, long non-coding RNAs and circular RNAs. Fourteen organisms are now included in the database, and associations of ncRNAs with 25 drugs, 47 sample types and 197 diseases. miRandola also classifies extracellular RNAs based on their extracellular form: Argonaute2 protein, exosome, microvesicle, microparticle, membrane vesicle, high density lipoprotein and circulating. We also implemented a new web interface to improve the user experience.

General information
State: Accepted/In press
Organisations: Department of Bio and Health Informatics, Integrative Systems Biology, Department of Systems Biology, Center for Biological Sequence Analysis, Integrative Systems Biology, Department of Biotechnology, University of Copenhagen, Nerviano Medical Sciences, Scuola Superiore Sant'Anna, University of Eastern Finland, The Ohio State University, University of Verona, Mount Sinai School of Medicine, National Research Council of Italy, University of Catania
Authors: Russo, F. (Ekstern), Di Bella, S. (Ekstern), Vannini, F. (Ekstern), Berti, G. (Ekstern), Scoyni, F. (Ekstern), Cook, H. V. (Ekstern), Santos, A. (Ekstern), Nigita, G. (Ekstern), Bonnici, V. (Ekstern), Laganà, A. (Ekstern), Geraci, F. (Ekstern), Pulvirenti, A. (Ekstern), Giugno, R. (Ekstern), De Masi, F. (Intern), Belling, K. G. (Intern), Jensen, L. J. (Intern), Brunak, S. (Intern), Pellegrini, M. (Ekstern), Ferro, A. (Ekstern)
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Main Research Area: Technical/natural sciences

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BFI (2018): BFI-level 2
BFI (2017): BFI-level 2
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 9.28 SJR 7.397 SNIP 2.657
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 7.239 SNIP 2.639 CiteScore 9.48
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 6.576 SNIP 2.568 CiteScore 8.74
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 6.582 SNIP 2.266 CiteScore 8.46
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 6.13 SNIP 2.392 CiteScore 8.62
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
MIToS.jl: mutual information tools for protein sequence analysis in the Julia language

Motivation: MIToS is an environment for mutual information analysis and a framework for protein multiple sequence alignments (MSAs) and protein structures (PDB) management in Julia language. It integrates sequence and structural information through SIFTS, making Pfam MSAs analysis straightforward. MIToS streamlines the implementation of any measure calculated from residue contingency tables and its optimization and testing in terms of protein contact prediction. As an example, we implemented and tested a BLOSUM62-based pseudo-count strategy in mutual information analysis.

Availability and Implementation: The software is totally implemented in Julia and supported for Linux, OS X and Windows. It’s freely available on GitHub under MIT license: http://mitos.leloir.org.ar.

Contacts: diegozea@gmail.com or cmb@leloir.org.ar

Supplementary information:
Supplementary data are available at Bioinformatics online.

General information
State: Published
Modifiable risk factors promoting neurodegeneration is associated with two novel brain degradation markers measured in serum

There has been limited success with blood-based biomarkers of neurodegeneration. One perceived reason is that blood has no direct contact to the brain. Recently developed blood-based biomarkers of tau-degradation have shown promise as potential tools for peripheral assessment of neurodegeneration; however, factors contributing to the levels of these in blood are poorly understood. Using multiple linear regression analysis in cross-sectional data from an observational cohort (n = 5626), the aim was to examine which factors correlate to the serological levels of two novel biomarkers measuring truncated tau fragments (Tau-A and Tau-C) in serum. Platelets, albumin and several modifiable risk factors, including Body Mass Index, high density lipoprotein and White Blood Cell count were associated with the serum level of tau fragments. The factors associated with tau in serum may promote neurodegeneration and alter the permeability of the Blood Brain Barrier through chronic inflammation and vascular dysfunction. These data are of key importance for understanding the mechanism of release and subsequent peripheral processing of tau from the brain and will assist in the development of future blood-based biomarkers.

General information
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Organisations: Department of Biotechnology and Biomedicine, Department of Systems Biology, Center for Biological Sequence Analysis, Regulatory Genomics, Disease Systems Immunology, Nordic Bioscience A/S, ProScion A/S
Authors: Neergaard, J. (Intern), Møller, K. D. (Intern), Christiansen, C. (Ekstern), Nielsen, H. B. (Ekstern), Workman, C. (Intern), Pedersen, S. B. (Intern), Henriksen, K. (Ekstern), Karsdal, M. A. (Ekstern)
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BFI (2017): BFI-level 1
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BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.74 SJR 1.37 SNIP 0.974
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.344 SNIP 0.902 CiteScore 3.23
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.363 SNIP 0.97 CiteScore 3.2
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.253 SNIP 0.919 CiteScore 2.96
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.18 SNIP 0.936 CiteScore 3.03
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.272 SNIP 0.854 CiteScore 2.97
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.577 SNIP 1.064
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.612 SNIP 0.997
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 1.404 SNIP 0.905
Scopus rating (2007): SJR 1.458 SNIP 1.031
Scopus rating (2006): SJR 1.264 SNIP 1.024
Scopus rating (2005): SJR 1.536 SNIP 1.088
Scopus rating (2004): SJR 1.371 SNIP 1.099
Scopus rating (2003): SJR 1.374 SNIP 1.014
Scopus rating (2002): SJR 1.175 SNIP 0.854
Modifications of TIGIT expression contribute to CD8 T cell exhaustion in chronic virus infection

General information
State: Published
Organisations: Department of Chemistry, Department of Systems Biology, Center for Biological Sequence Analysis, Department of Bio and Health Informatics, Genomic Epidemiology, Karolinska Institutet, University of Pennsylvania, National Institute of Respiratory Diseases, University of California, San Francisco
Authors: Tauriainen, J. (Ekstern), Scharf, L. (Ekstern), Frederiksen, J. W. (Intern), Naji, A. (Ekstern), Ljunggren, H. (Ekstern), Sonnerborg, A. (Ekstern), Lund, O. (Intern), Reyes-Teran, G. (Ekstern), Hecht, F. M. (Ekstern), Deeks, S. G. (Ekstern), Betts, M. R. (Ekstern), Buggert, M. (Ekstern), Karlsson, A. C. (Ekstern)
Pages: 318
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BFI (2017): BFI-level 1
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.03 SJR 0.951 SNIP 0.646
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.93 SNIP 0.684 CiteScore 1.97
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.898 SNIP 0.666 CiteScore 1.91
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 0.86 SNIP 0.712 CiteScore 2.05
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 0.88 SNIP 0.749 CiteScore 2.16
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 0.854 SNIP 0.66 CiteScore 2.06
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 0.844 SNIP 0.622
Neuroplasticity pathways and protein-interaction networks are modulated by vortioxetine in rodents

Background: The identification of biomarkers that predict susceptibility to major depressive disorder and treatment response to antidepressants is a major challenge. Vortioxetine is a novel multimodal antidepressant that possesses pro-cognitive properties and differentiates from other conventional antidepressants on various cognitive and plasticity measures. The aim of the present study was to identify biological systems rather than single biomarkers that may underlie vortioxetine's treatment effects. Results: We show that the biological systems regulated by vortioxetine are overlapping between mouse and rat in response to distinct treatment regimens and in different brain regions. Furthermore, analysis of complexes of physically-interacting proteins reveal that biomarkers involved in transcriptional regulation, neurodevelopment, neuroplasticity, and endocytosis are modulated by vortioxetine. A subsequent qPCR study examining the expression of targets in the protein-protein interactome space in response to chronic vortioxetine treatment over a range of doses provides further biological validation that vortioxetine engages neuroplasticity networks. Thus, the same biology is regulated in different species and sexes, different brain regions, and in response to distinct routes of administration and regimens. Conclusions: A recurring theme, based on the present study as well as previous findings, is that networks related to synaptic plasticity, synaptic transmission, signal transduction, and neurodevelopment are modulated in response to vortioxetine treatment. Regulation of these signaling pathways by vortioxetine may underlie vortioxetine's cognitive-enhancing properties.
BFI (2018): BFI-level 2
BFI (2017): BFI-level 2
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 5.96 SJR 4.682 SNIP 1.629
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 5.05 SNIP 1.709 CiteScore 6.33
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 5.274 SNIP 1.771 CiteScore 6.66
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 5.703 SNIP 1.872 CiteScore 7.22
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 5.671 SNIP 1.968 CiteScore 7.6
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 5.8 SNIP 1.912 CiteScore 7.51
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 5.954 SNIP 1.876
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 6.053 SNIP 1.871
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 6.567 SNIP 1.9
Scopus rating (2007): SJR 6.034 SNIP 1.928
Scopus rating (2006): SJR 5.863 SNIP 1.924
Scopus rating (2005): SJR 5.793 SNIP 1.978
Scopus rating (2004): SJR 5.862 SNIP 1.973
Scopus rating (2003): SJR 5.949 SNIP 2.054
Scopus rating (2002): SJR 5.972 SNIP 1.986
Scopus rating (2001): SJR 5.811 SNIP 2.051
Scopus rating (2000): SJR 6.158 SNIP 2.126
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Novel genes involved in pathophysiology of gonadotropin-dependent adrenal tumors in mice

Specific inbred strains and transgenic inhibin-α Simian Virus 40 T antigen (inhα/Tag) mice are genetically susceptible to gonadectomy-induced adrenocortical neoplasias. We identified altered gene expression in prepubertally gonadectomized (GDX) inhα/Tag and wild-type (WT) mice. Besides earlier reported Gata4 and Lhcgr, we found up-regulated Esr1, Prlr-rs1, and down-regulated Grb10, Mmp24, Sgcd, Rerg, Gnas, Nfatc2, Gnhr, Igf2 in inhα/Tag adrenal tumors. Sex-steroidogenic enzyme genes expression (Srd5a1, Cyp19a1) was up-regulated in tumors, but adrenal-specific steroidogenic enzyme (Cyp21a1, Cyp11b1, Cyp11b2) down-regulated. We localized novel Lhcgr transcripts in adrenal cortex parenchyma and in non-steroidogenic A cells, in GDX WT and in intact WT mice. We identified up-regulated Esr1 as a potential novel biomarker of gonadectomy-induced adrenocortical tumors in inhα/Tag mice presenting with an inverted adrenal-to-gonadal steroidogenic gene expression profile. A putative normal adrenal remodeling or tumor suppressor role of the down-regulated genes (e.g. Grb10, Rerg, Gnas, and Nfatc2) in the tumors remains to be addressed.

General information

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NutriChem 2.0: exploring the effect of plant-based foods on human health and drug efficacy

NutriChem is a database generated by text mining of 21 million MEDLINE abstracts that links plant-based foods with their small molecule components and human health effect. In this new, second release of NutriChem (NutriChem 2.0) we have integrated information on overlapping protein targets between FDA-approved drugs and small compounds in plant-based foods, which may have implications on drug pharmacokinetics and pharmacodynamics. NutriChem 2.0 contains predicted interactions between 428 drugs and 339 foods, supported by 107 jointly targeted proteins. Chemical bioactivity data were integrated, facilitating the comparison of activity concentrations between drugs and phytochemicals. In addition, we have added functionality that allows for user inspection of supporting evidence, the classification of food constituents based on KEGG "Phytochemical Compounds", phytochemical structure output in SMILES and network output in both static figure and Cytoscape-compatible xgmml format. The current update of NutriChem moves one step further towards a more comprehensive assessment of dietary effects on human health and drug treatment.
Obesity is associated with depot-specific alterations in adipocyte DNA methylation and gene expression

The present study aimed to identify genes exhibiting concomitant obesity-dependent changes in DNA methylation and gene expression in adipose tissues in the mouse using diet-induced obese (DIO) C57BL/6J and genetically obese ob/ob mice as models. Mature adipocytes were isolated from epididymal and inguinal adipose tissues of ob/ob and DIO C57BL/6J mice. DNA methylation was analyzed by MeDIP-sequencing and gene expression by microarray analysis. The majority of differentially methylated regions (DMRs) were hypomethylated in obese mice. Global methylation of long interspersed elements indicated that hypomethylation did not reflect methyl donor deficiency. In both DIO and ob/ob mice, we observed more obesity-associated methylation changes in epididymal than in inguinal adipocytes. Assignment of DMRs to promoter, exon, intron and intergenic regions demonstrated that DIO-induced changes in DNA methylation in C57BL/6J mice occurred primarily in exons, whereas inguinal adipocytes of ob/ob mice exhibited a higher enrichment of DMRs in promoter regions than in other regions of the genome, suggesting an influence of leptin on DNA methylation in inguinal adipocytes. We observed altered methylation and expression of 9 genes in epididymal adipocytes, including the known obesity-associated genes, Ehd2 and Kctd15, and a novel candidate gene, Irf8, possibly involved in immune type 1/type2 balance. The use of 2 obesity models enabled us to dissociate changes associated with high fat feeding from those associated with obesity per se. This information will be of value in future studies on the mechanisms governing the development of obesity and changes in adipocyte function associated with obesity.
as the observation that the presence of this genus is reduced in diseases that involve inflammation.
Phase behavior of supported lipid bilayers: A systematic study by coarse-grained molecular dynamics simulations

Solid-supported lipid bilayers are utilized by experimental scientists as models for biological membranes because of their stability. However, compared to free standing bilayers, their close proximity to the substrate may affect their phase behavior. As this is still poorly understood, and few computational studies have been performed on such systems thus far, here we present the results from a systematic study based on molecular dynamics simulations of an implicit-solvent model for solid-supported lipid bilayers with varying lipid-substrate interactions. The attractive interaction between the substrate and the lipid head groups that are closest to the substrate leads to an increased translocation of the lipids from the distal to the proximal bilayer-leaflet. This thereby leads to a transbilayer imbalance of the lipid density, with the lipid density of the proximal leaflet higher than that of the distal leaflet. Consequently, the order parameter of the proximal leaflet is found to be higher than that of the distal leaflet, the higher the strength of lipid interaction is, the stronger the effect. The proximal leaflet exhibits gel and fluid phases with an abrupt melting transition between the two phases. In contrast, below the melting temperature of the proximal leaflet, the distal leaflet is inhomogeneous with coexisting gel and fluid domains. The size of the fluid domains increases with increasing the strength of the lipid interaction. At low temperatures, the inhomogeneity of the distal leaflet is due to its reduced lipid density.

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Background
Antibiotic resistance is a major health problem, as drugs that were once highly effective no longer cure bacterial infections. WGS has previously been shown to be an alternative method for detecting horizontally acquired antimicrobial resistance genes. However, suitable bioinformatics methods that can provide easily interpretable, accurate and fast results for antimicrobial resistance associated with chromosomal point mutations are still lacking.

Methods
Phenotypic antimicrobial susceptibility tests were performed on 150 isolates covering three different bacterial species: Salmonella enterica, Escherichia coli and Campylobacter jejuni. The web-server ResFinder-2.1 was used to identify acquired antimicrobial resistance genes and two methods, the novel PointFinder (using BLAST) and an in-house method (mapping of raw WGS reads), were used to identify chromosomal point mutations. Results were compared with phenotypic antimicrobial susceptibility testing results. Results
A total of 685 different phenotypic tests associated with chromosomal resistance to quinolones, polymyxin, rifampicin,
Macrolides and tetracyclines resulted in 98.4% concordance. Eleven cases of disagreement between tested and predicted susceptibility were observed: two C. jejuni isolates with phenotypic fluoroquinolone resistance and two with phenotypic erythromycin resistance and five colistin-susceptible E. coli isolates with a detected pmrB V161G mutation when assembled with Velvet, but not when using SPAdes or when mapping the reads.

Conclusions
PointFinder proved, with high concordance between phenotypic and predicted antimicrobial susceptibility, to be a user-friendly web tool for detection of chromosomal point mutations associated with antimicrobial resistance.

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Positive diversifying selection is a pervasive adaptive force throughout the Drosophila radiation

The growing genomic information on non-model organisms eases exploring the evolutionary history of biodiversity. This is particularly true for Drosophila flies, in which the number of sequenced species doubled recently. Because of its outstanding diversity of species, Drosophila has become one of the most important systems to study adaptive radiation. In this study, we performed a genome-wide analysis of positive diversifying selection on more than 2000 single-copy orthologous groups in 25 species using a recent method of increased accuracy for detecting positive diversifying selection. Adopting this novel approach enabled us to find a consistent selection signal throughout the genus Drosophila, and a total of 1342 single-copy orthologous groups were identified with a putative signal of positive diversifying selection, corresponding to 1.9% of all loci. Specifically, in lineages leading to D. grimshawi, a strong putative signal of positive diversifying selection was found related to cell, morphological, neuronal, and sensorial development and function. A recurrent signal of positive diversifying selection was found on genes related to aging and lifespan, suggesting that selection had shaped lifespan diversity in Drosophila, including extreme longevity. Our study, one of the largest and most comprehensive ones on genome-wide positive diversifying selection to date, shows that positive diversifying selection has promoted species-specific differentiation among evolutionary lineages throughout the Drosophila radiation. Acting on the same biological processes via different routes, positive diversifying selection has promoted diversity of functions and adaptive divergence.
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Quantification of within-sample genetic heterogeneity from SNP-array data
Intra-tumour genetic heterogeneity (ITH) fosters drug resistance and is a critical hurdle to clinical treatment. ITH can be well-measured using multi-region sampling but this is costly and challenging to implement. There is therefore a need for tools to estimate ITH in individual samples, using standard genomic data such as SNP-arrays, that could be implemented routinely. We designed two novel scores S and R, respectively based on the Shannon diversity index and Ripley's L statistic of spatial homogeneity, to quantify ITH in single SNP-array samples. We created in-silico and in-vitro mixtures of tumour clones, in which diversity was known for benchmarking purposes. We found significant but highly-variable associations of our scores with diversity in-silico (p <0.001) and moderate associations in-vitro (p = 0.015 and p = 0.085).
Our scores were also correlated to previous ITH estimates from sequencing data but heterogeneity in the fraction of tumour cells present across samples hampered accurate quantification. The prognostic potential of both scores was moderate but significantly predictive of survival in several tumour types (corrected p = 0.03). Our work thus shows how individual SNP-arrays reveal intra-sample clonal diversity with moderate accuracy.

Sequencing and de novo assembly of 150 genomes from Denmark as a population reference

Hundreds of thousands of human genomes are now being sequenced to characterize genetic variation and use this information to augment association mapping studies of complex disorders and other phenotypic traits. Genetic variation is identified mainly by mapping short reads to the reference genome or by performing local assembly. However, these approaches are biased against discovery of structural variants and variation in the more complex parts of the genome. Hence, large-scale de novo assembly is needed. Here we show that it is possible to construct excellent de novo assemblies from high-coverage sequencing with mate-pair libraries extending up to 20 kilobases. We report de novo assemblies of 150 individuals (50 trios) from the GenomeDenmark project. The quality of these assemblies is similar to those obtained using the more expensive long-read technology. We use the assemblies to identify a rich set of structural
variants including many novel insertions and demonstrate how this variant catalogue enables further deciphering of known association mapping signals. We leverage the assemblies to provide 100 completely resolved major histocompatibility complex haplotypes and to resolve major parts of the Y chromosome. Our study provides a regional reference genome that we expect will improve the power of future association mapping studies and hence pave the way for precision medicine initiatives, which now are being launched in many countries including Denmark.

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Spontaneous Lipid Flip-Flop in Membranes: A Still Unsettled Picture from Experiments and Simulations

Biomembrane asymmetry, whose regulation is important for function, is maintained by the movement of lipids from one bilayer leaflet to the other (flip-flop). During the last decades a number of studies have been done to characterize this process, and it was found that it can be spontaneous or assisted by protein transporters. It can be accelerated or inhibited by various factors, e.g., it can be induced by mechanical stresses. It was also found that flip-flop rate and mechanism strongly depend on the molecular structure of the flipping lipid and on the composition and physical state of the membrane. Yet, large discrepancies exist among the data available in the literature, and a quantitative and comprehensive understanding of this process is still missing. This chapter reviews our current knowledge of the molecular aspects of spontaneous (or passive) flip-flop. An overview of experimental studies is presented, together with a summary of the state of the art of computer simulation studies, which enable a direct insight at the molecular level. The achievements and limitations of experimental and computational approaches are pointed out, as well as the challenges that remain to be addressed.
Synthesis and biological evaluation of dihydropyrano-[2,3-c]pyrazoles as a new class of PPARγ partial agonists

Peroxisome proliferator-activated receptor γ (PPARγ) is a well-known target for thiazolidinedione antidiabetic drugs. In this paper, we present the synthesis and biological evaluation of a series of dihydropyrano[2,3-c]pyrazole derivatives as a novel family of PPARγ partial agonists. Two analogues were found to display high affinity for PPARγ with potencies in the micro molar range. Both of these hits were selective against PPARγ, since no activity was measured when tested against PPARα, PPARδ and RXRα. In addition, a novel modelling approach based on multiple individual flexible alignments was developed for the identification of ligand binding interactions in PPARγ. In combination with cell-based transactivation experiments, the flexible alignment model provides an excellent analytical tool to evaluate and visualize the effect of ligand chemical structure with respect to receptor binding mode and biological activity.

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**The CGE Tool Box**
As whole genome sequence data of microorganisms are becoming easily accessible and cheap to produce, a transformation of the traditional methods used for typing, phenotyping and phylogenetic analysis of microorganisms is on the way. Following the anticipation that most clinical microbiological and food safety laboratories will soon have a sequencer in use on a daily basis, there is a growing need for easy-to-use bioinformatics methods that can quickly convert the sequence data into useful information on, e.g., the type of bacteria, whether it is resistant towards any types of antibiotics, and whether it is part of an outbreak. The Center for Genomic Epidemiology, which is located at the Technical University of Denmark, has since its beginning in 2010 developed such bioinformatics methods and made them freely available as web-services. These web-services and their use is the focus of this chapter.

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Ulcerative colitis, Crohn's disease, and irritable bowel syndrome have different profiles of extracellular matrix turnover, which also reflects disease activity in Crohn's disease
Increased protease activity is a key pathological feature of inflammatory bowel disease (IBD). However, the differences in extracellular matrix remodelling (ECM) in Crohn's disease (CD) and ulcerative colitis (UC) are not well described. An increased understanding of the inflammatory processes may provide optimized disease monitoring and diagnostics. We investigated the tissue remodelling in IBD and IBS patients by using novel blood-based biomarkers reflecting ECM remodelling. Five ECM biomarkers (VICM, BGM, EL-NE, C5M, Pro-C5) were measured by competitive ELISAs in serum from 72 CD patients, 60 UC patients, 22 patients with irritable bowel syndrome (IBS), and 24 healthy donors. One-way analysis of variance, Mann-Whitney U-test, logistic regression models, and receiver operator characteristics (ROC) curve analysis was carried out to evaluate the diagnostic accuracy of the biomarkers. The ECM remodelling was significantly different in UC compared to CD. The best biomarker combination to differentiate UC from CD and colonic CD was BGM and VICM (AUC = 0.98, P5mg/mL), correlation of Pro-C5 (r = 0.36) with CDAI was slightly improved compared to CRP (r = 0.27) corrected for the use of immunosuppressant. Furthermore, BGM and EL-NE biomarkers were highly associated with colon inflammation in CD patients. ECM fragments of tissue remodelling in IBD affect UC and CD differently, and may aid in differentiating IBD from IBS (EL-NE, BGM, Pro-C5), and UC from CD patients (BGM, VICM). Formation of type V collagen is related to the level of inflammation in CD and may reflect disease activity in CD.

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ISI indexed (2011): ISI indexed no
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 2.631 SNIP 1.161
Web of Science (2010): Indexed yes
Weight Change and Risk of Hyperglycaemia in Elderly Women

Background

Hyperglycaemia increases the risk of type 2 diabetes, heart disease and stroke, and is influenced by weight. However, the impact of preceding weight change on blood glycemia levels in late-life is less well understood.

Aim

We studied the interplay between weight change and risk of hyperglycaemia in a prospective cohort of elderly women.

Methods

Elderly Caucasian women (age: 67.1 years at baseline, n = 1173) enrolled in the Prospective Epidemiological Risk Factor study with baseline and 13-year follow-up measurements of BMI and fasting glucose levels (FPG) and no previous history of diabetes or impaired fasting glucose. Multivariate logistic regression was used to determine risk of hyperglycaemia (FPG ≥ 5.6 mmol/L or HbA1c ≥ 42 mmol/mol) in normalweight (BMI ≤ 25 kg/m²), overweight (BMI = 25–29.9 kg/m²) and obese (BMI ≥ 30 kg/m²) women who either lost weight, were weight-stable or had gained weight at follow-up.

Results

Overweight and obese elderly women who had gained weight at follow-up presented an increased risk of hyperglycaemia, OR = 2.7 (1.6–4.6) and OR = 3.2 (1.5–6.8), compared to weight-stable normalweight women. Overweight and obese women who lost weight decreased their risk of hyperglycaemia to a level comparable to weight-stable normalweight women. Overweight and obese women with stable weight presented a two-fold increased risk of hyperglycaemia compared to normalweight weight-stable women.

Conclusions

Losing weight in late life had a positive effect on the risk of hyperglycaemia in overweight and obese women, while further weight gain increased the risk of hyperglycaemia. The study highlights that strategies to reduce weight in obese and overweight elderly women could have a positive influence on disease burden in late-life.
Method for identification of tissue or organ localization of a tumour
The invention relates to a method for predicting the localization of a primary tumour, wherein said method comprises the use of genomic profile data, and wherein the method is capable of predicting the type of cancer by a classification score ranking among a variety of the possible tumour types.

General information
15-year follow-up of the Second Nordic Mantle Cell Lymphoma trial (MCL2): prolonged remissions without survival plateau

In recent decades, the prognosis of Mantle Cell Lymphoma (MCL) has been significantly improved by intensified first-line regimens containing cytarabine, rituximab and consolidation with high-dose-therapy and autologous stem cell transplantation. One such strategy is the Nordic MCL2 regimen, developed by the Nordic Lymphoma Group. We here present the 15-year updated results of the Nordic MCL2 study after a median follow-up of 11·4 years: For all patients on an intent-to-treat basis, the median overall and progression-free survival was 12·7 and 8·5 years, respectively. The MCL International Prognostic Index (MIPI), biological MIPI, including Ki67 expression (MIPI-B) and the MIPI-B including miR-18b expression (MIPI-B-miR), in particular, significantly divided patients into distinct risk groups. Despite very long response durations of the low and intermediate risk groups, we observed a continuous pattern of relapse and the survival curves never reached a plateau. In conclusion, despite half of the patients being still alive and 40% in first remission after more than 12 years, we still see an excess disease-related mortality, even among patients experiencing long remissions. Even though we consider the Nordic regimen as a very good choice of regimen, we recommend inclusion in prospective studies to explore the benefit of novel agents in the frontline treatment of MCL.
A Bacterial Analysis Platform: An Integrated System for Analysing Bacterial Whole Genome Sequencing Data for Clinical Diagnostics and Surveillance

Recent advances in whole genome sequencing have made the technology available for routine use in microbiological laboratories. However, a major obstacle for using this technology is the availability of simple and automatic bioinformatics tools. Based on previously published and already available web-based tools we developed a single pipeline for batch uploading of whole genome sequencing data from multiple bacterial isolates. The pipeline will automatically identify the bacterial species and, if applicable, assemble the genome, identify the multilocus sequence type, plasmids, virulence genes and antimicrobial resistance genes. A short printable report for each sample will be provided and an Excel spreadsheet containing all the metadata and a summary of the results for all submitted samples can be downloaded. The pipeline was benchmarked using datasets previously used to test the individual services. The reported results enable a rapid overview of the major results, and comparing that to the previously found results showed that the platform is reliable and able to correctly predict the species and find most of the expected genes automatically. In conclusion, a combined bioinformatics platform was developed and made publicly available, providing easy-to-use automated analysis of bacterial whole genome sequencing data. The platform may be of immediate relevance as a guide for investigators using whole genome sequencing for clinical diagnostics and surveillance. The platform is freely available at: https://cge.cbs.dtu.dk/services/CGEpipeline-1.1 and it is the intention that it will continue to be expanded with new features as these become available.

General information
State: Published
A combined prediction strategy increases identification of peptides bound with high affinity and stability to porcine MHC class I molecules SLA-1*04:01, SLA-2*04:01, and SLA-3*04:01

Affinity and stability of peptides bound by major histocompatibility complex (MHC) class I molecules are important factors in presentation of peptides to cytotoxic T lymphocytes (CTLs). In silico prediction methods of peptide-MHC binding followed by experimental analysis of peptide-MHC interactions constitute an attractive protocol to select target peptides from the vast pool of viral proteome peptides. We have earlier reported the peptide binding motif of the porcine MHC-I molecules SLA-1*04:01 and SLA-2*04:01, identified by an ELISA affinity-based positional scanning combinatorial peptide library (PSCPL) approach. Here, we report the peptide binding motif of SLA-3*04:01 and combine two prediction methods and analysis of both peptide binding affinity and stability of peptide-MHC complexes to improve rational peptide selection. Using a peptide prediction strategy combining PSCPL binding matrices and in silico prediction algorithms (NetMHCpan), peptide ligands from a repository of 8900 peptides were predicted for binding to SLA-1*04:01, SLA-2*04:01, and SLA-3*04:01 and validated by affinity and stability assays. From the pool of predicted peptides for SLA-1*04:01, SLA-2*04:01, and SLA-3*04:01, a total of 71, 28, and 38 % were binders with affinities below 500 nM, respectively. Comparison of peptide-SLA binding affinity and complex stability showed that peptides of high affinity generally, but not always, produce complexes of high stability. In conclusion, we demonstrate how state-of-the-art prediction and in vitro immunology tools in combination can be used for accurate selection of peptides for MHC class I binding, hence providing an expansion of the field of peptide-MHC analysis also to include pigs as a livestock experimental model.

General information
State: Published
Organisations: National Veterinary Institute, Immunological Bioinformatics, Department of Systems Biology, Center for Biological Sequence Analysis, Section for Immunology and Vaccinology, University of Copenhagen
Authors: Pedersen, L. E. (Intern), Rasmussen, M. (Ekstern), Harndahl, M. (Ekstern), Nielsen, M. (Intern), Buus, S. (Ekstern), Jungersen, G. (Intern)
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BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.2 SJR 1.231 SNIP 0.703
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.551 SNIP 0.819 CiteScore 2.47
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.221 SNIP 0.833 CiteScore 2.28
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.231 SNIP 0.763 CiteScore 2.48
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.365 SNIP 0.943 CiteScore 2.91
ISI indexed (2012): ISI indexed yes
A comprehensive profile of recurrent glioblastoma

In spite of relentless efforts to devise new treatment strategies, primary glioblastomas invariably recur as aggressive, therapy-resistant relapses and patients rapidly succumb to these tumors. Many therapeutic agents are first tested in clinical trials involving recurrent glioblastomas. Remarkably, however, fundamental knowledge on the biology of recurrent glioblastoma is just slowly emerging. Here, we review current knowledge on recurrent glioblastoma and ask whether and how therapies change intra-tumor heterogeneity, molecular traits and growth pattern of glioblastoma, and to which extent this information can be exploited for therapeutic decision-making. We conclude that the ability to characterize and predict therapy-induced changes in recurrent glioblastoma will determine, whether, one day, glioblastoma can be contained in a state of chronic disease. Oncogene advance online publication, 4 April 2016; doi:10.1038/onc.2016.85.
A comprehensive survey of the mutagenic impact of common cancer cytotoxics

Background: Genomic mutations caused by cytotoxic agents used in cancer chemotherapy may cause secondary malignancies as well as contribute to the evolution of treatment-resistant tumour cells. The stable diploid genome of the chicken DT40 lymphoblast cell line, an established DNA repair model system, is well suited to accurately assay genomic mutations. Results: We use whole genome sequencing of multiple DT40 clones to determine the mutagenic effect of eight common cytotoxics used for the treatment of millions of patients worldwide. We determine the spontaneous mutagenesis rate at $2.3 \times 10^{-10}$ per base per cell division and find that cisplatin, cyclophosphamide and etoposide induce extra base substitutions with distinct spectra. After four cycles of exposure, cisplatin induces 0.8 mutations per Mb, equivalent to the median mutational burden in common leukaemias. Cisplatin-induced mutations, including short insertions and deletions, are mainly located at sites of putative intrastrand crosslinks. We find two of the newly defined cisplatin-specific mutation types as causes of the reversion of BRCA2 mutations in emerging cisplatin-resistant tumours or cell clones. Gemcitabine,
5-fluorouracil, hydroxyurea, doxorubicin and paclitaxel have no measurable mutagenic effect. The cisplatin-induced mutation spectrum shows good correlation with cancer mutation signatures attributed to smoking and other sources of guanine-directed base damage. Conclusion: This study provides support for the use of cell line mutagenesis assays to validate or predict the mutagenic effect of environmental and iatrogenic exposures. Our results suggest genetic reversion due to cisplatin-induced mutations as a distinct mechanism for developing resistance.

**General information**

State: Published

Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Cancer Systems Biology, Hungarian Academy of Sciences, UCL Cancer Institute, Eötvös Loránd University


Number of pages: 1
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BFI (2018): BFI-level 2
BFI (2017): BFI-level 1
BFI (2016): BFI-level 1
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 11.12 SJR 10.484 SNIP 2.846
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 8.65 SNIP 2.608 CiteScore 9.08
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 8.188 SNIP 2.224 CiteScore 8.34
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 8.557 SNIP 2.418 CiteScore 8.55
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 7.9 SNIP 2.372 CiteScore 8.14
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 5.989 SNIP 1.973 CiteScore 6.69
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 5.012 SNIP 1.819
BFI (2009): BFI-level 1
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 3.713 SNIP 1.154
Scopus rating (2007): SJR 3.218 SNIP 0.721
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 2.523 SNIP 0.331
Scopus rating (2005): SJR 2.021 SNIP 0.229
Scopus rating (2004): SJR 1.336 SNIP 0.174
Web of Science (2004): Indexed yes
A fast and robust method for whole genome sequencing of the Aleutian Mink Disease Virus (AMDV) genome

Aleutian Mink Disease Virus (AMDV) is a frequently encountered pathogen associated with commercial mink breeding. AMDV infection leads to increased mortality and compromised animal health and welfare. Currently little is known about the molecular evolution of the virus, and the few existing studies have focused on limited regions of the viral genome. This paper describes a robust, reliable, and fast protocol for amplification of the full AMDV genome using long-range PCR. The method was used to generate next generation sequencing data for the non-virulent cell-culture adapted AMDV-G strain as well as for the virulent AMDV-Utah strain. Comparisons at nucleotide- and amino acid level showed that, in agreement with existing literature, the highest variability between the two virus strains was found in the left open reading frame, which encodes the non-structural (NS1–3) genes. This paper also reports a number of differences that potentially can be linked to virulence and host range. To the authors' knowledge, this is the first study to apply next generation sequencing on the entire AMDV genome. The results from the study will facilitate the development of new diagnostic tools and can form the basis for more detailed molecular epidemiological analyses of the virus.

General information
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Organisations: Department of Systems Biology, Molecular Evolution, National Veterinary Institute, Section for Virology, Center for Biological Sequence Analysis, Copenhagen
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Journal: Journal of Virological Methods
Volume: 234
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Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): SJR 0.87 SNIP 0.736 CiteScore 1.78
Web of Science (2016): Indexed Yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.868 SNIP 0.799 CiteScore 1.68
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.893 SNIP 0.952 CiteScore 1.87
A genomic history of Aboriginal Australia

The population history of Aboriginal Australians remains largely uncharacterized. Here we generate high-coverage genomes for 83 Aboriginal Australians (speakers of Pama-Nyungan languages) and 25 Papuans from the New Guinea Highlands. We find that Papuan and Aboriginal Australian ancestors diversified 25-40 thousand years ago (kya), suggesting pre-Holocene population structure in the ancient continent of Sahul (Australia, New Guinea and Tasmania). However, all of the studied Aboriginal Australians descend from a single founding population that differentiated ~10-32
kya. We infer a population expansion in northeast Australia during the Holocene epoch (past 10,000 years) associated with limited gene flow from this region to the rest of Australia, consistent with the spread of the Pama-Nyungan languages. We estimate that Aboriginal Australians and Papuans diverged from Eurasians 51-72 kya, following a single out-of-Africa dispersal, and subsequently admixed with archaic populations. Finally, we report evidence of selection in Aboriginal Australians potentially associated with living in the desert.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Copenhagen, Aarhus University, Griffith University Queensland, University of Bern, Barcelona Institute of Science and Technology, Instituto Gulbenkian de Ciência, Wellcome Trust Genome Campus, University of California at Berkeley
Number of pages: 8
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Journal: Nature
Volume: 538
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Ratings:
BFI (2018): BFI-level 3
BFI (2017): BFI-level 2
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 13.33
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): CiteScore 14.38
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): CiteScore 14.22
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): CiteScore 14.96
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): CiteScore 14.01
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): CiteScore 13.96
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 2
Web of Science (2008): Indexed yes
Web of Science (2007): Indexed yes
A Drosophila Genome-Wide Screen Identifies Regulators of Steroid Hormone Production and Developmental Timing

Steroid hormones control important developmental processes and are linked to many diseases. To systematically identify genes and pathways required for steroid production, we performed a Drosophila genome-wide in vivo RNAi screen and identified 1,906 genes with potential roles in steroidogenesis and developmental timing. Here, we use our screen as a resource to identify mechanisms regulating intracellular levels of cholesterol, a substrate for steroidogenesis. We identify a conserved fatty acid elongase that underlies a mechanism that adjusts cholesterol trafficking and steroidogenesis with nutrition and developmental programs. In addition, we demonstrate the existence of an autophagosomal cholesterol mobilization mechanism and show that activation of this system rescues Niemann-Pick type C1 deficiency that causes a disorder characterized by cholesterol accumulation. These cholesterol-trafficking mechanisms are regulated by TOR and feedback signaling that couples steroidogenesis with growth and ensures proper maturation timing. These results reveal genes regulating steroidogenesis during development that likely modulate disease mechanisms.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Copenhagen, University of California, University of Alberta, National Institute of Genetics, University of Southern Denmark, University of Minnesota
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Journal: Developmental Cell
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Ratings:
BFI (2018): BFI-level 2
BFI (2017): BFI-level 2
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 6.88 SJR 6.38 SNIP 2.115
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 7.265 SNIP 2.211 CiteScore 7.26
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 7.484 SNIP 2.383 CiteScore 7.61
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 9.099 SNIP 2.576 CiteScore 8.73
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 9.672 SNIP 2.769 CiteScore 9.72
Alpha proteobacterial ancestry of the \([\text{Fe-Fe}]\)-hydrogenases in anaerobic eukaryotes

Eukaryogenesis, a major transition in evolution of life, originated from the symbiogenic fusion of an archaea with a metabolically versatile bacterium. By general consensus, the latter organism belonged to a proteobacteria, subsequently evolving into the mitochondrial organelle of our cells. The consensus is based upon genetic and metabolic similarities between mitochondria and aerobic α proteobacteria but fails to explain the origin of several enzymes found in the mitochondria-derived organelles of anaerobic eukaryotes such as Trichomonas and Entamoeba. These enzymes are thought to derive from bacterial lineages other than a proteobacteria, e.g., Clostridium - an obligate anaerobe. \([\text{FeFe}]\)-hydrogenase constitutes the characteristic enzyme of this anaerobic metabolism and is present in different types also in Entamoeba and other anaerobic eukaryotes. Here we show that a proteobacteria derived from metagenomic studies possess both the cytosolic and organellar type of \([\text{FeFe}]\)-hydrogenase, as well as all the proteins required for hydrogenase maturation. These organisms are related to cultivated members of the Rhodospirillales order previously suggested to be close relatives of mitochondrial ancestors. For the first time, our evidence supports an a proteobacterial ancestry for both the anaerobic and the aerobic metabolism of eukaryotes. Reviewers: This article was reviewed by William Martin and Nick Lane, both suggested by the Authors.
Angiotensinogen and HLA class II predict bevacizumab response in recurrent glioblastoma patients

Background: Bevacizumab combination therapy is among the most frequently used treatments in recurrent glioblastoma and patients who achieve response to bevacizumab have improved survival as well as quality of life. Accordingly, the aim of this study was to identify predictive biomarkers for bevacizumab response in recurrent glioblastoma patients. Methods: The study included a total of 82 recurrent glioblastoma patients treated with bevacizumab combination therapy whom were both response and biomarker evaluable. Gene expression of tumor tissue was analyzed by using a customized NanoString platform covering 800 genes. Candidate gene predictors associated with response were analyzed by multivariate logistic and Cox regression analysis. Results: Two genes were independently associated with response: Low expression of angiotensinogen (2-fold decrease in AGT; OR = 2.44; 95% CI: 1.45-4.17; P = 0.0009) and high expression of a HLA class II gene (2-fold increase in HLA-DQA1; OR = 1.22; 95% CI: 1.01-1.47; P = 0.04). These two genes were included in a model that is able predict response to bevacizumab combination therapy in clinical practice. When stratified for a validated prognostic index, the predictive model for response was significantly associated with improved overall survival. Conclusion: Two genes (low angiotensinogen and high HLA-class II expression) were predictive for bevacizumab response and were included in a predictive model for response. This model can be used in clinical practice to identify patients who will benefit from bevacizumab combination therapy.

General information
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Rigshospitalet, Hvidovre Hospital, University of Copenhagen
Authors: Urup, T. (Ekstern), Michaelsen, S. R. (Ekstern), Olsen, L. R. (Intern), Toft, A. (Ekstern), Christensen, I. J. (Ekstern), Grunnet, K. (Ekstern), Winther, O. (Ekstern), Broholm, H. (Ekstern), Kosteljanetz, M. (Ekstern), Issazadeh-Navikas, S. (Ekstern), Poulsen, H. S. (Ekstern), Lassen, U. (Ekstern)
Number of pages: 9
Pages: 1160-1168
A novel approach to probe host-pathogen interactions of bovine digital dermatitis, a model of a complex polymicrobial infection

Polymicrobial infections represent a great challenge for the clarification of disease etiology and the development of comprehensive diagnostic or therapeutic tools, particularly for fastidious and difficult-to-cultivate bacteria. Using bovine digital dermatitis (DD) as a disease model, we introduce a novel strategy to study the pathogenesis of complex infections. The strategy combines meta-transcriptomics with high-density peptide-microarray technology to screen for in vivo-expressed microbial genes and the host antibody response at the site of infection. Bacterial expression patterns supported the assumption that treponemes were the major DD pathogens but also indicated the active involvement of other phyla (primarily Bacteroidetes). Bacterial genes involved in chemotaxis, flagellar synthesis and protection against oxidative and acidic stress were among the major factors defining the disease. The extraordinary diversity observed in bacterial expression, antigens and host antibody responses between individual cows pointed toward microbial variability as a hallmark of DD. Persistence of infection and DD reinfection in the same individual is common; thus, high microbial diversity may undermine the host's capacity to mount an efficient immune response and maintain immunological memory towards DD. The common antigenic markers identified here using a high-density peptide microarray address this issue and may be useful for future preventive measures against DD.
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, National Veterinary Institute, Section for Bacteriology, Pathology and Parasitology, Metagenomics, Hospital of Southern Jutland, Schafer-N ApS
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BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 4.05 SJR 2.065 SNIP 1.122
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.287 SNIP 1.172 CiteScore 4.3
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.297 SNIP 1.205 CiteScore 4.18
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 2.141 SNIP 1.174 CiteScore 4.39
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 2.181 SNIP 1.225 CiteScore 4.61
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 2.271 SNIP 1.197 CiteScore 4.38
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 2.109 SNIP 1.038
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 2.181 SNIP 1.015
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 2.067 SNIP 1.005
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 1.846 SNIP 1.04
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 1.431 SNIP 0.895
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 1.994 SNIP 0.894
Web of Science (2005): Indexed yes
Scopus rating (2004): SJR 1.852 SNIP 0.617
Web of Science (2004): Indexed yes
Application of WGS data for O-specific antigen analysis and in silico serotyping of Pseudomonas aeruginosa isolates

Accurate typing methods are required for efficient infection control. The emergence of whole genome sequencing (WGS) technologies has enabled the development of genomics-based methods applicable for routine typing and surveillance of bacterial pathogens. In this study, we developed the Pseudomonas aeruginosa serotyper (PAst) program, which enabled in silico serotyping of P. aeruginosa isolates using WGS data. PAst has been made publically available as a web-service, and aptly facilitate high-throughput serotyping analysis. The program overcomes critical issues such as the loss of in vitro typeability often associated with P. aeruginosa isolates from chronic infections, and quickly determines the serogroup of an isolate based on the sequence of the O-specific antigen (OSA) gene cluster. Here, PAst analysis of 1649 genomes resulted in successful serogroup assignments in 99.27% of the cases. This frequency is rarely achievable by conventional serotyping methods. The limited number of non-typeable isolates found using PAst was the result of either complete absence of OSA genes in the genomes or the artifact of genomic misassembly. With PAst, P. aeruginosa serotype data can be obtained from WGS information alone. PAst is a highly efficient alternative to conventional serotyping methods in relation to outbreak surveillance of serotype O12 and other high-risk clones, while maintaining backward compatibility to historical serotype data.

General information
State: Published
Organisations: Department of Systems Biology, National Food Institute, Infection Microbiology, Center for Biological Sequence Analysis, University of Guelph
Authors: Thrane, S. W. (Intern), Taylor, V. L. (Ekstern), Lund, O. (Intern), Lam, J. S. (Ekstern), Jelsbak, L. (Intern)
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Main Research Area: Technical/natural sciences

Publication information
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Issue number: 7
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BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.57 SJR 2.14 SNIP 1.417
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.204 SNIP 1.448 CiteScore 3.56
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.205 SNIP 1.538 CiteScore 3.84
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 2.414 SNIP 1.646 CiteScore 4.18
ISI indexed (2013): ISI indexed yes
A robust prognostic gene expression signature for early stage lung adenocarcinoma

Stage I lung adenocarcinoma is usually not treated with adjuvant chemotherapy; however, around half of these patients do not survive 5 years. Therefore, a reliable prognostic biomarker for early stage patients would be critical to identify those most likely to benefit from early additional treatments. Several studies have searched for gene expression prognostic biomarkers for lung adenocarcinoma, but these have not yielded a widely accepted prognosticator. We analyzed gene expression from seven published lung adenocarcinoma cohorts for which we included only stage I and II patients who were not given adjuvant therapy. Seven genes consistently obtained statistical significance in Cox regression for overall survival. The combined signature has a weighted mean hazard ratio of 3.2 in all cohorts and 3.0 (C.I. 1.3-7.4, p

General information
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Asparaginase-associated pancreatitis: a study on phenotype and genotype in the NOPHO ALL2008 protocol

Asparaginase (ASP)-associated pancreatitis (AAP) occurs during acute lymphoblastic leukemia treatment. Among 1285 children (1.0-17.9 years) diagnosed during July 2008-December 2014 and treated according to the Nordic/Baltic ALL2008 protocol, 86 (cumulative incidence = 6.8%) developed AAP. Seventy-three cases were severe (diagnostic AAP criteria persisting 472 h) and 13 mild. Cases were older than controls (median: 6.5 vs 4.5 years; P = 0.001). Pseudocysts developed in 28%. Of the 20 re-exposed to ASP, 9 (45%) developed a second AAP. After a median follow-up of 2.3 years, 8% needed permanent insulin therapy, and 7% had recurrent abdominal pain. Germline DNA on 62 cases and 638 controls was genotyped on Omni2.5exome-8-v1.2 BeadChip arrays. Overall, the ULK2 variant rs281366 showed the strongest association with AAP (P = 5.8x10^-7; odds ratio (OR) = 6.7). Cases with the rs281366 variant were younger (4.3 vs 8 years; P = 0.015) and had lower risk of AAP-related complications (15% vs 43%; P = 0.13) compared with cases without this variant. Among 45 cases and 517 controls
Automated Clustering Analysis of Immunoglobulin Sequences in Chronic Lymphocytic Leukemia Based on 3D Structural Descriptors

Immunoglobulins (Igs) are crucial for the defense against pathogens, but they are also important in many clinical and biotechnological applications. Their characteristics, and ultimately their function, depend on their three-dimensional (3D) structure; however, the procedures to experimentally determine it are extremely laborious and demanding. Hence, the ability to gain insight into the structure of Igs at large relies on the availability of tools and algorithms for producing accurate Ig structural models based on their primary sequence alone. These models can then be used to determine structural and eventually functional similarities between different Igs. An example of such a task is the clustering of Igs based on their structure to determine meaningful common features such as the possible existence of common molecular targets (antigens). Several approaches have been proposed in order to achieve an optimal solution to this task yet their results were hindered mainly due to the lack of efficient clustering methods based on the similarity of 3D structure.
descriptors. Here, we present a novel workflow for robust Ig 3D modeling and automated clustering. We validated our protocol in chronic lymphocytic leukemia (CLL), where the clonotypic Igs are critically implicated in the disease ontogeny and evolution. Indeed, immunogenetic studies on the clonotypic Igs have strongly implicated antigen selection in the pathogenesis of CLL, while also providing robust prognostic information. In the present study, we used the structure prediction tools PIGS and I-TASSER for creating the 3D models and the TM-align algorithm to superpose them. The innovation of the current methodology resides in the usage of methods adapted from 3D content-based search methodologies to determine the local structural similarity between the 3D models. The Fast Point Feature Histograms descriptors derived from the structurally aligned parts are used to compute a distance matrix, which is then used as input for the clustering procedure. Clustering analysis on the data is performed through the application of the agglomerative and density-based clustering approaches. The first method is unsupervised whereas the second belongs to the semi-supervised type, i.e. requires a predefined number of clusters. To evaluate the quality of the herein described workflow, we performed a supervised analysis of 125 Ig 3D models originating from 5 CLL stereotyped subsets i.e. subgroups sharing (quasi) identical Igs, namely subsets #1, #2, #4, #6, #8. The reasoning behind this choice was that (i) homologous Ig primary sequences can be reasonably anticipated to be reflected in overall similar 3D structures, hence providing a reference for evaluating the developed workflow; and, (ii) these subsets are well characterized at both the clinical and biological levels. Subset size distribution was as follows: subset #1 (IGHV clan I/IGKV1(D)-39), n=37; subset #2 (IGHV3-21/IGLV3-21), n=43; subset #4 (IGHV4-34/IGKV2-30), n=22; subset #6 (IGHV1-69/IGKV3-20), n=12; and, subset #8 (IGHV4-39/IGKV1(D)-39), n=11. Overall, we obtained a high level of clustering accuracy i.e. Ig 3D model clusters matched to a very high degree the subsets defined by Ig primary sequence similarity. In detail, 5 Ig 3D model clusters were produced by: (i) cluster 1 containing 37/37 (100%) subset #1 models and one (8.3%) subset #6 model, (ii) cluster 2 containing 43/43 (100%) subset #2 models, (iii) cluster 3 containing 21/22 (95.5%) subset #4 models, (iv) cluster 4 containing 11/12 (91.7%) #6 models, and, (v) cluster 5 containing 11/11 (100%) subset #8 models along with a single (4.5%) subset #4 model (subsets #4 and #8 concern IgG CLL, in itself a rarity for CLL). These findings support that the innovative workflow described here enables robust clustering of 3D models produced from Ig sequences from patients with CLL. Furthermore, they indicate that CLL classification based on stereotypy of Ig primary sequences is likely also verified at the Ig 3D structural level. Studies are ongoing for both addressing the minor discrepancies observed here and producing the unsupervised 3D clustering of the Igs from a large series of both stereotyped and non-stereotyped CLL cases.
BCL9L Dysfunction Impairs Caspase-2 Expression Permitting Aneuploidy Tolerance in Colorectal Cancer

Chromosomal instability (CIN) contributes to cancer evolution, intratumor heterogeneity, and drug resistance. CIN is driven by chromosome segregation errors and a tolerance phenotype that permits the propagation of aneuploid genomes. Through genomic analysis of colorectal cancers and cell lines, we find frequent loss of heterozygosity and mutations in BCL9L in aneuploid tumors. BCL9L deficiency promoted tolerance of chromosome missegregation events, propagation of aneuploidy, and genetic heterogeneity in xenograft models likely through modulation of Wnt signaling. We find that BCL9L dysfunction contributes to aneuploidy tolerance in both TP53-WT and mutant cells by reducing basal caspase-2 levels and preventing cleavage of MDM2 and BID. Efforts to exploit aneuploidy tolerance mechanisms and the BCL9L/caspase-2/BID axis may limit cancer diversity and evolution.
Benchmarking of methods for identification of antimicrobial resistance genes in bacterial whole genome data

Next generation sequencing (NGS) may be an alternative to phenotypic susceptibility testing for surveillance and clinical diagnosis. However, current bioinformatics methods may be associated with false positives and negatives. In this study, a novel mapping method was developed and benchmarked to two different methods in current use for identification of antibiotic resistance genes in bacterial WGS data. A novel method, KmerResistance, which examines the co-occurrence of k-mers between the WGS data and a database of resistance genes, was developed. The performance of this method was compared with two previously described methods; ResFinder and SRST2, which use an assembly/BLAST method and BWA, respectively, using two datasets with a total of 339 isolates, covering five species, originating from the Oxford University Hospitals NHS Trust and Danish pig farms. The predicted resistance was compared with the observed phenotypes for all isolates. To challenge further the sensitivity of the in silico methods, the datasets were also downsampled to 1% of the reads and reanalysed. The best results were obtained by identification of resistance genes by mapping directly against the raw reads. This indicates that information might be lost during assembly. KmerResistance performed significantly better than the other methods, when data were contaminated or only contained few sequence reads. Read mapping is superior to assembly-based methods and the new KmerResistance seemingly outperforms currently available methods particularly when including datasets with few reads.
Benchtop Whole-Genome Sequencing for Identification of Nosocomial Outbreaks in Tanzania

General information
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, National Food Institute, Research Group for Genomic Epidemiology, Kilimanjaro Christian Medical Centre, University of Copenhagen
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BFI (2014): BFI-level 1
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BFI (2012): BFI-level 1
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BFI (2011): BFI-level 1
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Scopus rating (2010): SJR 2.305 SNIP 1.518
BFI (2009): BFI-level 1
Capturing One of the Human Gut Microbiome's Most Wanted: Reconstructing the Genome of a Novel Butyrate-Producing, Clostridial Scavenger from Metagenomic Sequence Data

The role of the microbiome in health and disease is attracting great attention, yet we still know little about some of the most prevalent microorganisms inside our bodies. Several years ago, Human Microbiome Project (HMP) researchers generated a list of "most wanted" taxa: bacteria both prevalent among healthy volunteers and distantly related to any sequenced organisms. Unfortunately, the challenge of assembling high quality genomes from a tangle of metagenomic reads has slowed progress in learning about these uncultured bacteria. Here, we describe how recent advances in sequencing and analysis allowed us to assemble "most wanted" genomes from metagenomic data collected from four stool samples. Using a combination of both de novo and guided assembly methods, we assembled and binned over 100 genomes from an initial data set of over 1,300 Gbp. One of these genome bins, which met HMP's criteria for a "most wanted" taxa, contained three essentially complete genomes belonging to a previously uncultivated species. This species is most closely related to Eubacterium desmolans and the clostridial cluster IV/Clostridium leptum subgroup species Butyncicoccus pullicaecorum (71-76% average nucleotide identity). Gene function analysis indicates that the species is an obligate anaerobe, forms spores, and produces the antiinflammatory short-chain fatty acids acetate and butyrate. It also appears to take up metabolically costly molecules such as cobalamin, methionine, and branch-chained amino acids from the environment, and to lack virulence genes. Thus, the evidence is consistent with a secondary degrader that occupies a host-dependent, nutrient scavenging niche within the gut; its ability to produce butyrate, which is thought to play an anti-inflammatory role, makes it intriguing for the study of diseases such as colon cancer and inflammatory bowel disease. In conclusion, we have assembled essentially complete genomes from stool metagenomic data, yielding valuable information about uncultured organisms' metabolic and ecologic niches, factors that may be required to successfully culture these bacteria, and their role in maintaining health and causing disease.

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OBJECTIVE: HIV-2 represents an attenuated form of HIV, where many infected individuals remain “aviremic” without antiretroviral therapy (ART). However, aviremic HIV-2 disease progression exits, and in the current study we therefore aimed to examine if specific pathological characteristics of CD4+ T cells are linked to such outcome. DESIGN: HIV-seronegative (n=25), HIV-1 (n=33), HIV-2 (n=39, of whom 26 were aviremic), and HIV-1/2 dually (HIV-D) (n=13) infected subjects were enrolled from an occupational cohort in Guinea-Bissau. METHODS:: CD4+ T cell differentiation, activation, exhaustion, senescence, and transcription factors were assessed by polychromatic flow cytometry. Multidimensional clustering bioinformatic tools were used to identify CD4+ T cell subpopulations linked to infection type and disease stage. RESULTS: HIV-2-infected individuals had early- and late-differentiated CD4+ T cell clusters with lower activation (CD38+HLA-DR+) and exhaustion (PD-1) than HIV-1 and HIV-D-infected subjects. We also noted that aviremic HIV-2-infected individuals possessed fewer CD4+ T cells with pathological signs compared to other HIV-infected groups. Still, compared to HIV-seronegatives, aviremic HIV-2-infected subjects had T-bet+ CD4+ T cells that showed elevated immune activation/exhaustion, and particularly the frequencies of PD-1+ cells were associated with suboptimal percentage of CD4+ T cells. CONCLUSIONS: Increased frequencies of CD4+ T cells with an activated/exhausted phenotype correlate with exacerbated immunodeficiency in aviremic HIV-2-infected individuals. Thus, these findings encourage studies on the introduction of ART also to individuals with aviremic HIV-2 infection.
Characterisation of Non-Histone Lysine Acetyltransferases and Deacetylases in Probiotics

General information
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Organisations: Department of Systems Biology, Enzyme and Protein Chemistry, Center for Biological Sequence Analysis, Proteomics Platform
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BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.998 SNIP 0.903 CiteScore 2.99
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.805 SNIP 0.855 CiteScore 2.77
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.982 SNIP 0.819 CiteScore 2.96
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.932 SNIP 0.818 CiteScore 2.76
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.937 SNIP 0.959 CiteScore 2.94
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.737 SNIP 0.809
Web of Science (2010): Indexed yes
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Scopus rating (2009): SJR 2.255 SNIP 0.997
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 2.322 SNIP 0.919
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 2.297 SNIP 1.008
Scopus rating (2006): SJR 2.378 SNIP 1.042
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 2.515 SNIP 1.129
Web of Science (2005): Indexed yes
Scopus rating (2004): SJR 2.32 SNIP 1.187
Scopus rating (2003): SJR 2.473 SNIP 1.143
Web of Science (2003): Indexed yes
Chemosensory perception, symptoms and autonomic responses during chemical exposure in multiple chemical sensitivity

Purpose: Multiple chemical sensitivity (MCS) is a prevalent medically unexplained symptom characterized by symptom reactions to everyday chemical exposure below hygienic thresholds. The aim of this study was to investigate the expressions of hyper-reactivity in MCS during whole-body exposure to low concentrations of the odorant n-butanol.

Methods: We exposed 18 participants with MCS and 18 non-ill controls to a low concentration of the odorant n-butanol using an exposure chamber. The first 10 min constituted blank exposure, after which the n-butanol concentration increased and reached a plateau at 11.5 mg/m³. Results: MCS participants, compared with controls, reported greater perceived odor intensities, more unpleasantness to the exposure and increasing symptoms over time. MCS participants also expressed higher pulse rate and lower pulse rate variability than controls did. No group differences were found for breathing rate or tonic electrodermal activity responses. Conclusions: We conclude that MCS sufferers differ from healthy controls in terms of autonomic responses, symptoms and chemosensory perception during chemical exposure.
ChemProt-3.0: a global chemical biology diseases mapping

ChemProt is a publicly available compilation of chemical-protein-disease annotation resources that enables the study of systems pharmacology for a small molecule across multiple layers of complexity from molecular to clinical levels. In this third version, ChemProt has been updated to more than 1.7 million compounds with 7.8 million bioactivity measurements for 19,504 proteins. Here, we report the implementation of global pharmacological heatmap, supporting a user-friendly navigation of chemogenomics space. This facilitates the visualization and selection of chemicals that share similar structural properties. In addition, the user has the possibility to search by compound, target, pathway, disease and clinical effect. Genetic variations associated to target proteins were integrated, making it possible to plan pharmacogenetic studies and to suggest human response variability to drug. Finally, Quantitative Structure-Activity Relationship models for 850 proteins having sufficient data were implemented, enabling secondary pharmacological profiling predictions from molecular structure.

General information
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Copenhagen
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Colonic transit time is related to bacterial metabolism and mucosal turnover in the gut

Little is known about how colonic transit time relates to human colonic metabolism and its importance for host health, although a firm stool consistency, a proxy for a long colonic transit time, has recently been positively associated with gut microbial richness. Here, we show that colonic transit time in humans, assessed using radio-opaque markers, is associated with overall gut microbial composition, diversity and metabolism. We find that a long colonic transit time associates with high microbial richness and is accompanied by a shift in colonic metabolism from carbohydrate fermentation to protein catabolism as reflected by higher urinary levels of potentially deleterious protein-derived metabolites. Additionally, shorter colonic transit time correlates with metabolites possibly reflecting increased renewal of the colonic mucosa. Together, this suggests that a high gut microbial richness does not per se imply a healthy gut microbial ecosystem and points at colonic transit time as a highly important factor to consider in microbiome and metabolomics studies.

Colonic transit time is related to bacterial metabolism and mucosal turnover in the human gut

Little is known about how colonic transit time relates to human colonic metabolism and its importance for host health, although stool consistency, a proxy for colonic transit time, has recently been negatively associated with gut microbial richness. To address the relationships between colonic transit time and the gut microbial composition and metabolism, we
assessed the colonic transit time of 98 subjects using radiopaque markers, and profiled their gut microbiota by 16S rRNA gene sequencing and their urine metabolome by ultra performance liquid chromatography mass spectrometry. Based on correlation analyses, we show that colonic transit time is associated with overall gut microbial composition, diversity and metabolism. A relatively prolonged colonic transit time associates with high microbial species richness and a shift in colonic metabolism from carbohydrate fermentation to protein catabolism as reflected by higher urinary levels of potentially deleterious protein-derived metabolites. Additionally, shorter colonic transit time correlates with metabolites likely reflecting increased renewal of the colonic mucosa. Together, this suggests that a high gut microbial richness does not per se imply a healthy gut microbial ecosystem and points at colonic transit time as a highly important factor to consider in microbiome and metabolomics studies.

**General information**

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**Organisations:** National Food Institute, Research Group for Gut Microbiology and Immunology, Department of Systems Biology, Center for Biological Sequence Analysis, Functional Human Variation, Department of Bio and Health Informatics, Research Group for Analytical Food Chemistry, DTU Multi Assay Core, Metagenomics, Department of Biotechnology, Copenhagen Center for Health Technology, University of Copenhagen, Bispebjerg University Hospital  
**Authors:** Roager, H. M. (Intern), Hansen, L. B. S. (Intern), Bahl, M. I. (Intern), Frandsen, H. L. (Intern), Carvalho, V. (Intern), Gøbel, R. J. (Ekstern), Dalgaard, M. D. (Intern), Plichta, D. R. (Intern), Sparholt, M. (Ekstern), Vestergaard, H. (Ekstern), Hansen, T. (Ekstern), Sicheritz-Pontén, T. (Intern), Nielsen, H. B. (Intern), Pedersen, O. (Ekstern), Lauritzen, L. (Ekstern), Kristensen, M. (Ekstern), Licht, T. R. (Intern)  
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**Colonic transit time relates to bacterial metabolism and mucosal turnover in the human gut**

Little is known about how colonic transit time relates to human colonic metabolism, and its importance for host health, although stool consistency, a proxy for colonic transit time, has recently been negatively associated with gut microbial richness. To address the relationships between colonic transit time and the gut microbial composition and metabolism, we assessed the colonic transit time of 98 subjects using radiopaque markers, and profiled their gut microbiota by 16S rRNA gene sequencing and their urine metabolome by ultra performance liquid chromatography mass spectrometry. Based on correlation analyses, we show that colonic transit time is associated with overall gut microbial composition, diversity and metabolism. A relatively prolonged colonic transit time associates with high microbial species richness and a shift in colonic metabolism from carbohydrate fermentation to protein catabolism as reflected by microbial metabolites in urine. This results in a number of potentially deleterious protein-derived metabolites. Additionally, longer colonic transit time correlates with metabolites likely reflecting reduced renewal of the colonic mucosa. Together, this suggests that a high gut microbial richness does not per se imply a healthy gut microbiota, and contributes to the understanding of the pathophysiology of diseases where increased transit time is a risk factor. Finally, our findings highlight the colonic transit time as an important physiological variable, which should be considered in gut microbiota and metabolomics studies.

**General information**

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**Organisations:** National Food Institute, Research Group for Gut Microbiology and Immunology, Department of Systems Biology, Center for Biological Sequence Analysis, Functional Human Variation, Research Group for Analytical Food Chemistry, DTU Multi Assay Core, Copenhagen Center for Health Technology, Bispebjerg University Hospital, University of Copenhagen, Technical University of Denmark  
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Control of lysosomal biogenesis and Notch-dependent tissue patterning by components of the TFEB-V-ATPase axis in *Drosophila melanogaster*

In vertebrates, TFEB (transcription factor EB) and MITF (microphthalmia-associated transcription factor) family of basic Helix-Loop-Helix (bHLH) transcription factors regulates both lysosomal function and organ development. However, it is not clear whether these 2 processes are interconnected. Here, we show that Mitf, the single TFEB and MITF ortholog in *Drosophila*, controls expression of vacuolar-type H⁺-ATPase pump (V-ATPase) subunits. Remarkably, we also find that expression of Vha16-1 and Vha13, encoding 2 key components of V-ATPase, is patterned in the wing imaginal disc. In particular, Vha16-1 expression follows differentiation of proneural regions of the disc. These regions, that will form sensory organs in the adult, appear to possess a distinctive endo-lysosomal compartment and Notch (N) localization. Modulation of Mitf activity in the disc in vivo alters endo-lysosomal function and disrupts proneural patterning. Similar to our findings in *Drosophila*, in human breast epithelial cells we observe that impairment of the Vha16-1 human ortholog ATP6V0C changes the size and function of the endo-lysosomal compartment and that depletion of TFEB reduces ligand-independent N signaling activity. Our data suggest that lysosomal-associated functions regulated by the TFEB-V-ATPase axis might play a conserved role in shaping cell fate.

**General information**

State: Published
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- Scopus rating (2016): SJR 3.035 SNIP 1.427 CiteScore 5.69
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- BFI (2013): BFI-level 2
- Scopus rating (2013): SJR 3.326 SNIP 1.631 CiteScore 5.2
- BFI (2012): BFI-level 2
- Scopus rating (2012): SJR 2.853 SNIP 1.196 CiteScore 5.15
- BFI (2011): BFI-level 2
- Scopus rating (2011): SJR 3.102 SNIP 1.116 CiteScore 4.75
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- Scopus rating (2010): SJR 4.16 SNIP 0.929
- BFI (2009): BFI-level 1
- Scopus rating (2009): SJR 4.6 SNIP 1.07
- BFI (2008): BFI-level 2
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Web of Science (2017): Indexed Yes
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Scopus rating (2015): SJR 2.511 SNIP 1.627 CiteScore 5.89
BFI (2014): BFI-level 1
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BFI (2013): BFI-level 1
Scopus rating (2013): SJR 2.218 SNIP 1.691 CiteScore 5.81
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BFI (2012): BFI-level 1
Scopus rating (2012): SJR 2.099 SNIP 1.67 CiteScore 5.51
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Defining the HLA class I-associated viral antigen repertoire from HIV-1-infected human cells

Recognition and eradication of infected cells by cytotoxic T lymphocytes is a key defense mechanism against intracellular pathogens. High-throughput definition of HLA class I-associated immunopeptidomes by mass spectrometry is an increasingly important analytical tool to advance our understanding of the induction of T-cell responses against pathogens such as HIV-1. We utilized a liquid chromatography tandem mass spectrometry workflow including de novo-assisted database searching to define the HLA class I-associated immunopeptidome of HIV-1-infected human cells. We here report for the first time the identification of 75 HIV-1-derived peptides bound to HLA class I complexes that were purified directly from HIV-1-infected human primary CD4+ T cells and the C8166 human T-cell line. Importantly, one-third of eluted HIV-1 peptides had not been previously known to be presented by HLA class I. Over 82% of the identified sequences originated from viral protein regions for which T-cell responses have previously been reported but for which the precise HLA class I-binding sequences have not yet been defined. These results validate and expand the current knowledge of virus-specific antigenic peptide presentation during HIV-1 infection and provide novel targets for T-cell vaccine development.
Delivery of TLR7 agonist to monocytes and dendritic cells by DCIR targeted liposomes induces robust production of anti-cancer cytokines.

General information
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Dhurrin metabolism in the developing grain of Sorghum bicolor (L.) Moench investigated by metabolite profiling and novel clustering analyses of time-resolved transcriptomic data

Background: The important cereal crop Sorghum bicolor (L.) Moench biosynthesize and accumulate the defensive compound dhurrin during development. Previous work has suggested multiple roles for the compound including a function as nitrogen storage/buffer. Crucial for this function is the endogenous turnover of dhurrin for which putative pathways have been suggested but not confirmed.

Results: In this study, the biosynthesis and endogenous turnover of dhurrin in the developing sorghum grain was studied by metabolite profiling and time-resolved transcriptome analyses. Dhurrin was found to accumulate in the early phase of grain development reaching maximum amounts 25 days after pollination. During the subsequent maturation period, the dhurrin content was turned over, resulting in only negligible residual dhurrin amounts in the mature grain. Dhurrin accumulation correlated with the transcript abundance of the three genes involved in biosynthesis. Despite the accumulation of dhurrin, the grains were acyanogenic as demonstrated by the lack of hydrogen cyanide release from macerated grain tissue and by the absence of transcripts encoding dhurrinases. With the missing activity of dhurrinases, the decrease in dhurrin content in the course of grain maturation represents the operation of hitherto uncharacterized endogenous dhurrin turnover pathways. Evidence for the operation of two such pathways was obtained by metabolite profiling and time-resolved transcriptome analysis. By combining cluster- and phylogenetic analyses with the metabolite profiling, potential gene candidates of glutathione S-transferases, nitrilases and glycosyl transferases involved in these pathways were identified. The absence of dhurrin in the mature grain was replaced by a high content of proanthocyanidins. Cluster- and phylogenetic analyses coupled with metabolite profiling, identified gene candidates involved in proanthocyanidin biosynthesis in sorghum.

Conclusions: The results presented in this article reveal the existence of two endogenous dhurrin turnover pathways in sorghum, identify genes putatively involved in these transformations and show that dhurrin in addition to its insect deterrent properties may serve as a storage form of reduced nitrogen. In the course of sorghum grain maturation, proanthocyanidins replace dhurrin as a defense compound. The lack of cyanogenesis in the developing sorghum grain renders this a unique experimental system to study CNglc synthesis as well as endogenous turnover.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Novozymes A/S, Seedtek, University of Copenhagen, Carlsberg Research Laboratory
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Diagnosis trajectories of prior multi-morbidity predict sepsis mortality

Sepsis affects millions of people every year, many of whom will die. In contrast to current survival prediction models for sepsis patients that primarily are based on data from within-admission clinical measurements (e.g. vital parameters and blood values), we aim for using the full disease history to predict sepsis mortality. We benefit from data in electronic medical records covering all hospital encounters in Denmark from 1996 to 2014. This data set included 6.6 million patients of whom almost 120,000 were diagnosed with the ICD-10 code: A41 'Other sepsis'. Interestingly, patients following recurrent trajectories of time-ordered co-morbidities had significantly increased sepsis mortality compared to those who did not follow a trajectory. We identified trajectories which significantly altered sepsis mortality, and found three major starting points in a combined temporal sepsis network: Alcohol abuse, Diabetes and Cardio-vascular diagnoses. Many cancers also increased sepsis mortality. Using the trajectory based stratification model we explain contradictory reports in relation to diabetes that recently have appeared in the literature. Finally, we compared the predictive power using 18.5 years of disease history to scoring based on within-admission clinical measurements emphasizing the value of long term data in novel patient scores that combine the two types of data.
Differential proteome and cellular adhesion analyses of the probiotic bacterium \textit{Lactobacillus acidophilus} NCFM grown on raffinose - an emerging prebiotic

Whole cell and surface proteomes were analyzed together with adhesive properties of the probiotic bacterium \textit{Lactobacillus acidophilus} NCFM (NCFM) grown on the emerging prebiotic raffinose, exemplifying a synbiotic. Adhesion of NCFM to mucin and intestinal HT-29 cells increased three-fold after culture with raffinose versus glucose, as also visualized by scanning electron microscopy. Comparative proteomics using 2D-DIGE showed 43 unique proteins to change in relative abundance in whole cell lysates from NCFM grown on raffinose compared to glucose. Furthermore, 14 unique proteins in 18 spots of the surface subproteome underwent changes identified by differential 2DE, including elongation factor G, thermostable pullulanase, and phosphate starvation inducible stress-related protein increasing in a range of $+2.1$ to $+4.7$ fold. By contrast five known moonlighting proteins decreased in relative abundance by up to $-2.4$ fold. Enzymes involved in raffinose catabolism were elevated in the whole cell proteome; $\alpha$-galactosidase ($+13.9$ fold); sucrose phosphorylase ($+5.4$ fold) together with metabolic enzymes from the Leloir pathway for galactose utilization and the glycolysis; $\beta$-galactosidase ($+5.7$ fold); galactose ($+2.9$/$+3.1$ fold) and fructose ($+2.8$ fold) kinases. The insights at the molecular and cellular levels contributed to the understanding of the interplay of a synbiotic composed of NCFM and raffinose with the host.
Divergent Response Profile in Activated Cord Blood T cells from First-born Child Implies Birth-order-associated in Utero Immune Programming

Background: First-born children are at higher risk for development of a range of immune-mediated diseases. The underlying mechanism of ‘birth-order-effects’ on disease risk is largely unknown, but in utero programming of the child's immune system may play a role. Objective: We studied the association between birth-order and the functional response of stimulated cord blood T cells. Method: Purified cord blood T cells were polyclonally activated with anti-CD3/CD28-coated beads in a subgroup of 28 children enrolled in the COPSAC_2010 birth cohort. Expression levels of seven activation markers on helper and cytotoxic T cells as well as the percentage of CD4+CD25+ T cells were assessed by flow cytometry. Production of IFN-γ, TNF-α, IL-17, IL-4, IL-5, IL-13 and IL-10 was measured in supernatants. Results: IL-10 secretion (P = 0.007) and CD25 expression on CD4+ helper T cells (P = 0.0003) in activated cord blood T cells were selectively reduced in first-born children, while the percentage of CD4+CD25+ cord blood T cells was independent of birth-order. Conclusion: First-born infants display a reduced anti-inflammatory profile in T cells at birth. This possible in utero ‘birth-order’ T cell programing may contribute to later development of immune-mediated diseases by increasing overall immune reactivity in first-born children as compared to younger siblings.
Do very small adipocytes in subcutaneous adipose tissue (a proposed risk factor for insulin insensitivity) have a fetal origin?

Previous studies have shown that fetal life malnutrition affects preferences for fat deposition in the body thereby predisposing for visceral adiposity and associated disorders in glucose-insulin regulation. In this study, we aimed to test the hypotheses that late-gestation undernutrition 1) has long-term differential impacts on development, expandability and metabolic features in subcutaneous as compared to perirenal and mesenteric adipose tissues, which 2) will predispose for visceral obesity upon exposure to an obesogenic diet in early postnatal life.

**General information**

State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, University of Copenhagen, Rigshospitalet
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**Effect of vitamin D3 supplementation during pregnancy on risk of persistent wheeze in the offspring: a randomised clinical trial**

**General information**

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Copenhagen University Hospital, Aarhus University Hospital, University of Copenhagen
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Effect of Vitamin D3 Supplementation During Pregnancy on Risk of Persistent Wheeze in the Offspring A Randomized Clinical Trial: A Randomized Clinical Trial

IMPORTANCE: Observational studies have suggested that increased dietary vitamin D intake during pregnancy may protect against wheezing in the offspring, but the preventive effect of vitamin D supplementation to pregnant women is unknown. OBJECTIVE: To determine whether supplementation of vitamin D3 during the third trimester of pregnancy reduces the risk of persistent wheeze in the offspring. DESIGN, SETTING, AND PARTICIPANTS: A double-blind, single-center, randomized clinical trial conducted within the Copenhagen Prospective Studies on Asthma in Childhood 2010 cohort. Enrollment began March 2009 with a goal of 708 participants, but due to delayed ethical approval, only 623 women were recruited at 24 weeks of pregnancy. Follow-up of the children (N = 581) was completed when the youngest child reached age 3 years in March 2014. INTERVENTIONS Vitamin D3 (2400 IU/d; n = 315) or matching placebo tablets (n = 308) from pregnancy week 24 to 1 week postpartum. All women received 400 IU/d of vitamin D3 as part of usual pregnancy care. MAIN OUTCOMES AND MEASURES: Age at onset of persistent wheeze in the first 3 years of life. Secondary outcomes included number of episodes of troublesome lung symptoms, asthma, respiratory tract infections, and neonatal airway immunology. Adverse events were assessed. RESULTS: Of the 581 children, persistent wheeze was diagnosed during the first 3 years of life in 47 children (16%) in the vitamin D3 group and 57 children (20%) in the control group. Vitamin D3 supplementation was not associated with the risk of persistent wheeze, but the number of episodes of troublesome lung symptoms was reduced, and the airway immune profile was up-regulated (principal component analysis, P=.04). There was no effect on additional end points. Intrauterine death was observed in 1 fetus (<1%) in the vitamin D3 group vs 3 fetuses (1%) in the control group and congenital malformations in 17 neonates (5%) in the vitamin D3 group vs 23 neonates (8%) in the control group. CONCLUSIONS AND RELEVANCE: The use of 2800 IU/d of vitamin D3 during the third trimester of pregnancy compared with 400 IU/d did not result in a statistically significant reduced risk of persistent wheeze in the offspring through age 3 years. However, interpretation of the study is limited by a wide CI that includes a clinically important protective effect.
Engineering a CTL-Tailored Replicon RNA Vaccine against PRRSV

The development of vaccines against porcine reproductive and respiratory syndrome virus (PRRSV) has been hampered by the high mutation rate and the multiple immunoevasive strategies of the virus. With the overall aim of designing a broad coverage vaccine that induces an effective CTL response against PRRSV, we have used a bioinformatics approach to identify common PRRSV type 2 epitopes predicted to react broadly with predominant swine MHC (SLA) alleles.

All possible 9- and 10-mer peptides derived from 104 wild-type strains were analyzed in silico for their predicted binding affinity to 3 common SLA class I alleles and ranked according to genomic conservation and SLA binding coverage. Of the 53 top-ranked peptides, 33 were verified in vitro as high affinity binders. Polyepitope gene cassettes of these peptides, flanked by an upstream ubiquitin sequence and a downstream FLAG tag, were cloned into a classical swine fever virus (CSFV)-derived replicon vector. Virus replicon particles (VRP) were rescued by transfection of a complementing cell line with replicon RNA. Polyepitope expression and subsequent proteasomal degradation was confirmed indirectly by increased FLAG-tagged protein detection in the presence of a proteasome inhibitor.

Finally, a vaccination-challenge experiment using 18 SLA-matched pigs is currently being conducted until July 2016 in
which a test group and a control group are being vaccinated twice with VRPs expressing PRRSV epitopes and non-sense control epitopes, respectively, before challenged with live wild type PRRSV. The induced epitope specific cell-mediated immune responses are being monitored by ELISPOT, flow cytometry and cytotoxicity assays, and the degree of protection against infection will be characterized by qPCR and antibody analysis. The results will be available for IVIS.

This study exemplifies how bioinformatics epitope prediction, recombinant SLA molecules and RNA virus replicon design can be used to engineer a replicating non-propagating vaccine tailored to deliver conserved and immunogenic CTL epitopes.

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Organisations: National Veterinary Institute, Section for Virology, Department of Systems Biology, Center for Biological Sequence Analysis, Department of Bio and Health Informatics, Section for Immunology and Vaccinology, Institute of Virology and Immunology
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Enhanced base excision repair capacity in carotid atherosclerosis may protect nuclear DNA but not mitochondrial DNA
Lesional and systemic oxidative stress has been implicated in the pathogenesis of atherosclerosis, potentially leading to accumulation of DNA base lesions within atherosclerotic plaques. Although base excision repair (BER) is a major pathway counteracting oxidative DNA damage, our knowledge on BER and accumulation of DNA base lesions in clinical atherosclerosis is scarce. Here, we evaluated the transcriptional profile of a wide spectrum of BER components as well as DNA damage accumulation in atherosclerotic and non-atherosclerotic arteries. BER gene expression levels were analyzed in 162 carotid plaques, 8 disease-free carotid specimens from patients with carotid plaques and 10 non-atherosclerotic control arteries. Genomic integrity, mitochondrial (mt) DNA copy number, oxidative DNA damage and BER proteins were evaluated in a subgroup of plaques and controls. Our major findings were: (i) The BER pathway showed a global increased transcriptional response in plaques as compared to control arteries, accompanied by increased expression of several BER proteins. (ii) Whereas nuclear DNA stability was maintained within carotid plaques, mtDNA integrity and copy number were decreased. (iii) Within carotid plaques, mRNA levels of several BER genes correlated with macrophage markers. (iv) In vitro, some of the BER genes were highly expressed in the anti-inflammatory and pro-resolving M2 macrophages, showing increased expression upon exposure to modified lipids. The increased transcriptional response of BER genes in atherosclerosis may contribute to lesional nuclear DNA stability but appears insufficient to maintain mtDNA integrity, potentially influencing mitochondrial function in cells within the atherosclerotic lesion.

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Scopus rating (2016): CiteScore 5.66 SJR 2.276 SNIP 1.529
Evaluating prediction strategies for identification of T cell responsive mutation-derived neoepitopes in cancer

Increasing evidences point to an important role of mutation-derived antigens in immune recognition of cancer. Current strategies for prediction of immunogenic neoepitopes results in large personalized peptide libraries, but only a minority (<1%) elicit T cell responses at detectable levels. Neoepitopes are of potential valuable as predictors of response to therapy and targets for personalized immunotherapeutic approached. Consequently, there is an unmet need to understand the rules identifying immunogenic neoepitopes. Both tumor mutation mapping via exome sequencing and mass-spectrometry-based elution for MHC class I presented peptides has been applied in different studies, combined with RNA sequencing to determine the expression level of relevant transcripts. Additionally, neoepitopes may be defined based on either autologous tumor cell lines or snapfrozen tumor material. We present here a study in which all the above mentioned strategies are assessed in three melanoma patients. Predicted large peptide libraries matching the HLA expression of the patients was identified and selected based on any of the strategies given above. This resulted in a total of ~3000 peptides for the three patients. We investigated the T cell recognition of these personalized peptide libraries using a new technology based on DNA-barcode labeled MHC multimers to detect multiple, potentially >1000, different neoepitope specific T cell populations in a single sample. Through this unbiased comparison, we evaluate selection strategies for prediction of immunogenic cancer-associated neoepitopes, and identify rules for precise prediction. Precise prediction is
essential for future application of neoepitopes both as predictors of responses to therapy and immunotherapeutic targets.
Excessive collagen turnover products are released during colorectal cancer progression and elevated in serum from metastatic colorectal cancer patients

During cancer progression, the homeostasis of the extracellular matrix becomes imbalanced with an excessive collagen remodeling by matrix metalloproteinases. As a consequence, small protein fragments of degraded collagens are released into the circulation. We have investigated the potential of protein fragments of collagen type I, III and IV as novel biomarkers for colorectal cancer. Specific fragments of degraded type I, III and IV collagen (C1M, C3M, C4M) and type III collagen formation (Pro-C3) were assessed in serum from colorectal cancer patients, subjects with adenomas and matched healthy controls using well-characterized and validated ELISAs. Serum levels of the biomarkers were significantly elevated in colorectal cancer patients compared to subjects with adenomas (C1M, Pro-C3, C3M) and controls (C1M, Pro-C3). When patients were stratified according to their tumour stage, all four biomarkers were able to differentiate stage IV metastatic patients from all other stages. Combination of all markers with age and gender in a logistic regression model discriminated between metastatic and non-metastatic patients with an AUROC of 0.80. The data suggest that the levels of these collagen remodeling biomarkers may be a measure of tumour activity and invasiveness and may provide new clinical tools for monitoring of patients with advanced stage colorectal cancer.
Expanding specificity of class I restricted CD8+ T cells for viral epitopes following multiple inoculations of swine with a human adenovirus vectored foot-and-mouth disease virus (FMDV) vaccine

The immune response to the highly acute foot-and-mouth disease virus (FMDV) is routinely reported as a measure of serum antibody. However, a critical effector function of immune responses combating viral infection of mammals is the cytotoxic T lymphocyte (CTL) response mediated by virus specific CD8+ expressing T cells. This immune mechanism arrests viral spread by killing virus infected cells before new, mature virus can develop. We have previously shown that infection of swine by FMDV results in a measurable CTL response and have correlated CTL killing of virus-infected cells with specific class I major histocompatibility complex (MHC) tetramer staining. We also showed that a modified replication defective human adenovirus 5 vector expressing the FMDV structural proteins (Ad5-FMDV-T vaccine) targets the induction of a CD8(+) CTL response with a minimal humoral response. In this report, we show that the specificity of the CD8(+) T cell response to Ad5-FMDV-T varies between cohorts of genetically identical animals. Further, we demonstrate epitope specificity of CD8(+) T cells expands following multiple immunizations with this vaccine.
Fish Oil-Derived Fatty Acids in Pregnancy and Wheeze and Asthma in Offspring

Background: Reduced intake of n-3 long-chain polyunsaturated fatty acids (LCPUFAs) may be a contributing factor to the increasing prevalence of wheezing disorders. We assessed the effect of supplementation with n-3 LCPUFAs in pregnant women on the risk of persistent wheeze and asthma in their offspring. Methods: We randomly assigned 736 pregnant women at 24 weeks of gestation to receive 2.4 g of n-3 LCPUFA (fish oil) or placebo (olive oil) per day. Their children formed the Copenhagen Prospective Studies on Asthma in Childhood2010 (COPSAC2010) cohort and were followed prospectively with extensive clinical phenotyping. Neither the investigators nor the participants were aware of group
assignments during follow-up for the first 3 years of the children's lives, after which there was a 2-year follow-up period during which only the investigators were unaware of group assignments. The primary end point was persistent wheeze or asthma, and the secondary end points included lower respiratory tract infections, asthma exacerbations, eczema, and allergic sensitization.

Results: A total of 695 children were included in the trial, and 95.5% completed the 3-year, double-blind follow-up period. The risk of persistent wheeze or asthma in the treatment group was 16.9%, versus 23.7% in the control group (hazard ratio, 0.69; 95% confidence interval [CI], 0.49 to 0.97; P=0.035), corresponding to a relative reduction of 30.7%. Prespecified subgroup analyses suggested that the effect was strongest in the children of women whose blood levels of eicosapentaenoic acid and docosahexaenoic acid were in the lowest third of the trial population at randomization: 17.5% versus 34.1% (hazard ratio, 0.46; 95% CI, 0.25 to 0.83; P=0.011). Analyses of secondary end points showed that supplementation with n-3 LCPUFA was associated with a reduced risk of infections of the lower respiratory tract (31.7% vs. 39.1%; hazard ratio, 0.75; 95% CI, 0.58 to 0.98; P=0.033), but there was no statistically significant association between supplementation and asthma exacerbations, eczema, or allergic sensitization.

Conclusions: Supplementation with n-3 LCPUFA in the third trimester of pregnancy reduced the absolute risk of persistent wheeze or asthma and infections of the lower respiratory tract in offspring by approximately 7 percentage points, or one third. (Funded by the Lundbeck Foundation and others; ClinicalTrials.gov number, NCT00798226.).
Fish oil supplementation from 9 to 18 months of age affects the insulin-like growth factor axis in a sex-specific manner in Danish infants

Several studies have investigated the effects of fish oil (FO) on infant growth, but little is known about the effects of FO and sex on insulin-like growth factor-1 (IGF-1), the main regulator of growth in childhood. We explored whether FO v. sunflower oil (SO) supplementation from 9 to 18 months of age affected IGF-1 and its binding protein-3 (IGFBP-3) and whether the potential effects were sex specific. Danish infants (n 115) were randomly allocated to 5 ml/d FO (1.2 g/d n-3 long-chain PUFA (n-3 LCPUFA)) or SO. We measured growth, IGF-1, IGFBP-3 and erythrocyte EPA, a biomarker of n-3 LCPUFA intake and status, at 9 and 18 months. Erythrocyte EPA increased strongly with FO compared with SO (P <0·001). There were no effects of FO compared with SO on IGF-1 in the total population, but a sex×group interaction (P =0·02). Baseline-adjusted IGF-1 at 18 months was 11·1 µg/l (95 % CI 0·4, 21·8;P=0·04) higher after FO compared with SO supplementation among boys only. The sex×group interaction was borderline significant in the model of IGFBP-3 (P =0·09), with lower IGFBP-3 with FO compared with SO among girls only (P=0·03). The results were supported by sex-specific dose–response associations between changes in erythrocyte EPA and changes in IGF-1 and IGFBP-3 (both P <0·03). Moreover, IGF-1 was sex specifically associated with BMI and length. In conclusion, FO compared with SO resulted in higher IGF-1 among boys and lower IGFBP-3 among girls. The potential long-term implications for growth and body composition should be investigated further.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, University of Copenhagen
Authors: Damsgaard, C. T. (Ekstern), Harsløf, L. B. S. (Ekstern), Andersen, A. D. (Ekstern), Hellgren, L. (Intern), Michaelsen, K. F. (Ekstern), Lauritzen, L. (Ekstern)
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From Fangs to Pharmacology: The Future of Snakebite Envenoming Therapy

The snake is the symbol of medicine due to its association with Asclepius, the Greek God of medicine, and so with good reasons. More than 725 species of venomous snakes have toxins specifically evolved to exert potent bioactivity in prey or
victims, and snakebites constitute a public health hazard of high impact in Asia, Africa, Latin America, and parts of Oceania. Parenteral administration of antivenoms is the mainstay in snakebite envenoming therapy. However, despite well-demonstrated efficacy and safety of many antivenoms worldwide, they are still being produced by traditional animal immunization procedures, and therefore present a number of drawbacks. Technological advances within biopharmaceutical development and medicinal chemistry could pave the way for rational drug design approaches against snake toxins. This could minimize the use of animals and bring forward more effective therapies for snakebite envenomings. In this review, current state-of-the-art in biopharmaceutical antitoxin development is presented together with an overview of available bioinformatics and structural data on snake venom toxins. This growing body of scientific and technological tools could define the basis for introducing a rational drug design approach into the field of snakebite envenoming therapy.

**General information**

State: Published
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- Scopus rating (2014): SJR 1.279 SNIP 0.958 CiteScore 3.26
- Web of Science (2014): Indexed yes
- BFI (2013): BFI-level 2
- Scopus rating (2013): SJR 1.278 SNIP 0.987 CiteScore 3.41
- BFI (2012): BFI-level 2
- Scopus rating (2012): SJR 1.263 SNIP 1.056 CiteScore 3.67
- BFI (2011): BFI-level 2
- Scopus rating (2011): SJR 1.382 SNIP 1.115 CiteScore 3.96
- BFI (2010): BFI-level 2
- Scopus rating (2010): SJR 1.628 SNIP 1.249
- BFI (2009): BFI-level 2
- Scopus rating (2009): SJR 1.581 SNIP 1.161
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- Scopus rating (2008): SJR 1.61 SNIP 1.199
- Scopus rating (2007): SJR 1.76 SNIP 1.344
- Scopus rating (2006): SJR 1.769 SNIP 1.453
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- Scopus rating (2004): SJR 1.379 SNIP 1.381
- Scopus rating (2003): SJR 1.346 SNIP 1.389
- Scopus rating (2002): SJR 1.12 SNIP 1.238
- Scopus rating (2001): SJR 1.142 SNIP 1.026
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Functional Analysis of a Novel Genome-Wide Association Study Signal in SMAD3 That Confers Protection From Coronary Artery Disease

OBJECTIVE—A recent genome-wide association study meta-analysis identified an intronic single nucleotide polymorphism in SMAD3, rs56062135C>T, the minor allele (T) which associates with protection from coronary artery disease. Relevant to atherosclerosis, SMAD3 is a key contributor to transforming growth factor-β pathway signaling. Here, we seek to identify ≥1 causal coronary artery disease-associated single nucleotide polymorphisms at the SMAD3 locus and characterize mechanisms whereby the risk allele(s) contribute to coronary artery disease risk.

APPROACH AND RESULTS—By genetic and epigenetic fine mapping, we identified a candidate causal single nucleotide polymorphism rs17293632C>T (D', 0.97; r, 0.94 with rs56062135) in intron 1 of SMAD3 with predicted functional effects. We show that the sequence encompassing rs17293632 acts as a strong enhancer in human arterial smooth muscle cells. The common allele (C) preserves an activator protein (AP)-1 site and enhancer function, whereas the protective (T) allele disrupts the AP-1 site and significantly reduces enhancer activity. PT single nucleotide polymorphism represents a novel functional cis-acting element at the SMAD3 locus. The protective (T) allele of rs17293632 disrupts a consensus AP-1 binding site in a SMAD3 intron 1 enhancer, reduces enhancer activity and SMAD3 expression, altering human arterial smooth muscle cells proliferation.

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State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Integrative Systems Biology
Authors: Turner, A. W. (Ekstern), Martinuk, A. (Ekstern), Silva, A. (Ekstern), Lau, P. (Ekstern), Nikpay, M. (Ekstern), Eriksson, P. (Ekstern), Folkersen, L. (Intern), Perisic, L. (Ekstern), Hedin, U. (Ekstern), Soubeyrand, S. (Ekstern), McPherson, R. (Ekstern)
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BFI (2017): BFI-level 2
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 5.28 SJR 3.419 SNIP 1.608
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 3.535 SNIP 1.63 CiteScore 5.44
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 3.503 SNIP 1.624 CiteScore 5.58
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 3.012 SNIP 1.71 CiteScore 5.58
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 3.177 SNIP 1.759 CiteScore 5.99
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 3.706 SNIP 1.774 CiteScore 6.2
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 2
Gapped sequence alignment using artificial neural networks: application to the MHC class I system

Motivation: Many biological processes are guided by receptor interactions with linear ligands of variable length. One such receptor is the MHC class I molecule. The length preferences vary depending on the MHC allele, but are generally limited to peptides of length 8–11 amino acids. On this relatively simple system, we developed a sequence alignment method based on artificial neural networks that allows insertions and deletions in the alignment. Results: We show that prediction methods based on alignments that include insertions and deletions have significantly higher performance than methods trained on peptides of single lengths. Also, we illustrate how the location of deletions can aid the interpretation of the modes of binding of the peptide-MHC, as in the case of long peptides bulging out of the MHC groove or protruding at either terminus. Finally, we demonstrate that the method can learn the length profile of different MHC molecules, and quantified the reduction of the experimental effort required to identify potential epitopes using our prediction algorithm.

Availability and implementation: The NetMHC-4.0 method for the prediction of peptide-MHC class I binding affinity using gapped sequence alignment is publicly available at: http://www.cbs.dtu.dk/services/NetMHC-4.0.
Thrombotic diseases are among the leading causes of morbidity and mortality in the world. To add insights into the genetic regulation of thrombotic disease, we conducted a genome-wide association study (GWAS) of 6135 self-reported blood clots events and 252,827 controls of European ancestry belonging to the 23andMe cohort of research participants. Eight loci exceeded genome-wide significance. Among the genome-wide significant results, our study replicated previously known venous thromboembolism (VTE) loci near the F5, FGA-FGG, F11, F2, PROCR and ABO genes, and the more recently discovered locus near SLC44A2. In addition, our study reports for the first time a genome-wide significant association between rs114209171, located upstream of the F8 structural gene, and thrombosis risk. Analyses of expression profiles and expression quantitative trait loci across different tissues suggested SLC44A2, ILF3 and AP1M2 as the three most plausible candidate genes for the chromosome 19 locus, our only genome-wide significant thrombosis-related locus that does not harbor likely coagulation-related genes. In addition, we present data showing that this locus also acts as a novel risk factor for stroke and coronary artery disease (CAD). In conclusion, our study reveals novel common genetic risk factors for VTE, stroke and CAD and provides evidence that self-reported data on blood clots used in a GWAS yield results that are comparable with those obtained using clinically diagnosed VTE. This observation opens up the potential for larger meta-analyses, which will enable elucidation of the genetics of thrombotic diseases, and serves as
an example for the genetic study of other diseases.

**General information**

State: Published

Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Integrative Systems Biology, 23andMe, University of Geneva Medical School, Pfizer Inc., Sant Pau Biomedical Research Institute, University of Munich, Sorbonne Universités, Ludwig-Maximilians-University Munich, Karolinska University Hospital, Karolinska Institutet, University of Virginia Health System


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Publication date: 2016

Main Research Area: Technical/natural sciences

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Web of Science (2017): Indexed yes

BFI (2016): BFI-level 2

Scopus rating (2016): CiteScore 5.16 SJR 3.504 SNIP 1.241

Web of Science (2016): Indexed yes

BFI (2015): BFI-level 2

Scopus rating (2015): SJR 4.272 SNIP 1.407 CiteScore 5.96

Web of Science (2015): Indexed yes

BFI (2014): BFI-level 2

Scopus rating (2014): SJR 4.541 SNIP 1.497 CiteScore 6.54

Web of Science (2014): Indexed yes

BFI (2013): BFI-level 2

Scopus rating (2013): SJR 4.981 SNIP 1.587 CiteScore 7.42

ISI indexed (2013): ISI indexed yes

BFI (2012): BFI-level 2

Scopus rating (2012): SJR 5.093 SNIP 1.787 CiteScore 8.08

ISI indexed (2012): ISI indexed yes

BFI (2011): BFI-level 2

Scopus rating (2011): SJR 4.873 SNIP 1.71 CiteScore 7.34

ISI indexed (2011): ISI indexed yes

Web of Science (2011): Indexed yes

BFI (2010): BFI-level 2

Scopus rating (2010): SJR 5.479 SNIP 1.666

BFI (2009): BFI-level 2

Scopus rating (2009): SJR 5.14 SNIP 1.707

BFI (2008): BFI-level 2

Scopus rating (2008): SJR 5.652 SNIP 1.725

Scopus rating (2007): SJR 5.602 SNIP 1.807

Scopus rating (2006): SJR 5.859 SNIP 1.837

Scopus rating (2005): SJR 5.446 SNIP 1.97

Scopus rating (2004): SJR 5.736 SNIP 1.918

Web of Science (2004): Indexed yes

Scopus rating (2003): SJR 5.592 SNIP 2.035

Scopus rating (2002): SJR 5.863 SNIP 1.955
Global Genomic Epidemiology of *Salmonella enterica* Serovar Typhimurium DT104

It has been 30 years since the initial emergence and subsequent rapid global spread of multidrug-resistant *Salmonella enterica* serovar Typhimurium DT104 (MDR DT104). Nonetheless, its origin and transmission route have never been revealed. We used whole-genome sequencing (WGS) and temporally structured sequence analysis within a Bayesian framework to reconstruct temporal and spatial phylogenetic trees and estimate the rates of mutation and divergence times of 315S Typhimurium DT104 isolates sampled from 1969 to 2012 from 21 countries on six continents. DT104 was estimated to have emerged initially as antimicrobial susceptible in ∼1948 (95% credible interval [CI], 1934 to 1962) and later became MDR DT104 in ∼1972 (95% CI, 1972 to 1988) through horizontal transfer of the 13-kb *Salmonella* genomic island 1 (SGI1) MDR region into susceptible strains already containing SGI1. This was followed by multiple transmission events, initially from central Europe and later between several European countries. An independent transmission to the United States and another to Japan occurred, and from there MDR DT104 was probably transmitted to Taiwan and Canada. An independent acquisition of resistance genes took place in Thailand in ∼1975 (95% CI, 1975 to 1990). In Denmark, WGS analysis provided evidence for transmission of the organism between herds of animals. Interestingly, the demographic history of Danish MDR DT104 provided evidence for the success of the program to eradicate *Salmonella* from pig herds in Denmark from 1996 to 2000. The results from this study refute several hypotheses on the evolution of DT104 and suggest that WGS may be useful in monitoring emerging clones and devising strategies for prevention of *Salmonella* infections.
High breast milk IL-1β level is associated with reduced risk of childhood eczema

We recently demonstrated a dual effect of breastfeeding with increased risk of eczema and decreased risk of wheezing in early childhood by increasing breastfeeding length. We hypothesize that immune mediators in breast milk could explain such association either through a direct effect or as a surrogate marker of maternal immune constitution.
Highlights from the eleventh ISCB Student Council Symposium 2015
This report summarizes the scientific content and activities of the annual symposium organized by the Student Council of the International Society for Computational Biology (ISCB), held in conjunction with the Intelligent Systems for Molecular Biology (ISMB) / European Conference on Computational Biology (ECCB) conference in Dublin, Ireland on July 10, 2015.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Cornell University, University of South Wales, Universidad de Buenos Aires, Institute of Tropical Medicine, University of Arizona, University of Copenhagen, University College Dublin
Number of pages: 3
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Main Research Area: Technical/natural sciences

Publication information
Journal: B M C Bioinformatics
Volume: 17
Issue number: Suppl. 3
ISSN (Print): 1471-2105
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BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.54 SJR 1.467 SNIP 0.946
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.656 SNIP 1.077 CiteScore 2.77
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.836 SNIP 1.202 CiteScore 2.91
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.932 SNIP 1.335 CiteScore 3.38
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.857 SNIP 1.155 CiteScore 3.24
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.655 SNIP 1.215 CiteScore 3.34
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.756 SNIP 1.15
Web of Science (2010): Indexed yes
High-resolution kinetics and modeling of hydrogen peroxide degradation in live cells
Although the role of oxidative stress factors and their regulation is well studied, the temporal dynamics of stress recovery is still poorly understood. In particular, measuring the kinetics of stress recovery in the first minutes after acute exposure provides a powerful technique for assessing the role of regulatory proteins or enzymes through the use of mutant backgrounds. This project endeavors to screen the temporal dynamics of intracellular oxidant levels in live cells as a function of gene deletion in the budding yeast, Saccharomyces cerevisiae. Using the detailed time dynamics of extra- and intra-cellular peroxide we have developed a mathematical model that describes two distinct kinetic processes, an initial rapid degradation in the first 10–20 min followed by a slower process. Using this model, a qualitative comparison allowed us to assign the dependence of temporal events to genetic factors. Surprisingly, we found that the deletion of transcription factors Yap1p or Skn7p was sufficient to disrupt the establishment of the second degradation phase but not the initial phase. A better fundamental understanding of the role protective factors play in the recovery from oxidative stress may lead to strategies for protecting or sensitizing cell to this stress.
Yeast, Oxidative stress response, Kinetic modeling

DOIs: 10.1016/j.freeradbiomed.2016.10.006

High-throughput epitope profiling of snake venom toxins: unveiling the complexity of antigen-antibody interactions of antivenoms

Insight into the molecular details of polyclonal antivenom antibody specificity is a prerequisite for accurate prediction of cross-reactivity and can provide a basis for design of novel antivenoms. In this work, a high-throughput approach was applied to characterize linear elements in epitopes in 82 toxins from four African mamba and three neurotoxic cobra snakes obtained from public databases.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Network Engineering of Eukaryotic Cell Factories, Integrative Systems Biology, Roche NimbleGen, Universidad de Costa Rica
High-throughput immuno-profiling of mamba (*Dendroaspis*) venom toxin epitopes using high-density peptide microarrays

Snakebite envenoming is a serious condition requiring medical attention and administration of antivenom. Current antivenoms are antibody preparations obtained from the plasma of animals immunised with whole venom(s) and contain antibodies against snake venom toxins, but also against other antigens. In order to better understand the molecular interactions between antivenom antibodies and epitopes on snake venom toxins, a high-throughput immuno-profiling study on all manually curated toxins from *Dendroaspis* species and selected African *Naja* species was performed based on custom-made high-density peptide microarrays displaying linear toxin fragments. By detection of binding for three different antivenoms and performing an alanine scan, linear elements of epitopes and the positions important for binding were identified. A strong tendency of antivenom antibodies recognizing and binding to epitopes at the functional sites of toxins was observed. With these results, high-density peptide microarray technology is for the first time introduced in the field of toxinology and molecular details of the evolution of antibody-toxin interactions based on molecular recognition of distinctive toxic motifs are elucidated.

**General information**

State: Published

Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Network Engineering of Eukaryotic Cell Factories, Roche NimbleGen, Universidad de Costa Rica


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Main Research Area: Technical/natural sciences

**Publication information**

Journal: Scientific Reports

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Scopus rating (2016): CiteScore 4.63 SJR 1.625 SNIP 1.401
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.057 SNIP 1.684 CiteScore 5.3
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.103 SNIP 1.544 CiteScore 4.75
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.886 SNIP 1.51 CiteScore 4.06
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.458 SNIP 0.896 CiteScore 2.44
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
HostPhinder: A Phage Host Prediction Tool

The current dramatic increase of antibiotic resistant bacteria has revitalised the interest in bacteriophages as alternative antibacterial treatment. Meanwhile, the development of bioinformatics methods for analysing genomic data places high-throughput approaches for phage characterization within reach. Here, we present HostPhinder, a tool aimed at predicting the bacterial host of phages by examining the phage genome sequence. Using a reference database of 2196 phages with known hosts, HostPhinder predicts the host species of a query phage as the host of the most genomically similar reference phages. As a measure of genomic similarity the number of co-occurring k-mers (DNA sequences of length k) is used. Using an independent evaluation set, HostPhinder was able to correctly predict host genus and species for 81% and 74% of the phages respectively, giving predictions for more phages than BLAST and significantly outperforming BLAST on phages for which both had predictions. HostPhinder predictions on phage draft genomes from the INTESTI phage cocktail corresponded well with the advertised targets of the cocktail. Our study indicates that for most phages genomic similarity correlates well with related bacterial hosts. HostPhinder is available as an interactive web service [1] and as a stand alone download from the Docker registry [2].
How biotechnology could offer hope for snakebite victims

Snakebite is a major public health burden for low-income countries in tropical parts of the world. There are around 5 million bites and 150,000 deaths every year. And about 400,000 victims become permanently disabled annually.

Bibliographical note
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Source: FindIt
Source-ID: 2304187571
Publication: Research - peer-review › Journal article – Annual report year: 2016

How compelling are the data for Epstein-Barr virus being a trigger for systemic lupus and other autoimmune diseases?

Systemic lupus erythematosus (SLE) is caused by a combination of genetic and acquired immunodeficiencies and environmental factors including infections. An association with Epstein-Barr virus (EBV) has been established by numerous studies over the past decades. Here, we review recent experimental studies on EBV, and present our integrated theory of SLE development.

Bibliographical note
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Source: FindIt
Source-ID: 2304187571
Publication: Research - peer-review › Journal article – Annual report year: 2016
Human gut microbes impact host serum metabolome and insulin sensitivity

Insulin resistance is a forerunner state of ischaemic cardiovascular disease and type 2 diabetes. Here we show how the human gut microbiome impacts the serum metabolome and associates with insulin resistance in 277 non-diabetic Danish individuals. The serum metabolome of insulin-resistant individuals is characterized by increased levels of branched-chain amino acids (BCAAs), which correlate with a gut microbiome that has an enriched biosynthetic potential for BCAAs and is deprived of genes encoding bacterial inward transporters for these amino acids. Prevotella copri and Bacteroides vulgatus are identified as the main species driving the association between biosynthesis of BCAAs and insulin resistance, and in mice we demonstrate that P. copri can induce insulin resistance, aggravate glucose intolerance and augment circulating levels of BCAAs. Our findings suggest that microbial targets may have the potential to diminish insulin resistance and reduce the incidence of common metabolic and cardiovascular disorders.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Integrative Systems Biology, Technical Information Center of Denmark, Orebro University, University of Copenhagen, European Molecular Biology Laboratory, Université Paris-Saclay, KU Leuven, VTT - Technical Research Centre of Finland, Steno Diabetes Centre, Vrije Universiteit Brussel, University of Turku
Number of pages: 20
Pages: 376-381
Publication date: 2016
Main Research Area: Technical/natural sciences

Publication information
Journal: Nature
Identification of common bacterial antigenic markers from bovine digital dermatitis lesions using meta-transcriptomics in combination with high-density peptide-microarrays

Bovine digital dermatitis (DD) is the most important infectious cause of lameness in dairy cattle, and a major contributing factor to welfare problems and economic losses in the dairy cattle industry worldwide. DD is a disease that involves chronic dermal inflammatory processes and destruction of collagenous and connective tissues. Multiple Treponema species, many of which are not-yet-cultivable, are strongly implicated in disease progression. Despite the economic and welfare importance of this disease, no effective vaccine is available; and there is presently very little knowledge...
concerning efficacious immunoprophylactic antigens against DD. It is highly likely that DD-associated treponemes possess considerable antigenic variation, as cows exhibit a variable humoral response against different isolates of Treponema. Hence, combinations of antigens from multiple Treponema species should be used for the development of disease prevention measures. As treponemes from DD lesions are extremely difficult to culture, identification of these antigens is challenging. To circumvent this problem, we studied the in situ gene expression patterns of the microbiome in DD-affected skin lesions and the host antibody response directed at the site of infection. By metatranscriptomics we measured the in situ genome-wide transcriptome of the bacterial population in DD-affected skin lesions from 21 dairy cows. From the transcriptome data, we identified a panel of Treponema genes that were highly expressed in multiple animals, and we monitored the host immune response to these target genes using high-density peptide microarrays. By this approach, we identified a small group of antigenic proteins, which were expressed in the majority of the samples, and demonstrated antigenicity when screened against sera from infected animal. Future studies will show if these proteins represent candidates for the development of novel biomarkers or vaccines.

**General information**

State: Published
Organisations: National Veterinary Institute, Section for Bacteriology, Pathology and Parasitology, Center for Biological Sequence Analysis, Department of Bio and Health Informatics, Immunoinformatics and Machine Learning, Metagenomics, Schafer-N, Technical University of Denmark
Number of pages: 1
Publication date: 2016
Main Research Area: Technical/natural sciences
Publication: Research - peer-review › Conference abstract for conference – Annual report year: 2016

**Identification of differentially IgA-coated bacteria in inflammation-induced colorectal cancer**

**General information**

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Copenhagen
Authors: Eriksen, C. (Intern), Holm, J. B. (Ekstern), Yassin, M. (Ekstern), Olsen, J. (Ekstern), Pedersen, A. E. (Ekstern), Kristiansen, K. (Ekstern), Brix, S. (Intern)
Number of pages: 1
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Main Research Area: Technical/natural sciences
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Source-ID: 127798497
Publication: Research › Poster – Annual report year: 2016

**Identification of Known and Novel Recurrent Viral Sequences in Data from Multiple Patients and Multiple Cancers**

Virus discovery from high throughput sequencing data often follows a bottom-up approach where taxonomic annotation takes place prior to association to disease. Albeit effective in some cases, the approach fails to detect novel pathogens and remote variants not present in reference databases. We have developed a species independent pipeline that utilises sequence clustering for the identification of nucleotide sequences that co-occur across multiple sequencing data instances. We applied the workflow to 686 sequencing libraries from 252 cancer samples of different cancer and tissue types, 32 non-template controls, and 24 test samples. Recurrent sequences were statistically associated to biological, methodological or technical features with the aim to identify novel pathogens or plausible contaminants that may associate to a particular kit or method. We provide examples of identified inhabitants of the healthy tissue flora as well as experimental contaminants. Unmapped sequences that co-occur with high statistical significance potentially represent the unknown sequence space where novel pathogens can be identified.

**General information**

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Integrative Systems Biology, Metagenomics, University of Copenhagen, Statens Serum Institut
Number of pages: 16
Immunogenicity of HLA Class I and II Double Restricted Influenza A-Derived Peptides

The aim of the present study was to identify influenza A-derived peptides which bind to both HLA class I and -II molecules and by immunization lead to both HLA class I and class II restricted immune responses. Eight influenza A-derived 9-11mer peptides with simultaneous binding to both HLA-A*02:01 and HLA-DRB1*01:01 molecules were identified by bioinformatics and biochemical technology. Immunization of transgenic HLA-A*02:01/HLA-DRB1*01:01 mice with four of these double binding peptides gave rise to both HLA class I and class II restricted responses by CD8 and CD4 T cells, respectively, whereas four of the double binding peptides did result in HLA-A*02:01 restricted responses only. According to their cytokine profile, the CD4 T cell responses were of the Th2 type. In influenza infected mice, we were unable to detect natural processing in vivo of the double restricted peptides and in line with this, peptide vaccination did not decrease virus titres in the lungs of intranasally influenza challenged mice. Our data show that HLA class I and class II double binding peptides can be identified by bioinformatics and biochemical technology. By immunization, double binding peptides can give rise to both HLA class I and class I restricted responses, a quality which might be of potential interest for peptide-based vaccine development.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Copenhagen, Statens Serum Institut
Authors: Pedersen, S. R. (Ekstern), Christensen, J. P. (Ekstern), Buus, S. (Ekstern), Rasmussen, M. (Ekstern), Korsholm, K. S. (Ekstern), Nielsen, M. (Intern), Claesson, M. H. (Ekstern)
Number of pages: 16
Publication date: 2016
Main Research Area: Technical/natural sciences
Impact Of Mutation-derived Antigens In Immune Recognition Of Hematological Malignancies, Specifically Myeloid Dysplastic Syndromes (MDS)

Mutation-derived neoepitopes have been suggested as a major component for immune recognition of solid tumors with a high mutational load, e.g. Melanoma and Non-Small-Cell Lung Cancer (NSCLC). Myelodysplastic syndromes (MDS) are a heterogeneous group of myeloid neoplasms characterized by increasing bone marrow failure due to clonal expansion of immature dysplastic cells in the bone marrow. Compared to Melanoma and NSCLC, these dysplastic cells carry low
numbers of point mutations, but high levels of frameshifts, indels, splice variations or epigenetic changes. All of which may contribute to the generation of tumor-specific neoepitopes.

**General information**

**State:** Published

**Organisations:** National Veterinary Institute, Section for Immunology and Vaccinology, Department of Systems Biology, Center for Biological Sequence Analysis, Cancer Systems Biology, Technical University of Denmark, Georg-Speyer-Haus

**Authors:** Saini, S. K. (Intern), Dorfmüller, S. (Ekstern), Bjerregaard, A. (Intern), Bentzen, A. K. (Intern), Eklund, A. C. (Intern), Medyouf, H. (Ekstern), Hadrup, S. R. (Intern)

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**Pages:** 66-66

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**Conference:** 21st Congress of the European Hematology Association, Copenhagen, Denmark, 09/06/2016 - 09/06/2016

**Main Research Area:** Technical/natural sciences

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- BFI (2016): BFI-level 1
- Scopus rating (2016): SJR 2.811 SNIP 1.687 CiteScore 4.1
- Web of Science (2016): Indexed yes
- BFI (2015): BFI-level 1
- Scopus rating (2015): SJR 2.989 SNIP 1.815 CiteScore 4.22
- BFI (2014): BFI-level 1
- Scopus rating (2014): SJR 2.651 SNIP 1.715 CiteScore 3.96
- Web of Science (2014): Indexed yes
- BFI (2013): BFI-level 1
- Scopus rating (2013): SJR 2.722 SNIP 1.653 CiteScore 4.09
- ISI indexed (2013): ISI indexed yes
- BFI (2012): BFI-level 1
- Scopus rating (2012): SJR 2.433 SNIP 1.571 CiteScore 4.11
- ISI indexed (2012): ISI indexed yes
- BFI (2011): BFI-level 1
- Scopus rating (2011): SJR 2.434 SNIP 1.523 CiteScore 3.89
- ISI indexed (2011): ISI indexed yes
- BFI (2010): BFI-level 1
- Scopus rating (2010): SJR 1.951 SNIP 1.466
- Web of Science (2010): Indexed yes
- BFI (2009): BFI-level 1
- Scopus rating (2009): SJR 1.666 SNIP 1.263
- Web of Science (2009): Indexed yes
- BFI (2008): BFI-level 2
- Scopus rating (2008): SJR 1.261 SNIP 1.075
- Scopus rating (2007): SJR 1.033 SNIP 0.911
- Scopus rating (2006): SJR 0.865 SNIP 0.895
- Scopus rating (2005): SJR 0.697 SNIP 0.903
- Scopus rating (2004): SJR 0.627 SNIP 0.841
- Scopus rating (2003): SJR 0.548 SNIP 0.777
- Scopus rating (2002): SJR 0.512 SNIP 0.71
- Scopus rating (2001): SJR 0.502 SNIP 0.646
Improved pan-specific prediction of MHC class I peptide binding using a novel receptor clustering data partitioning strategy

Pan-specific prediction of receptor-ligand interaction is conventionally done using machine-learning methods that integrate information about both receptor and ligand primary sequences. To achieve optimal performance using machine learning, dealing with overfitting and data redundancy is critical. Most often so-called ligand clustering methods have been used to deal with these issues in the context of pan-specific receptor-ligand predictions, and the MHC system the approach has proven highly effective for extrapolating information from a limited set of receptors with well characterized binding motifs, to others with no or very limited experimental characterization. The success of this approach has however proven to depend strongly on the similarity of the query molecule to the molecules with characterized specificity using in the machine-learning process. Here, we outline an alternative strategy with the aim of altering this and construct data sets optimal for training of pan-specific receptor-ligand predictions focusing on receptor similarity rather than ligand similarity. We show that this receptor clustering method consistently in benchmarks covering affinity predictions, MHC ligand and MHC epitope identification perform better than the conventional ligand clustering method on the alleles with remote similarity to the training set.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Evaxion Biotech, University of Copenhagen
Authors: Mattsson, A. H. (Intern), Kringelum, J. V. (Ekstern), Garde, C. (Ekstern), Nielsen, M. (Intern)
Number of pages: 6
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Scopus rating (2016): SJR 0.458 SNIP 0.352 CiteScore 0.87
Scopus rating (2015): SJR 0.752 SNIP 0.638
Scopus rating (2014): SJR 0.677 SNIP 0.671
Scopus rating (2013): SJR 1.004 SNIP 1.353
Scopus rating (2012): SJR 0.665 SNIP 0.965
Scopus rating (2011): SJR 0.745 SNIP 0.834
Scopus rating (2010): SJR 0.593 SNIP 0.664
Scopus rating (2009): SJR 0.62 SNIP 0.7
Scopus rating (2008): SJR 0.681 SNIP 0.806
Scopus rating (2007): SJR 0.87 SNIP 1.137
Scopus rating (2006): SJR 1.191 SNIP 1.23
Scopus rating (2005): SJR 1.56 SNIP 0.801
Scopus rating (2004): SJR 0.853 SNIP 0.731
Scopus rating (2003): SJR 0.822 SNIP 0.788
Scopus rating (2002): SJR 1.02 SNIP 1.069
Scopus rating (2001): SJR 1.429 SNIP 1.115
Scopus rating (2000): SJR 1.233 SNIP 1.036
Scopus rating (1999): SJR 1.21 SNIP 0.97
Original language: English

MHC binding specificity, MHC class I, T-cell epitope, artificial neural networks, clustering, peptide-MHC binding
Integration of Known DNA, RNA and Protein Biomarkers Provides Prediction of Anti-TNF Response in Rheumatoid Arthritis: results from the COMBINE study

OBJECTIVE: In rheumatoid arthritis (RA) several recent efforts have sought to discover means of predicting which patients would benefit from treatment. However, results have been discrepant with few successful replications. Our objective was to build a biobank with DNA, RNA and protein measurements to test the claim that the current state-of-the-art precision medicine will benefit RA patients. METHODS: We collected 451 blood samples from 61 healthy individuals and 185 RA patients initiating treatment, before treatment initiation and at a 3 month follow-up time. All samples were subjected to high-throughput RNA sequencing, DNA genotyping, extensive proteomics and flow cytometry measurements, as well as comprehensive clinical phenotyping. Literature review identified 2 proteins, 52 single-nucleotide polymorphisms (SNPs) and 72 gene-expression biomarkers that had previously been proposed as predictors of TNF inhibitor response (ΔDAS28-CRP). RESULTS: From these published TNFi biomarkers we found that 2 protein, 2 SNP and 8 mRNA biomarkers could be replicated in the 59 TNF initiating patients. Combining these replicated biomarkers into a single signature we found that we could explain 51% of the variation in ΔDAS28-CRP. This corresponds to a sensitivity of 0.73 and specificity of 0.78 for the prediction of three month ΔDAS28-CRP better than -1.2. CONCLUSIONS: The COMBINE biobank is currently the largest collection of multi-omics data from RA patients with high potential for discovery and replication. Taking advantage of this we surveyed the current state-of-the-art of drug-response stratification in RA, and identified a small set of previously published biomarkers available in peripheral blood which predicts clinical response to TNF blockade in this independent cohort.
Integrative analysis of miRNA and gene expression reveals regulatory networks in tamoxifen-resistant breast cancer

Tamoxifen is an effective anti-estrogen treatment for patients with estrogen receptor-positive (ER+) breast cancer, however, tamoxifen resistance is frequently observed. To elucidate the underlying molecular mechanisms of tamoxifen resistance, we performed a systematic analysis of miRNA-mediated gene regulation in three clinically-relevant tamoxifen-resistant breast cancer cell lines (TamRs) compared to their parental tamoxifen-sensitive cell line. Alterations in the expression of 131 miRNAs in tamoxifen-resistant vs. parental cell lines were identified, 22 of which were common to all TamRs using both sequencing and LNA-based quantitative PCR technologies. Although the target genes affected by the altered miRNA in the three TamRs differed, good agreement in terms of affected molecular pathways was observed. Moreover, we found evidence of miRNA-mediated regulation of ESR1, PGR1, FOXM1 and 14-3-3 family genes.

Integrating the inferred miRNA-target relationships, we investigated the functional importance of 2 central genes, SNAI2 and FYN, which showed increased expression in TamR cells, while their corresponding regulatory miRNA were downregulated. Using specific chemical inhibitors and siRNA-mediated gene knockdown, we showed that both SNAI2 and FYN significantly affect the growth of TamR cell lines. Finally, we show that a combination of 2 miRNAs (miR-190b and miR-516a-5p) exhibiting altered expression in TamR cell lines were predictive of treatment outcome in a cohort of ER+ breast cancer patients receiving adjuvant tamoxifen mono-therapy. Our results provide new insight into the molecular mechanisms of tamoxifen resistance and may form the basis for future medical intervention for the large number of women with tamoxifen-resistant ER+ breast cancer.
Investigating the impact of missense mutations in hCES1 by in silico structure-based approaches

Genetic variations in drug-metabolizing enzymes have been reported to influence pharmacokinetics, drug dosage and other aspects that affect therapeutic outcomes. Most particularly, non-synonymous single-nucleotide polymorphisms (nsSNPs) resulting in amino acid changes disrupt potential functional sites responsible for protein activity, structure, or stability, which can account for individual susceptibility to disease and drug response. Investigating the impact of nsSNPs at a protein's structural level is a key step in understanding the relationship between genetic variants and the resulting phenotypic changes. For this purpose, in silico structure-based approaches have proven their relevance in providing an atomic-level description of the underlying mechanisms. The present review focuses on nsSNPs in human carboxylesterase 1 (hCES1), an enzyme involved in drug metabolism. We highlight how prioritization of functional nsSNPs through computational prediction techniques in combination with structure-based approaches, namely molecular docking and molecular dynamics simulations, is a powerful tool in providing insight into the underlying molecular mechanisms of nsSNPs phenotypic effects at microscopic level. Examples of in silico studies of carboxylesterases (CESs) are discussed, ranging from exploring the effect of mutations on enzyme activity to predicting the metabolism of new hCES1 substrates as well as to guiding rational design of CES-selective inhibitors.

General information
State: Published
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**Plasmodium falciparum var genes expressed in children with severe malaria encode CIDRα1 domains**

Most severe *Plasmodium falciparum* infections are experienced by young children. Severe symptoms are precipitated by vascular sequestration of parasites expressing a particular subset of the polymorphic *P. falciparum* erythrocyte membrane protein 1 (PFEMP1) adhesion molecules. Parasites binding human endothelial protein C receptor (EPCR) through the CIDRα1 domain of certain PFEMP1 were recently associated with severe malaria in children. However, it has remained unclear to which extend the EPCR-binding CIDRα1 domains epitomize PFEMP1 expressed in severe malaria. Here, we characterized the near full-length transcripts dominating the var transcriptome in children with severe malaria and found that the only common feature of the encoded PFEMP1 was CIDRα1 domains. Such genes were highly and dominantly expressed in both children with severe malarial anaemia and cerebral malaria. These observations support the hypothesis that the CIDRα1-EPCR interaction is key to the pathogenesis of severe malaria and strengthen the rationale for pursuing a vaccine or adjunctive treatment aiming at inhibiting or reducing the damaging effects of this interaction.

**General information**

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Metagenomics, KCRI Kilimanjaro Clinical Research Institute, National Institute for Medical Research, University of Copenhagen
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**Publication information**

Journal: EMBO Molecular Medicine
**Propionibacterium acnes: disease-causing agent or common contaminant? Detection in diverse patient samples by next generation sequencing**

*Propionibacterium acnes* is the most abundant bacterium on human skin, particularly in sebaceous areas. *P. acnes* is suggested to be an opportunistic pathogen involved in the development of diverse medical conditions, but is also a proven contaminant of human samples and surgical wounds. Its significance as a pathogen is consequently a matter of debate. In the present study we investigated the presence of *P. acnes* DNA in 250 next generation sequencing datasets generated from 180 samples of 20 different sample types, mostly of cancerous origin. The samples were either subjected to microbial enrichment, involving nuclease treatment to reduce the amount of host nucleic acids, or shotgun-sequenced. We detected high proportions of *P. acnes* in enriched samples, particularly skin derived and other tissue samples, with levels being higher in enriched compared to shotgun-sequenced samples. *P. acnes* reads were detected in most samples analysed, though the proportions in most shotgun-sequenced samples were low. Our results show that *P. acnes* can be detected in practically all sample types when employing molecular methods such as next generation sequencing. The possibility of contamination from the patient or other sources, including laboratory reagents or environment, should therefore always be considered carefully when *P. acnes* is detected in clinical samples. We advocate that detection of *P. acnes* is always accompanied by experiments validating the association between this bacterium and any clinical condition.

**General information**

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10.15252/emmm.201606188
Staphylococcus aureus Transcriptome Architecture: From Laboratory to Infection-Mimicking Conditions

Staphylococcus aureus is a major pathogen that colonizes about 20% of the human population. Intriguingly, this Gram-positive bacterium can survive and thrive under a wide range of different conditions, both inside and outside the human body. Here, we investigated the transcriptional adaptation of S. aureus HG001, a derivative of strain NCTC 8325, across experimental conditions ranging from optimal growth in vitro to intracellular growth in host cells. These data establish an extensive repertoire of transcription units and non-coding RNAs, a classification of 1412 promoters according to their dependence on the RNA polymerase sigma factors SigA or SigB, and allow identification of new potential targets for several known transcription factors. In particular, this study revealed a relatively low abundance of antisense RNAs in S. aureus, where they overlap only 6% of the coding genes, and only 19 antisense RNAs not co-transcribed with other genes were found. Promoter analysis and comparison with Bacillus subtilis links the small number of antisense RNAs to a less profound impact of alternative sigma factors in S. aureus. Furthermore, we revealed that Rho-dependent transcription termination suppresses pervasive antisense transcription, presumably originating from abundant spurious transcription initiation in this A+T-rich genome, which would otherwise affect expression of the overlapped genes. In summary, our study provides genome-wide information on transcriptional regulation and non-coding RNAs in S. aureus as well as new insights into the biological function of Rho and the implications of spurious transcription in bacteria.
Toxoplasma gondii peptide ligands open the gate of the HLA class I binding groove

HLA class I presentation of pathogen-derived peptide ligands is essential for CD8+ T cell recognition of Toxoplasma gondii infected cells. Currently, little data exist pertaining to peptides that are presented after T. gondii infection. Herein we purify HLA-A*02:01 complexes from T. gondii infected cells and characterize the peptide ligands using LCMS. We identify 195 T. gondii encoded ligands originating from both secreted and cytoplasmic proteins. Surprisingly, T. gondii ligands are significantly longer than uninfected host ligands, and these longer pathogen derived peptides maintain a canonical N-terminal binding core yet exhibit a C-terminal extension of 1-30 amino acids. Structural analysis demonstrates that binding of extended peptides opens the HLA class I F' pocket, allowing the C-terminal extension to protrude through one end of the binding groove. In summary, we demonstrate that unrealized structural flexibility makes MHC class I receptive to parasite-derived ligands that exhibit unique C-terminal peptide extensions.
KinMutRF: a random forest classifier of sequence variants in the human protein kinase superfamily

Background: The association between aberrant signal processing by protein kinases and human diseases such as cancer was established long time ago. However, understanding the link between sequence variants in the protein kinase superfamily and the mechanistic complex traits at the molecular level remains challenging: cells tolerate most genomic alterations and only a minor fraction disrupt molecular function sufficiently and drive disease. Results: KinMutRF is a novel random-forest method to automatically identify pathogenic variants in human kinases. Twenty six decision trees implemented as a random forest ponder a battery of features that characterize the variants: a) at the gene level, including membership to a Kinbase group and Gene Ontology terms; b) at the PFAM domain level; and c) at the residue level, the types of amino acids involved, changes in biochemical properties, functional annotations from UniProt, Phospho.ELM and FireDB. KinMutRF identifies disease-associated variants satisfactorily (Acc: 0.88, Prec:0.82, Rec:0.75, F-score:0.78, MCC:0.68) when trained and cross-validated with the 3689 human kinase variants from UniProt that have been annotated as neutral or pathogenic. All unclassified variants were excluded from the training set. Furthermore, KinMutRF is discussed with respect to two independent kinase-specific sets of mutations no included in the training and testing, Kin-Driver (643 variants) and Pon-BTK (1495 variants). Moreover, we provide predictions for the 848 protein kinase variants in UniProt that remained unclassified. A public implementation of KinMutRF, including documentation and examples, is available online (http://kinmut2.bioinfo.cnio.es). The source code for local installation is released under a GPL version 3 license, and can be downloaded from https://github.com/Rbbt-Workflows/KinMut2. Conclusions: KinMutRF is capable of classifying kinase variation with good performance. Predictions by KinMutRF compare favorably in a benchmark with other state-of-the-art methods (i.e. SIFT, Polyphen-2, MutationAssesor, MutationTaster, LRT, CADD, FATHMM, and VEST). Kinase-specific features rank as the most elucidatory in terms of information gain and are likely the improvement in prediction performance. This advocates for the development of family-specific classifiers able to exploit the discriminatory power of features unique to individual protein families.
Large-scale detection of antigen-specific T cells using peptide-MHC-I multimers labeled with DNA barcodes

Identification of the peptides recognized by individual T cells is important for understanding and treating immune-related diseases. Current cytometry-based approaches are limited to the simultaneous screening of 10-100 distinct T-cell specificities in one sample. Here we use peptide-major histocompatibility complex (MHC) multimers labeled with individual DNA barcodes to screen >1,000 peptide specificities in a single sample, and detect low-frequency CD8 T cells specific for virus- or cancer-restricted antigens. When analyzing T-cell recognition of shared melanoma antigens before and after adoptive cell therapy in melanoma patients, we observe a greater number of melanoma-specific T-cell populations compared with cytometry-based approaches. Furthermore, we detect neoepitope-specific T cells in tumor-infiltrating lymphocytes and peripheral blood from patients with non-small cell lung cancer. Barcode-labeled pMHC multimers enable the combination of functional T-cell analysis with large-scale epitope recognition profiling for the characterization of T-cell recognition in various diseases, including in small clinical samples.

General information
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Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 16.443 SNIP 5.433 CiteScore 11.4
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BFI (2013): BFI-level 2
Scopus rating (2013): SJR 13.849 SNIP 5.416 CiteScore 10.45
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 10.76 SNIP 4.96 CiteScore 8.44
ISI indexed (2012): ISI indexed yes
Aims: Processes in the development of atherosclerotic lesions can lead to plaque rupture or erosion, which can in turn elicit myocardial infarction or ischaemic stroke. The aims of this study were to determine whether Toll-like receptor 7 (TLR7) gene expression levels influence patient outcome and to explore the mechanisms linked to TLR7 expression in atherosclerosis. Methods and Results: Atherosclerotic plaques were removed by carotid endarterectomy (CEA) and subjected to gene array expression analysis (n=123). Increased levels of TLR7 transcript in the plaques were associated with better outcome in a follow-up study over a maximum of 8 years. Patients with higher TLR7 transcript levels had a lower risk of experiencing major cardiovascular and cerebrovascular events (MACCE) during the follow-up period after CEA (hazard ratio: 2.38, p=0.012, 95% CI 1.21-4.67). TLR7 was expressed in all plaques by T cells, macrophages and endothelial cells in capillaries, as shown by immunohistochemistry. In short-term tissue cultures, ex vivo treatment of plaques with the TLR7 ligand imiquimod elicited dose-dependent secretion of IL-10, TNF-α, GM-CSF, and IL-12/IL-23p40. This secretion was blocked with a TLR7 inhibitor. Immunofluorescent tissue analysis after TLR7 stimulation showed IL-10 expression in T cells, macrophages and vascular smooth muscle cells. TLR7 mRNA levels in the plaques were correlated with IL-10 receptor (r=0.4031, p<0.0001) and GM-CSF receptor A (r=0.4354, p<0.0001) transcripts. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Conclusions These findings demonstrate that TLR7 is abundantly expressed in human atherosclerotic plaques. TLR7 ligation elicits the secretion of pro-inflammatory and anti-inflammatory cytokines, and high TLR7 expression in plaques is associated with better patient outcome, suggesting that TLR7 is a potential therapeutic target for prevention of complications of atherosclerosis.
LOX1 inhibition with small molecules

Lipoxygenases (LOXs) are nonheme, iron-containing dioxygenases that catalyze the dioxygenation of polyunsaturated fatty acids and are widely distributed among plant and animal species. Human LOXs, now identified as key enzymes in the pathogenesis of major disorders, have increasingly drawn attention as targets and great effort has been made for the discovery and design of suitable inhibitors, to which end both pharmacological and computational methods have been employed. In the present work, using pharmacophore modeling and docking, we attempt to elucidate the inhibition of LOX1 with a new inhibitor, albidoside, an iridoid glucoside isolated from plants of the Scutellaria genus. Through a pharmacophore approach, complementarities between the ligand and the binding site are explored and a plausible mode of binding with the protein is suggested for albidoside.

General information
State: Published
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  Scopus rating (2016): SJR 0.517 SNIP 0.735 CiteScore 1.77
  Web of Science (2016): Indexed yes
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  Scopus rating (2015): SJR 0.474 SNIP 0.673 CiteScore 1.87
  BFI (2014): BFI-level 1
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  BFI (2013): BFI-level 1
  Scopus rating (2013): SJR 0.574 SNIP 0.783 CiteScore 2.23
  ISI indexed (2013): ISI indexed yes
  BFI (2012): BFI-level 1
  Scopus rating (2012): SJR 0.746 SNIP 0.869 CiteScore 2.28
  ISI indexed (2012): ISI indexed yes
  Web of Science (2012): Indexed yes
  BFI (2011): BFI-level 1
  Scopus rating (2011): SJR 0.637 SNIP 0.843 CiteScore 2.21
  ISI indexed (2011): ISI indexed yes
  BFI (2010): BFI-level 1
  Scopus rating (2010): SJR 0.681 SNIP 0.891
  Web of Science (2010): Indexed yes
  BFI (2009): BFI-level 1
  Scopus rating (2009): SJR 0.642 SNIP 0.889
  BFI (2008): BFI-level 1
  Scopus rating (2008): SJR 0.815 SNIP 0.829
  Scopus rating (2007): SJR 0.804 SNIP 0.762
  Scopus rating (2006): SJR 0.71 SNIP 0.877
  Scopus rating (2005): SJR 0.936 SNIP 1.076
  Scopus rating (2004): SJR 0.942 SNIP 1.176
Maximum-Entropy Models of Sequenced Immune Repertoires Predict Antigen-Antibody Affinity

The immune system has developed a number of distinct complex mechanisms to shape and control the antibody repertoire. One of these mechanisms, the affinity maturation process, works in an evolutionary-like fashion: after binding to a foreign molecule, the antibody-producing B-cells exhibit a high-frequency mutation rate in the genome region that codes for the antibody active site. Eventually, cells that produce antibodies with higher affinity for their cognate antigen are selected and clonally expanded. Here, we propose a new statistical approach based on maximum entropy modeling in which a scoring function related to the binding affinity of antibodies against a specific antigen is inferred from a sample of sequences of the immune repertoire of an individual. We use our inference strategy to infer a statistical model on a data set obtained by sequencing a fairly large portion of the immune repertoire of an HIV-1 infected patient. The Pearson correlation coefficient between our scoring function and the IC50 neutralization titer measured on 30 different antibodies of known sequence is as high as 0.77 (p-value 10^-6), outperforming other sequence- and structure-based models.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Sapienza University of Rome, Human Genetic Foundation
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BFI (2017): BFI-level 1
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Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 3.43 SNIP 1.447 CiteScore 4.69
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 3.359 SNIP 1.44 CiteScore 4.74
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 3.295 SNIP 1.457 CiteScore 4.91
ISI indexed (2013): ISI indexed yes
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Scopus rating (2012): SJR 3.329 SNIP 1.642 CiteScore 5.36
ISI indexed (2012): ISI indexed no
MECP2 Is a Frequently Amplified Oncogene with a Novel Epigenetic Mechanism That Mimics the Role of Activated RAS in Malignancy

An unbiased genome-scale screen for unmutated genes that drive cancer growth when overexpressed identified methyl cytosine-guanine dinucleotide (CpG) binding protein 2 (MECP2) as a novel oncogene. MECP2 resides in a region of the X-chromosome that is significantly amplified across 18% of cancers, and many cancer cell lines have amplified, overexpressed MECP2 and are dependent on MECP2 expression for growth. MECP2 copy-number gain and RAS family member alterations are mutually exclusive in several cancer types. The MECP2 splicing isoforms activate the major growth factor pathways targeted by activated RAS, the MAPK and PI3K pathways. MECP2 rescued the growth of a KRAS(G12C)-addicted cell line after KRAS downregulation, and activated KRAS rescues the growth of an MECP2-addicted cell line after MECP2 downregulation. MECP2 binding to the epigenetic modification 5-hydroxymethylcytosine is required for efficient transformation. These observations suggest that MECP2 is a commonly amplified oncogene with an unusual epigenetic mode of action. MECP2 is a commonly amplified oncogene in human malignancies with a unique epigenetic mechanism of action. Cancer Discov; 6(1); 45-58. ©2015 AACR. This article is highlighted in the In This Issue feature, p. 1.
Background: A high proportion of Extended-Spectrum-Beta-Lactamase (ESBL) producing Enterobacteriaceae is causing common infections in all regions of the world. The burden of antibiotic resistance due to ESBL in East Africa is large but information is scarce and thus it is unclear how big the problem really is. To gain insight into the magnitude and molecular epidemiology of ESBL-producing Enterobacteriaceae in East Africa a literature search was performed in PubMed on 31 July 2015 to retrieve articles with relevant information on ESBL. Methods and results: Meta-analysis was performed to determine overall proportion estimate of ESBL-producing Enterobacteriaceae. A total of 4076 bacterial isolates were included in the analysis. The overall pooled proportion of ESBL-producing Enterobacteriaceae among included surveys done in East African hospitals was found to be 0.42 (95 % CI: 0.34-0.50). Heterogeneity (I²) between countries’ proportions in ESBL was significantly high (96.95 % and p <0.001). The frequently detected genes encoding ESBL were CTX-M, TEM, SHV and OXA while the most infrequent reported genes were KPC and NDM. Conclusion: The available studies show a very wide variation in resistance due to ESBL between countries. This highlights a need for active surveillance systems which can help understand the actual epidemiology of ESBL, aid in formulating national or regional guidelines for proper screening of ESBL, and support developing standardized approaches for managing patients colonized with ESBL.
Metabolic syndrome and subsequent risk of type 2 diabetes and cardiovascular disease in elderly women Challenging the current definition: Challenging the current definition

The prognostic value of the metabolic syndrome (MetS) is believed to vary with age. With an elderly population expecting to triple by 2060, it is important to evaluate the validity of MetS in this age group. We examined the association of MetS risk factors with later risk of type 2 diabetes (T2DM) and cardiovascular disease (CVD) in elderly Caucasian women. We further investigated if stratification of individuals not defined with MetS would add predictive power in defining future disease prevalence of individuals with MetS. The Prospective Epidemiological Risk Factor Study, a community-based cohort study, followed 3905 Danish women since 2000 (age: 70.1±6.5) with no previous diagnosis of T2DM or CVD, holding all measurements used for MetS definition; central obesity, hypertension, hyperlipidemia, and hyperglycemia combined with register-based follow-up information. Elderly women with defined MetS presented a 6.3-fold increased risk of T2DM (95% confidence interval: [3.74-10.50]) and 1.7-fold increased risk of CVD (1.44-2.05) compared to women with no MetS risk factors. Subdividing the control group without defined MetS revealed that both centrally obese controls and controls holding other MetS risk factors also had increased risk of T2DM (hazard ratio (HR)=2.21 [1.25-3.93] and HR=1.75 [1.04-2.96]) and CVD (HR=1.51 [1.25-1.83] and HR=1.36 [1.15-1.60]) when compared to controls with no MetS risk factors. MetS in elderly Caucasian women increased risk of future T2DM and CVD. While not defined with MetS, women holding only some risk factors for MetS were also at increased risk of T2DM or CVD compared to women with no MetS risk factors.

General information
State: Published
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Web of Science (2016): Indexed yes
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Scopus rating (2014): CiteScore 6.13
Scopus rating (2013): CiteScore 5.87
Scopus rating (2012): CiteScore 5.11
Scopus rating (2011): CiteScore 4.94
Metagenomic analysis of rapid gravity sand filter microbial communities suggests novel physiology of *Nitrospira* spp

Rapid gravity sand filtration is a drinking water production technology widely used around the world. Microbially catalyzed processes dominate the oxidative transformation of ammonia, reduced manganese and iron, methane and hydrogen sulfide, which may all be present at millimolar concentrations when groundwater is the source water. In this study, six metagenomes from various locations within a groundwater-fed rapid sand filter (RSF) were analyzed. The community gene catalog contained most genes of the nitrogen cycle, with particular abundance in genes of the nitrification pathway. Genes involved in different carbon fixation pathways were also abundant, with the reverse tricarboxylic acid cycle pathway most abundant, consistent with an observed *Nitrospira* dominance. From the metagenomic data set, 14 near-complete genomes were reconstructed and functionally characterized. On the basis of their genetic content, a metabolic and geochemical model was proposed. The organisms represented by draft genomes had the capability to oxidize ammonium, nitrite, hydrogen sulfide, methane, potentially iron and manganese as well as to assimilate organic compounds. A composite *Nitrospira* genome was recovered, and amo-containing *Nitrospira* genome contigs were identified. This finding, together with the high *Nitrospira* abundance, and the abundance of atypical amo and hao genes, suggests the potential for complete ammonium oxidation by *Nitrospira*, and a major role of *Nitrospira* in the investigated RSFs and potentially other nitrifying environments.

General information

State: Published
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Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 5.056 SNIP 2.181 CiteScore 8.42
Web of Science (2014): Indexed yes
Metagenomics and single-cell genomics reveal high abundance of comammox Nitrospira in a rapid gravity sand filter treating groundwater

The recent discovery of complete ammonia oxidizing (comammox) Nitrospira has revealed that the metabolic division of labor in nitrification is not obligate as was assumed during the last century. Despite the detection and enrichment of comammox Nitrospira from different nitrifying environments, the ecological relevance of comammox remains unknown. In this study, we analyzed the microbial communities from various locations within a groundwater-fed rapid sand filter (RSF), where Nitrospira were at very high relative abundances. Through metagenomics, a highly abundant composite multi-genome of Nitrospira genus was recovered harboring metabolic capacity for complete ammonia oxidation. We developed a cell extraction strategy that enables the disruption of Nitrospira cell clusters attached to the mineral coating of the sand. Individual cells were identified via fluorescent in situ hybridization (FISH) with Nitrospira-specific 16S rRNA probes and sorted via fluorescence-activated cell sorting (FACS). Sorted cells were screened and selected Nitrospira spp. were subject to whole-genome sequencing. The single cell genomes confirmed the genomic presence of a complete ammonia oxidation pathway and revealed clear taxonomic differences with the recently described comammox Nitrospira genomes. The high abundance of comammox Nitrospira spp. together with the low abundance of canonical ammonia oxidizing prokaryotes in the investigated RSF system suggests the essential role of this novel comammox Nitrospira in the RSFs and potentially other nitrifying environments.

General information

State: Published
Organisations: Department of Environmental Engineering, Water Technologies, Department of Systems Biology, Center for Biological Sequence Analysis, Metagenomics, Department of Bio and Health Informatics, Aarhus University
Authors: Palomo, A. (Intern), Fowler, J. (Intern), Gülay, A. (Intern), Rasmussen, S. (Intern), Schramm, A. (Ekstern), Sicheritz-Pontén, T. (Intern), Smets, B. F. (Intern)
Number of pages: 1
Publication date: 2016
Event: Abstract from 16th International Symposium on Microbial Ecology, Montreal, Canada.
Main Research Area: Technical/natural sciences
Electronic versions: ISME_Abstract_Palomo2016.pdf
MetaPhinder-Identifying Bacteriophage Sequences in Metagenomic Data Sets

Bacteriophages are the most abundant biological entity on the planet, but at the same time do not account for much of the genetic material isolated from most environments due to their small genome sizes. They also show great genetic diversity and mosaic genomes making it challenging to analyze and understand them. Here we present MetaPhinder, a method to identify assembled genomic fragments (i.e. contigs) of phage origin in metagenomic data sets. The method is based on a comparison to a database of whole genome bacteriophage sequences, integrating hits to multiple genomes to accommodate for the mosaic genome structure of many bacteriophages. The method is demonstrated to outperform both BLAST methods based on single hits and methods based on k-mer comparisons. MetaPhinder is available as a web service at the Center for Genomic Epidemiology https://cge.cbs.dtu.dk/services/MetaPhinder/, while the source code can be downloaded from https://bitbucket.org/genomicepidemiology/metaphinder or https://github.com/vanessajurtz/MetaPhinder.
MicroRNA 486-3P as a stability marker in acute coronary syndrome

Easily accessible biomarkers are needed to diagnose cardiovascular disease precisely-particularly, to distinguish between disease subtypes that are encountered in clinical practice. Per the hypothesis that plasma miRNA is valuable for this purpose, we performed complete transcriptional profiling of an miRNA discovery-set in 14 samples: three patients with ST-elevated acute myocardial infarction (STEMI) at baseline and after three months of follow-up, four with stable ischaemic heart disease (stable-IHD) and four healthy age-matched volunteers. Our aim was to determine whether we could distinguish patients with unstable plaques from stable patients following a STEMI event. After analysing miRNA profiles, we conducted a validation study comparing three-month STEMI (n=40) with stable-IHD (n=35), which confirmed that miR-486-3P differentiates patients with three-month STEMI from those with stable-IHD (P=0.019).

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Integrative Systems Biology, Bispebjerg University Hospital, Karolinska University Hospital
Authors: Wei, T. (Ekstern), Folkersen, L. (Intern), Ehrenborg, E. (Ekstern), Gabrielsen, A. (Ekstern)
Number of pages: 5
Publication date: 2016
Main Research Area: Technical/natural sciences

Publication information
Journal: Bioscience Reports
Volume: 36
Issue number: 3
ISSN (Print): 0144-8463
Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): SJR 0.892 SNIP 0.648 CiteScore 1.87
Web of Science (2016): Indexed Yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.051 SNIP 0.718 CiteScore 2.06
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.047 SNIP 0.692 CiteScore 1.91
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.25 SNIP 0.896 CiteScore 2.69
BFI (2012): BFI-level 1
Model studies of lipid flip-flop in membranes
Biomembranes, which are made of a lipid bilayer matrix where proteins are embedded or attached, constitute a physical barrier for cell and its internal organelles. With regard to the distribution of their molecular components, biomembranes are both laterally heterogeneous and transversally asymmetric, and because of this they are sites of vital biochemical activities. Lipids may translocate from one leaflet of the bilayer to the opposite either spontaneously or facilitated by proteins, hence they contribute to the regulation of membrane asymmetry on which cell functioning, differentiation, and growth heavily depend. Such transverse motion—commonly called flip-flop—has been studied both experimentally and computationally. Experimental investigations face difficulties related to time-scales and probe-induced membrane perturbation issues. Molecular dynamics simulations play an important role for the molecular-level understanding of flip-flop. In this review we present a summary of the state of the art of computational studies of spontaneous flip-flop of phospholipids, sterols and fatty acids. Also, we highlight critical issues and strategies that have been developed to solve them, and what remains to be solved.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Padova
Authors: Parisio, G. (Ekstern), Ferrarini, A. (Ekstern), Sperotto, M. M. (Intern)
Number of pages: 13
Pages: 134-146
Publication date: 2016
Main Research Area: Technical/natural sciences

Publication information
Journal: International Journal of Advances in Engineering Sciences and Applied Mathematics
Volume: 8
Issue number: 2
ISSN (Print): 0975-0770
Ratings:
Molecular characterization of atopic dermatitis: a meta-analysis

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Regulatory Genomics
Authors: Ewald, D. A. (Intern), Workman, C. (Intern), Suárez-Fariñas, M. (Ekstern), Guttman-Yassky, E. (Ekstern), Litman, T. (Ekstern)
Number of pages: 160
Publication date: 2016

Molecular characterization of irinotecan (SN-38) resistant human breast cancer cell lines

Background: Studies in taxane and/or anthracycline refractory metastatic breast cancer (mBC) patients have shown approximately 30 % response rates to irinotecan. Hence, a significant number of patients will experience irinotecan-induced side effects without obtaining any benefit. The aim of this study was to lay the groundwork for development of predictive biomarkers for irinotecan treatment in BC.

Methods: We established BC cell lines with acquired or de novo resistance to SN-38, by exposing the human BC cell lines MCF 7 and MDA MB 231 to either stepwise increasing concentrations over 6 months or an initial high dose of SN-38 (the active metabolite of irinotecan), respectively. The resistant cell lines were analyzed for cross-resistance to other anti-cancer drugs, global gene expression, growth rates, TOP1 and TOP2A gene copy numbers and protein expression, and inhibition of the breast cancer resistance protein (ABCG2/BCRP) drug efflux pump.

Results: We found that the resistant cell lines showed 7-100 fold increased resistance to SN-38 but remained sensitive to docetaxel and the non-camptothecin Top1 inhibitor LMP400. The resistant cell lines were characterized by Top1 down-regulation, changed isoelectric points of Top1 and reduced growth rates. The gene and protein expression of ABCG2/BCRP was up-regulated in the resistant sub-lines and functional assays revealed BCRP as a key mediator of SN-38 resistance.

Conclusions: Based on our preclinical results, we suggest analyzing the predictive value of the BCRP in breast cancer patients scheduled for irinotecan treatment. Moreover, LMP400 should be tested in a clinical setting in breast cancer patients with resistance to irinotecan.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, DTU Multi Assay Core, University of Copenhagen, Aarhus University, National Cancer Institute, Erasmus Medical Center, Danish Cancer Society
Authors: Jandu, H. (Ekstern), Aluzaite, K. (Ekstern), Fogh, L. (Ekstern), Thrane, S. W. (Ekstern), Noer, J. B. (Ekstern), Proszek, J. (Ekstern), Nguyen Do, K. (Intern), Hansen, S. N. (Ekstern), Damsgaard, B. (Ekstern), Nielsen, S. L. (Ekstern), Stougaard, M. (Ekstern), Knudsen, B. R. (Ekstern), Moreira, J. (Ekstern), Hamerlik, P. (Ekstern), Gajjar, M. (Ekstern), Smid, M. (Ekstern), Martens, J. (Ekstern), Foekens, J. (Ekstern), Pommier, Y. (Ekstern), Brunner, N. (Ekstern), Schrohl, A. (Ekstern), Stenvang, J. (Ekstern)
Number of pages: 13
Publication date: 2016
Main Research Area: Technical/natural sciences

Publication information
Journal: B M C Cancer
Molecular markers for tracking the origin and worldwide distribution of invasive strains of *Puccinia striiformis*

Investigating the origin and dispersal pathways is instrumental to mitigate threats and economic and environmental consequences of invasive crop pathogens. In the case of *Puccinia striiformis* causing yellow rust on wheat, a number of economically important invasions have been reported, e.g., the spreading of two aggressive and high temperature adapted strains to three continents since 2000. The combination of sequence-characterized amplified region (SCAR) markers, which were developed from two specific AFLP fragments, differentiated the two invasive strains, PstS1 and
PstS2 from all other *P. striiformis* strains investigated at a worldwide level. The application of the SCAR markers on 566 isolates showed that PstS1 was present in East Africa in the early 1980s and then detected in the Americas in 2000 and in Australia in 2002. PstS2 which evolved from PstS1 became widespread in the Middle East and Central Asia. In 2000, PstS2 was detected in Europe, where it never became prevalent. Additional SSR genotyping and virulence phenotyping revealed 10 and six variants, respectively, within PstS1 and PstS2, demonstrating the evolutionary potential of the pathogen. Overall, the results suggested East Africa as the most plausible origin of the two invasive strains. The SCAR markers developed in the present study provide a rapid, inexpensive, and efficient tool to track the distribution of *P. striiformis* invasive strains, PstS1 and PstS2.

**General information**

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Metagenomics, Aarhus University, Norwich Research Park, Regional Rust Research Center, National Institute of Agronomy of Tunisia, French National Institute for Agricultural Research, John Innes Centre, The Sainsbury Laboratory
Number of pages: 15
Pages: 2790-2804
Publication date: 2016
Main Research Area: Technical/natural sciences

**Publication information**
Journal: Ecology and Evolution
Volume: 6
Issue number: 9
ISSN (Print): 2045-7758
Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): SJR 1.579 SNIP 1.048 CiteScore 2.86
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.686 SNIP 0.939 CiteScore 2.66
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.37 SNIP 0.886 CiteScore 2.37
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 0.876 SNIP 0.725 CiteScore 1.66
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 0.58 SNIP 0.518
ISI indexed (2012): ISI indexed no
Web of Science (2012): Indexed yes
Web of Science (2011): Indexed yes
Original language: English
Aggressive strain, PCR-based markers, Plant pathogen, Wheat yellow rust/stripe rust
Electronic versions:
Molecular_markers_for_tracking_the_origin_and_worldwide_distribution_of_invasive_strains_of_Puccinia_striiformis.pdf
DOIs:
10.1002/ece3.2069

**Bibliographical note**
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Source: FindIt
Source-ID: 2303047498
Publication: Research - peer-review › Journal article – Annual report year: 2016
Multi-omic profiling of EPO-producing CHO cell panel reveals metabolic adaptation to heterologous protein production

The Chinese hamster ovary (CHO) cell line is the predominant mammalian cell factory for production of therapeutic glycoproteins. In this work, we aimed to study bottlenecks in the secretory pathway associated with the production of human erythropoietin (EPO) in CHO cells. In connection to this, we discovered indications of metabolic adaptation of the amino acid catabolism in favor of heterologous protein production. We established a panel of stably EPO expressing CHO-K1 clones spanning a 25-fold productivity range and characterized the clones in batch and chemostat cultures. For this, we employed a multi-omic physiological characterization including metabolic footprinting of amino acids, metabolite fingerprinting of glycolytic intermediates, NAD(P)H/NAD(P)+ and adenosine nucleotide phosphates. We used qPCR, qRT-PCR, western blots and Affymetrix CHO microarrays to assess EPO gene copy numbers, EPO gene expression, intracellular protein levels and genomewide differential gene expression analysis of genes functionally related to secretory protein processing, respectively. Finally, we generated a network reconstruction of the amino acid catabolism in CHO cells. There construction was utilized as a platform for interpretation of differential gene expression data in a biological meaningful manner. To identify bottlenecks in the protein secretory pathway, we compared EPO gene copy numbers, EPO gene expression levels, intracellular EPO retention and extracellular EPO levels for a high and low producing clone during chemostat culture. The EPO productivity levels were not reflected in EPO gene load, EPO gene expression or intracellular protein retention, indicating that these processes were not limiting EPO productivity. The global gene expression analysis did not identify significant differentially expressed genes related to secretory protein processing. However, when inspecting the gene expression landscape of the amino acid catabolism, we observed an apparent adaptation in favor of EPO production. That is, we discovered that the gene expression levels of amino acid catabolic genes had adapted to preserve the most abundant aminoacids in EPO in the high producing clone relative to the low producing clone. Based on these data, we speculate that the amino acid metabolism in CHO cells may undergo adaptation in favor of heterologous protein production during long-term cultivation.

General information

State: Published
Organisations: Department of Systems Biology, Network Engineering of Eukaryotic Cell Factories, Novo Nordisk Foundation Center for Biosustainability, CHO Cell Line Engineering and Design, Center for Biological Sequence Analysis, Metabolomics Platform, Novo Nordisk A/S
Number of pages: 1
Publication date: 2016
Event: Abstract from Cell Culture Engineering XV, La Quinta, CA, United States.
Main Research Area: Technical/natural sciences
Chinese hamster ovary, Metabolic adaptation, Chemostat, Metabolomics, Transcriptomics
Electronic versions:
Multi_omic_profiling_of_EPO-producing_CHO_cell_panel_reveals_meta
Publication: Research - peer-review » Conference abstract for conference – Annual report year: 2016

Neil3-dependent base excision repair regulates lipid metabolism and prevents atherosclerosis in Apoe-deficient mice

Increasing evidence suggests that oxidative DNA damage accumulates in atherosclerosis. Recently, we showed that a genetic variant in the human DNA repair enzyme NEIL3 was associated with increased risk of myocardial infarction. Here, we explored the role of Neil3/NEIL3 in atherogenesis by both clinical and experimental approaches. Human carotid plaques revealed increased NEIL3 mRNA expression which significantly correlated with mRNA levels of the macrophage marker CD68. Apoe<sup>−/−</sup> Neil3<sup>−/−</sup> mice on high-fat diet showed accelerated plaque formation as compared to Apoe<sup>−/−</sup> mice, reflecting an atherogenic lipid profile, increased hepatic triglyceride levels and attenuated macrophage cholesterol efflux capacity. Apoe<sup>−/−</sup> Neil3<sup>−/−</sup> mice showed marked alterations in several pathways affecting hepatic lipid metabolism, but no genotypic alterations in genome integrity or genome-wide accumulation of oxidative DNA damage. These results suggest a novel role for the DNA glycosylase Neil3 in atherogenesis in balancing lipid metabolism and macrophage function, potentially independently of genome-wide canonical base excision repair of oxidative DNA damage.

General information

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Integrative Systems Biology, Oslo University Hospital, Maastricht University, Karolinska University Hospital, University of Bergen, University of Oslo, Norwegian University of Science and Technology
Number of pages: 13
Background: Binding of peptides to MHC class I molecules (MHC-I) is essential for antigen presentation to cytotoxic T-cells. Results: Here, we demonstrate how a simple alignment step allowing insertions and deletions in a pan-specific MHC-I binding machine-learning model enables combining information across both multiple MHC molecules and peptide lengths. This pan-allele/pan-length algorithm significantly outperforms state-of-the-art methods, and captures differences in the length profile of binders to different MHC molecules leading to increased accuracy for ligand identification. Using this model, we demonstrate that percentile ranks in contrast to affinity-based thresholds are optimal for ligand identification due to uniform sampling of the MHC space. Conclusions: We have developed a neural network-based machine-learning algorithm leveraging information across multiple receptor specificities and ligand length scales, and demonstrated how this approach significantly improves the accuracy for prediction of peptide binding and identification of MHC ligands. The method is available at www.cbs.dtu.dk/services/NetMHCpan-3.0.
New Genome-Wide Algorithm Identifies Novel In-Vivo Expressed Mycobacterium Tuberculosis Antigens Inducing Human T-Cell Responses with Classical and Unconventional Cytokine Profiles

New strategies are needed to develop better tools to control TB, including identification of novel antigens for vaccination. Such Mtb antigens must be expressed during Mtb infection in the major target organ, the lung, and must be capable of eliciting human immune responses. Using genome-wide transcriptomics of Mtb infected lungs we developed data sets and methods to identify IVE-TB (in-vivo expressed Mtb) antigens expressed in the lung. Quantitative expression analysis of 2,068 Mtb genes from the predicted first operons identified the most upregulated IVE-TB genes during in-vivo pulmonary infection. By further analysing high-level conservation among whole-genome sequenced Mtb-complex strains (n = 219)
and algorithms predicting HLA-class-Ia and II presented epitopes, we selected the most promising IVE-TB candidate antigens. Several of these were recognized by T-cells from in-vitro Mtb-PPD and ESAT6/CFP10-positive donors by proliferation and multi-cytokine production. This was validated in an independent cohort of latently Mtb-infected individuals. Significant T-cell responses were observed in the absence of IFN-gamma-production. Collectively, the results underscore the power of our novel antigen discovery approach in identifying Mtb antigens, including those that induce unconventional T-cell responses, which may provide important novel tools for TB vaccination and biomarker profiling. Our generic approach is applicable to other infectious diseases.

**General information**

State: Published

Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Leiden University Medical Center, Stanford University, Harvard School of Public Health, CIBER Epidemiology and Public Health, Norwegian Institute of Public Health


Number of pages: 16

Publication date: 2016

Main Research Area: Technical/natural sciences

**Publication information**

Journal: Scientific Reports

Volume: 6

Article number: 37793

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BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 4.63 SJR 1.625 SNIP 1.401
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.057 SNIP 1.684 CiteScore 5.3
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.103 SNIP 1.544 CiteScore 4.75
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.886 SNIP 1.51 CiteScore 4.06
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.458 SNIP 0.896 CiteScore 2.44
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
ISI indexed (2011): ISI indexed no
Original language: English

Electronic versions:

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DOIs:

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Source: Findit

Source-ID: 2349315258

Publication: Research - peer-review › Journal article – Annual report year: 2016

**Next-generation detection of antigen-responsive T cells using DNA barcode-labeled peptide-major histocompatibility complex I multimers**

Identification of antigenic peptides recognized by T cells is important for understanding and treating immune related diseases. Current cytometry-based approaches are limited to simultaneous screening of T cell reactivity towards 10-100
distinct peptide specificities, which poorly match the large diversity of T cell recognition in humans. Consequently it has been impossible to comprehensively analyze T cell responsiveness in cancer, infectious and autoimmune diseases. We present and validate a novel technology that enables parallel detection of numerous different peptide-MHC responsive T cells in a single sample using >1000 different peptide-MHC multimers labeled with individual DNA barcodes. After isolation of MHC multimer binding T cells their recognition are revealed by amplification and sequencing of the MHC multimer-associated DNA barcodes. The relative frequency of the sequenced DNA barcodes originating from a given peptide-MHC motif relates to the size of the antigen-responsive T cell population. We have demonstrated the use of large panels of >1000 DNA barcoded MHC multimers for detection of rare T cell populations of virus and cancer-restricted origin in various tissues and compared with combinatorial encoding of fluorescent-labeled MHC multimers. Finally, we have demonstrated that this technology can be applied for multiplex T cell detection both in limited biological samples, such as uncultured tumor material, and for simultaneous assessment of target recognition and functional capability of T cells. This technology enables true high-throughput detection of antigen-responsive T cells and will advance our understanding of immune recognition from model antigens to genomewide immune assessments on a personalized basis.

**General information**

State: Published
Organisations: National Veterinary Institute, Section for Immunology and Vaccinology, Department of Systems Biology, Center for Biological Sequence Analysis, Copenhagen University Hospital, Immudex
Number of pages: 1
Pages: 8-8
Publication date: 2016
Conference: ICI 2016 International Congress of Immunology, Melbourne, Australia, 21/08/2016 - 21/08/2016
Main Research Area: Technical/natural sciences

**Publication information**

Journal: European Journal of Immunology
Volume: 46
Issue number: S1
Article number: 1831
ISSN (Print): 0014-2980
Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.61 SJR 2.47 SNIP 0.935
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.589 SNIP 0.979 CiteScore 3.85
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.65 SNIP 0.975 CiteScore 3.83
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 2.859 SNIP 1.049 CiteScore 4.3
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 2.934 SNIP 1.062 CiteScore 4.62
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 3.21 SNIP 1.027 CiteScore 4.69
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 3.293 SNIP 0.992
Nutritional Stress Induced by Tryptophan-Degrading Enzymes Results in ATF4-Dependent Reprogramming of the Amino Acid Transporter Profile in Tumor Cells

Tryptophan degradation is an immune escape strategy shared by many tumors. However, cancer cells’ compensatory mechanisms remain unclear. We demonstrate here that a shortage of tryptophan caused by expression of indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO) resulted in ATF4-dependent upregulation of several amino acid transporters, including SLC1A5 and its truncated isoforms, which in turn enhanced tryptophan and glutamine uptake. Importantly, SLC1A5 failed to be upregulated in resting human T cells kept under low tryptophan conditions but was enhanced upon cognate antigen T-cell receptor engagement. Our results highlight key differences in the ability of tumor and T cells to adapt to tryptophan starvation and provide important insights into the poor prognosis of tumors coexpressing IDO and SLC1A5.
Obesity and Bariatric Surgery Drive Epigenetic Variation of Spermatozoa in Humans

Obesity is a heritable disorder, with children of obese fathers at higher risk of developing obesity. Environmental factors epigenetically influence somatic tissues, but the contribution of these factors to the establishment of epigenetic patterns in human gametes is unknown. Here, we hypothesized that weight loss remodels the epigenetic signature of spermatozoa in human obesity. Comprehensive profiling of the epigenome of sperm from lean and obese men showed similar histone positioning, but small non-coding RNA expression and DNA methylation patterns were markedly different. In a separate cohort of morbidly obese men, surgery-induced weight loss was associated with a dramatic remodeling of sperm DNA...
methylation, notably at genetic locations implicated in the central control of appetite. Our data provide evidence that the epigenome of human spermatozoa dynamically changes under environmental pressure and offers insight into how obesity may propagate metabolic dysfunction to the next generation.

**General information**

State: Published

Organisations: Integrative Systems Biology, Department of Systems Biology, Center for Biological Sequence Analysis, Regulatory Genomics, University of Copenhagen, Copenhagen University Hospital, Steno Diabetes Centre, Hvidovre Hospital

Authors: Donkin, I. (Ekstern), Versteyhe, S. (Ekstern), Ingerslev, L. (Ekstern), Qian, K. (Ekstern), Mechta, M. (Ekstern), Nordkap, L. (Ekstern), Mortensen, B. (Ekstern), Appel, E. (Ekstern), Jørgensen, N. (Ekstern), Kristiansen, V. (Ekstern), Hansen, T. (Ekstern), Workman, C. (Intern), Zierath, J. (Ekstern), Barrès, R. (Ekstern)

Pages: 369–378

Publication date: 2016

Main Research Area: Technical/natural sciences

**Publication information**

Journal: Cell Metabolism

Volume: 23

Issue number: 2

ISSN (Print): 1550-4131

Ratings:

- BFI (2018): BFI-level 3
- BFI (2017): BFI-level 2
- Web of Science (2017): Indexed yes
- BFI (2016): BFI-level 2
- Scopus rating (2016): CiteScore 13.19 SJR 11.209 SNIP 2.941
- Web of Science (2016): Indexed yes
- BFI (2015): BFI-level 2
- Scopus rating (2015): SJR 11.801 SNIP 3.024 CiteScore 13.39
- BFI (2014): BFI-level 2
- Scopus rating (2014): SJR 11.468 SNIP 2.947 CiteScore 13.34
- Web of Science (2014): Indexed yes
- BFI (2013): BFI-level 2
- Scopus rating (2013): SJR 10.215 SNIP 2.9 CiteScore 12.23
- ISI indexed (2013): ISI indexed yes
- BFI (2012): BFI-level 2
- Scopus rating (2012): SJR 8.911 SNIP 2.917 CiteScore 11.03
- ISI indexed (2012): ISI indexed yes
- Web of Science (2012): Indexed yes
- BFI (2011): BFI-level 2
- Scopus rating (2011): SJR 9.865 SNIP 3.454 CiteScore 11.21
- ISI indexed (2011): ISI indexed yes
- BFI (2010): BFI-level 2
- BFI (2009): BFI-level 2
- BFI (2008): BFI-level 2
- Scopus rating (2008): SJR 10.027 SNIP 3.333
- Scopus rating (2006): SJR 9.269 SNIP 2.866

Original language: English

Electronic versions:

- BSOG_1_s2.0_S1550413115005719_main.pdf
- DOIs: 10.1016/j.cmet.2015.11.004

Source: FindIt

Source-ID: 2289620418

Publication: Research - peer-review › Journal article – Annual report year: 2016
Opposite prognostic roles of HIF1β and HIF2β expressions in bone metastatic clear cell renal cell cancer

BACKGROUND: Prognostic markers of bone metastatic clear cell renal cell cancer (ccRCC) are poorly established. We tested prognostic value of HIF1β/HIF2β and their selected target genes in primary tumors and corresponding bone metastases. RESULTS: Expression of HIF2β was lower in mRCC both at mRNA and protein levels (p/mRNA/ = 0.011, p/protein/ = 0.001) while HIF1β was similar to nmRCC. At the protein level, CAIX, GAPDH and GLUT1 were increased in mRCC. In all primary RCCs, low HIF2β and high HIF1β as well as CAIX, GAPDH and GLUT1 expressions correlated with adverse prognosis, while VEGFR2 and EPOR gene expressions were associated with favorable prognosis. Multivariate analysis confirmed high HIF2α protein expression as an independent risk factor. Prognostic validation of HIFs, LDH, EPOR and VEGFR2 in RNA-Seq data confirmed higher HIF1β gene expression in primary RCC as an adverse (p = 0.07), whereas higher HIF2β and VEGFR2 expressions as favorable prognostic factors. HIF1β/HIF2β-index (HIF-index) proved to be an independent prognostic factor in both the discovery and the TCGA cohort. PATIENTS AND METHODS: Expressions of HIF1β and HIF2β as well as their 7 target genes were analysed on the mRNA and protein level in 59 non-metastatic ccRCCs (nmRCC), 40 bone metastatic primary ccRCCs (mRCC) and 55 corresponding bone metastases. Results were validated in 399 ccRCCs from the TCGA project. CONCLUSIONS: We identified HIF2β protein as an independent marker of the metastatic potential of ccRCC, however, unlike HIF1β, increased HIF2β expression is a favorable prognostic factor. The HIF-index incorporated these two markers into a strong prognostic biomarker of ccRCC.

General information
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Cancer Systems Biology, Semmelweis University
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Outbreaks of Aleutian mink disease in farmed mink (Neovison vison) in Denmark: molecular characterization by partial NS1 gene sequencing

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Pan-HER - an antibody mixture targeting EGFR, HER2, and HER3 abrogates preformed and ligand-induced EGFR homo- and heterodimers: Pan-HER abrogates EGFR dimers

The human epidermal growth factor receptor (HER)-family is involved in development of many epithelial cancers. Therefore, HER-family members constitute important targets for anti-cancer therapeutics such as monoclonal antibodies (mAbs). A limitation to the success of single HER-targeting mAbs is development of acquired resistance through mechanisms such as altered receptor dimerization patterns and dependencies. Pan-HER is a mixture of six mAbs simultaneously targeting epidermal growth factor receptor (EGFR), HER2, and HER3 with two mAbs against each receptor. Pan-HER has previously demonstrated broader efficacy than targeting single or dual receptor combinations also in resistant settings. In light of this broad efficacy, we decided to investigate the effect of Pan-HER compared with single HER-targeting with single and dual mAbs on HER-family cross-talk and dimerization focusing on EGFR. The effect of Pan-HER on cell proliferation and HER-family receptor degradation was superior to treatment with single mAbs targeting either single receptor, and similar to targeting a single receptor with two non-overlapping antibodies. Furthermore, changes in EGFR-dimerization patterns after treatment with Pan-HER were investigated by in situ proximity ligation assay and co-immunoprecipitation, demonstrating that Pan-HER and the EGFR-targeting mAb mixture efficiently down-regulate basal EGFR homo- and heterodimerization in two tested cell lines, whereas single mAbs had limited effects. Pan-HER and the EGFR-targeting mAb mixture also blocked EGF-binding and thereby ligand-induced changes in EGFR-dimerization levels. These results suggest that Pan-HER reduces the cellular capability to switch HER-dependency and dimerization pattern in response to treatment and thus hold promise for future clinical development of Pan-HER in resistant settings. This article is protected by copyright. All rights reserved.
Pan-specific prediction of peptide-MHC Class I complex stability, a correlate of T cell immunogenicity

Binding of peptides to MHC class I (MHC-I) molecules is the most selective event in the processing and presentation of Ags to CTL, and insights into the mechanisms that govern peptide-MHC-I binding should facilitate our understanding of CTL biology. Peptide-MHC-I interactions have traditionally been quantified by the strength of the interaction, that is, the binding affinity, yet it has been shown that the stability of the peptide-MHC-I complex is a better correlate of immunogenicity compared with binding affinity. In this study, we have experimentally analyzed peptide-MHC-I complex stability of a large panel of human MHC-I allotypes and generated a body of data sufficient to develop a neural network-based pan-specific predictor of peptide-MHC-I complex stability. Integrating the neural network predictors of peptide-MHC-I complex stability with state-of-the-art predictors of peptide-MHC-I binding is shown to significantly improve the prediction of CTL epitopes. The method is publicly available at http://www.cbs.dtu.dk/services/NetMHCstabpan.

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It has been demonstrated recently in several solid tumors that thrombocytosis at diagnosis may correlate with tumor invasion, metastatic progression and worse outcome. Several details of the pathomechanism of the relationship of thrombocytosis and cancer have been elucidated; however, the complete process is not clearly understood. Several hypotheses have been proposed. Recently, it was suggested that in ovarian cancer elevated IL-6 production by the tumor may induce increased megakaryopoiesis via hepatic thrombopoietin production leading to thrombocytosis. The importance of the prognostic power of elevated platelet count is still debated in gastrointestinal cancer. The aims of this review were to evaluate the prognostic significance of thrombocytosis in gastrointestinal tumors, to see whether clinical practice confirmed the hypotheses and to reveal the causes of the inconsistent findings.
Tumor responses to programmed cell death protein 1 (PD-1) blockade therapy are mediated by T cells, which we characterized in 102 tumor biopsies obtained from 53 patients treated with pembrolizumab, an antibody to PD-1. Biopsies were dissociated, and single-cell infiltrates were analyzed by multicolor flow cytometry using two computational approaches to resolve the leukocyte phenotypes at the single-cell level. There was a statistically significant increase in the frequency of T cells in patients who responded to therapy. The frequency of intratumoral B cells and monocytic myeloid-derived suppressor cells significantly increased in patients' biopsies taken on treatment. The percentage of cells with a regulatory T-cell phenotype, monocytes, and natural killer cells did not change while on PD-1 blockade therapy. CD8+ memory T cells were the most prominent phenotype that expanded intratumorally on therapy. However, the frequency of CD4+ effector memory T cells significantly decreased on treatment, whereas CD4+ effector T cells significantly increased in nonresponding tumors on therapy. In peripheral blood, an unusual population of blood cells expressing CD56 was detected in two patients with regressing melanoma. In conclusion, PD-1 blockade increases the frequency of T cells, B cells, and myeloid-derived suppressor cells in tumors, with the CD8+ effector memory T-cell subset being the major T-cell phenotype expanded in patients with a response to therapy.

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of California, Columbia University, CytoAnalysis, Roswell Park Cancer Institute
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Pharmacogenomics in diabetes mellitus: insights into drug action and drug discovery

Genomic studies have greatly advanced our understanding of the multifactorial aetiology of type 2 diabetes mellitus (T2DM) as well as the multiple subtypes of monogenic diabetes mellitus. In this Review, we discuss the existing pharmacogenetic evidence in both monogenic diabetes mellitus and T2DM. We highlight mechanistic insights from the study of adverse effects and the efficacy of antidiabetic drugs. The identification of extreme sulfonylurea sensitivity in patients with diabetes mellitus owing to heterozygous mutations in HNF1A represents a clear example of how pharmacogenetics can direct patient care. However, pharmacogenomic studies of response to antidiabetic drugs in T2DM has yet to be translated into clinical practice, although some moderate genetic effects have now been described that merit follow-up in trials in which patients are selected according to genotype. We also discuss how future pharmacogenomic findings could provide insights into treatment response in diabetes mellitus that, in addition to other areas of human genetics, facilitates drug discovery and drug development for T2DM.
Picornavirus-Induced Airway Mucosa Immune Profile In Asymptomatic Neonates

Bacterial airway colonization is known to alter the airway mucosa immune response in neonates whereas the impact of viruses is unknown. The objective was therefore to examine the effect of respiratory viruses on the immune signature in the airways of asymptomatic neonates. Nasal aspirates from 571 asymptomatic 1-month-old neonates from the Copenhagen Prospective Studies on Asthma in Childhood 2010 birth cohort were investigated for respiratory viruses. Simultaneously, unstimulated airway mucosal lining fluid was obtained and quantified for levels of 20 immune mediators related to type 1, type 2, type 17, and regulatory immune paths. The association between immune mediator levels and viruses was tested by conventional statistics and partial least square discriminant analysis. Picornaviruses were detected in 58 neonates (10.2%) and other viruses in 10 (1.8%). A general up-regulation of immune mediators was found in the neonates with picornavirus (P <.0001; partial least square discriminant analysis). The association was pronounced for type 1- and type 2-related markers and was unaffected by comprehensive confounder adjustment. Detection of picornavirus and bacteria was associated with an additive general up-regulating effect. Asymptomatic presence of picornavirus in the neonatal airway is a potent activator of the topical immune response. This is relevant to understanding the immune potentiating effect of early life exposure to viruses.
When predicting the subcellular localization of proteins from their amino acid sequences, there are basically three approaches: signal-based, global property-based, and homology-based. Each of these has its advantages and drawbacks, and it is important when comparing methods to know which approach was used. Various statistical and machine learning algorithms are used with all three approaches, and various measures and standards are employed when reporting the performances of the developed methods. This chapter presents a number of available methods for prediction of sorting signals and subcellular localization, but rather than providing a checklist of which predictors to use, it aims to function as a guide for critical assessment of prediction methods.
Proteome-wide antigen discovery of novel protective vaccine candidates against \textit{Staphylococcus aureus} infection

Methicillin-resistant \textit{Staphylococcus aureus} (MRSA) is a rapidly growing problem, especially in hospitals where MRSA cause increased morbidity and mortality and a significant rise in health expenditures. As many strains of MRSA are resistant to other antimicrobials in addition to methicillin, there is an urgent need to institute non-antimicrobial measures, such as vaccination, against the spread of MRSA. With the aim of finding new protective antigens for vaccine development, this study used a proteome-wide in silico antigen prediction platform to screen the proteome of \textit{S. aureus} strain MRSA252. Thirty-five different \textit{S. aureus} proteins were identified, recombinantly expressed, and tested for protection in a lethal sepsis mouse model using \textit{S. aureus} strain MRSA252 as the challenge organism. We found that 13 of the 35 recombinant peptides yielded significant protection and that 12 of these antigens were highly conserved across 70 completely sequenced \textit{S. aureus} strains. Thus, this \textit{in silico} platform was capable of identifying novel candidates for inclusion in future vaccines against MRSA.
Quantification of fibronectin as a method to assess ex vivo extracellular matrix remodeling

Altered architecture, composition and quality of the extracellular matrix (ECM) are pathological hallmarks of several inflammatory and fibro-proliferative pathological processes such as osteoarthritis (OA), rheumatoid arthritis (RA), fibrosis and cancer. One of the most important components of the ECM is fibronectin. Fibronectin serves as an adhesion molecule anchoring cells to the underlying basement membrane through direct interaction with integrin receptors. Fibronectin hereby modulates the properties of the ECM and affects cellular processes. Quantification of fibronectin remodeling could therefore be used to assess the changes in the ECM that occur during progression of fibro-proliferative pathologies. Ex vivo models are becoming state-of-the-art tools to study ECM remodeling as the cellular composition and the organization of the ECM are preserved. Ex vivo models may therefore be a valuable tool to study the ECM remodeling that occurs during progression of fibro-proliferative pathologies. The aim of this study was to quantify fibronectin remodeling in ex vivo models of cartilage and cancer. A competitive The enzyme-linked immunosorbent assay (ELISA) against the C-terminus of fibronectin was developed (FBN-C). The assay was evaluated in relation to specificity, technical performance and as a marker for quantification of fibronectin in cartilage and cancer ex vivo models. The ELISA was specific and technically stable. Cleavage of tumor tissue with MMP-2 released significantly higher levels of FBN-C compared to tissue with buffer only and western blot analysis revealed that FBN-C recognizes both full length and degraded fibronectin. When ex vivo
cartilage cultures were stimulated with the anabolic factor TGF beta and catabolic factors TNE-alpha and OSM, significantly higher levels of FBN-C were found in the conditioned media. Lastly, FBN-C was released from a cancer ex vivo model. In conclusion, we were able to quantify fibronectin remodeling in ex vivo models of cartilage and cancer. Quantification of fibronectin remodeling could be a valuable tool to understand ECM remodeling in ex vivo models of fibro-proliferative pathologies. (C) 2016 Elsevier Inc. All rights reserved.
Quantification of oxidative stress phenotypes based on high-throughput growth profiling of protein kinase and phosphatase knockouts

Cellular responses to oxidative stress are important for restoring redox balance and ensuring cell survival. Genetic defects in response factors can lead to impaired response to oxidative damage and contribute to disease and aging. In single cell organisms, such as yeasts, the integrity of the oxidative stress response can be observed through its influences on growth characteristics. In this study, we investigated the time-dependent batch growth effects as a function of oxidative stress levels in protein kinase and phosphatase deletion backgrounds of *Saccharomyces cerevisiae*. In total, 41 different protein kinases and phosphatase mutants were selected for their known activities in oxidative stress or other stress response pathways and were investigated for their dosage-dependent response to hydrogen peroxide. Detailed growth profiles were analyzed after the induction of stress for growth rate, lag time duration and growth efficiency, and by a novel method to identify stress-induced diauxic shift delay. This approach extracts more phenotypic information than traditional plate-based methods due to the assessment of time dynamics in the time scale of minutes. With this approach, we were able to identify surprisingly diverse sensitivity and resistance patterns as a function of gene knockout.

**General information**

State: Published
Organisations: Fermentation Platform, Department of Systems Biology, Eucaryotic Molecular Cell Biology, Center for Biological Sequence Analysis, Regulatory Genomics, Technical University of Denmark
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As weight-loss surgery is an effective treatment for the glycaemic control of type 2 diabetes in obese patients, yet not all patients benefit, it is valuable to find predictive factors for this diabetic remission. This will help elucidating possible mechanistic insights and form the basis for prioritising obese patients with dysreglated diabetes for surgery where diabetes remission is of interest. In this study, we combine both clinical and genomic factors using heuristic methods, informed by prior biological knowledge in order to rank factors that would have a role in predicting diabetes remission, and indeed in identifying patients who may have low likelihood in responding to bariatric surgery for improved glycaemic control. Genetic variants from the Illumina CardioMetaboChip were prioritised through single-association tests and then seeded a larger selection from protein–protein interaction networks. Artificial neural networks allowing nonlinear correlations were trained to discriminate patients with and without surgery-induced diabetes remission, and the importance of each clinical and genetic parameter was evaluated. The approach highlighted insulin treatment, baseline HbA1c levels, use of insulin-sensitising agents and baseline serum insulin levels, as the most informative variables with a decent internal validation performance (74% accuracy, area under the curve (AUC) 0.81). Adding information for the eight top-ranked single nucleotide polymorphisms (SNPs) significantly boosted classification performance to 84% accuracy (AUC 0.92). The eight SNPs mapped to eight genes — ABCA1, ARHGEF12, CTNNBL1, GLI3, PROK2, RYBP, SMUG1 and STXB5 — three of which are known to have a role in insulin secretion, insulin sensitivity or obesity, but have not been indicated for diabetes remission after bariatric surgery before.
Remodeling of the Tumor Microenvironment Predicts Increased Risk of Cancer in Postmenopausal Women: The Prospective Epidemiologic Risk Factor (PERF I) Study

Background: An altered tumor microenvironment is one of the earliest signs of cancer and an important driver of the disease. We have seen previously that biomarkers reflecting tumor microenvironment modifications, such as matrix metalloproteinase (MMP)-degraded type 1 collagen (C1M), MMP-degraded type IV collagen (C4M), and citrullinated and MMP-degraded vimentin (VICM), were higher in the serum of cancer patients than in healthy controls. However, it is not known if these biomarkers could predict an increased risk of cancer. The aim of this study was to investigate whether C1M, C4M, and VICM were elevated prior to diagnosis of solid cancers in a large prospective study.

Methods: Between 1999 and 2001, 5,855 postmenopausal Danish women ages 48 to 89 years enrolled in the Prospective
Epidemiologic Risk Factor study. Baseline demographics and serum were collected at the time of registration. Follow up cancer diagnoses were obtained from the Danish Cancer Registry in 2014. Serum C1M, C4M, and VICM levels were measured by competitive ELISAs.

Results: A total of 881 women were diagnosed with solid cancers after baseline. C1M, C4M, and VICM levels were significantly elevated in women diagnosed less than 1 year after baseline. C1M and VICM, but not C4M, were independent predictors of increased risk of cancer.

Conclusion: C1M, C4M, and VICM are elevated prior to cancer diagnosis. C1M and VICM are both independent predictors of increased cancer risk.

Impact: C1M and VICM are predictors for increased risk of cancer. Cancer Epidemiol Biomarkers Prev; 25(9); 1348–55. ©2016 AACR.
Season of birth shapes neonatal immune function

Birth season has been reported to be a risk factor for several immune-mediated diseases. We hypothesized that this association is mediated by differential changes in neonatal immune phenotype and function with birth season. We sought to investigate the influence of season of birth on cord blood immune cell subsets and inflammatory mediators in neonatal airways. Cord blood was phenotyped for 26 different immune cell subsets, and at 1 month of age, 20 cytokines and chemokines were quantified in airway mucosal lining fluid. Multivariate partial least squares discriminant analyses were applied to determine whether certain immune profiles dominate by birth season, and correlations between individual cord blood immune cells and early airway immune mediators were defined. We found a birth season-related fluctuation in neonatal immune cell subsets and in early-life airway mucosal immune function. The seasonal airway immune pattern was associated with the number of activated and regulatory T cells in cord blood whereas it was independent of concomitant presence of pathogenic airway microbes. Specifically, summer newborns presented with the lowest levels of all cell types and mediators; fall newborns displayed high levels of activated T cells and mucosal IL-12p70, TNF-α, IL-13, IL-10, and IL-2; and winter newborns had the highest levels of innate immune cells, IL-5, type 17-related immune mediators, and activated T cells. Birth season fluctuations seem to affect neonatal immune development and result in differential potentiation of cord blood immune cells and early airway mucosal immune function.
Seed thioredoxin h

Thioredoxins are nearly ubiquitous disulfide reductases involved in a wide range of biochemical pathways in various biological systems, and also implicated in numerous biotechnological applications. Plants uniquely synthesize an array of thioredoxins targeted to different cell compartments, for example chloroplastic f- and m-type thioredoxins involved in regulation of the Calvin-Benson cycle. The cytosolic h-type thioredoxins act as key regulators of seed germination and are recycled by NADPH-dependent thioredoxin reductase. The present review on thioredoxin h systems in plant seeds focuses on occurrence, reaction mechanisms, specificity, target protein identification, three-dimensional structure and various applications. The aim is to provide a general background as well as an update covering the most recent findings. This article is part of a Special Issue entitled: Plant Proteomics — a bridge between fundamental processes and crop production, edited by Dr. Hans-Peter Mock.

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Proteomics Platform, Enzyme and Protein Chemistry, Carlsberg Research Laboratory, National Agriculture and Food Research Organization, Isfahan University of Technology, University of California at Berkeley, Novo Nordisk A/S
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Sequence diversity between class I MHC loci of African native and introduced Bos taurus cattle in Theileria parva endemic regions: in silico peptide binding prediction identifies distinct functional clusters

There is strong evidence that the immunity induced by live vaccination for control of the protozoan parasite Theileria parva is mediated by class I MHC-restricted CD8⁺ T cells directed against the schizont stage of the parasite that infects bovine lymphocytes. The functional competency of class I MHC genes is dependent on the presence of codons specifying certain critical amino acid residues that line the peptide binding groove. Compared with European Bos taurus in which class I MHC allelic polymorphisms have been examined extensively, published data on class I MHC transcripts in African taurines in T. parva endemic areas is very limited. We utilized the multiplexing capabilities of 454 pyrosequencing to make an initial assessment of class I MHC allelic diversity in a population of Ankole cattle. We also typed a population of exotic Holstein cattle from an African ranch for class I MHC and investigated the extent, if any, that their peptide-binding motifs overlapped with those of Ankole cattle. We report the identification of 18 novel allelic sequences in Ankole cattle and provide evidence of positive selection for sequence diversity, including in residues that predominantly interact with peptides. In silico functional analysis resulted in peptide binding specificities that were largely distinct between the two breeds. We also demonstrate that CD8⁺ T cells derived from Ankole cattle that are seropositive for T. parva do not recognize vaccine candidate antigens originally identified in Holstein and Boran (Bos indicus) cattle breeds.

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Organisations: Immunological Bioinformatics, Department of Systems Biology, Center for Biological Sequence Analysis, Freie Universität Berlin, Berlin Center for Genomics in Biodiversity Research, Leibniz Institute for Zoo and Wildlife Research
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BACKGROUND: Siblings have been shown to reduce the risk of later asthma and allergy, but the mechanism driving this association is unknown. The objective was to study whether siblings affect the airway immune response in healthy neonates. We hypothesized that siblings exert immune modulatory effects on neonates mirrored in the airway mucosa.

METHODS: We measured 20 immune-mediators related to the Type 1, Type 2, Type 17 or regulatory immune pathways in the airway mucosa of 571 one-month-old asymptomatic neonates from the Copenhagen Prospective Studies on Asthma in Childhood 2010 birth-cohort (COPSAC2010). The association between airway mediator levels and presence of siblings was investigated using conventional statistics and principle component analyses (PCA).

RESULTS: Neonates with siblings had an up-regulated level of airway immune-mediators, with predominance of Type 1- and Type 17-related mediators. This was supported by the PCA showing a highly significant difference between children with vs. without siblings: p<10^{-10}, which persisted after adjustment for potential confounders including pathogenic airway bacteria and viruses: p<0.0001. The immune priming effect was inversely associated with time since last childbirth: p=0.0015. CONCLUSIONS: Siblings mediate a Type 1/Type 17-related immune-stimulatory effect in the airways of asymptomatic neonates, also after adjustment for pathogenic bacteria and viruses, indicating that siblings exert a transferable early immune modulatory effect. These findings may represent an in-utero immune priming effect of the fetal immune system caused by previous pregnancies as the effect was attenuated with time since last childbirth or presence of unidentified microbes, but further studies are needed to confirm our findings.

Siblings Promote a Type 1/Type 17-oriented immune response in the airways of asymptomatic neonates
Significance of Primary Tumor Location and Histology for Brain Metastasis Development and Peritumoral Brain Edema in Lung Cancer

Background: Brain metastasis of lung cancer adversely affects overall survival (OS) and quality of life, while peritumoral brain edema is responsible for life-threatening complications. Methods: We retrospectively analyzed the clinicopathological and cerebral radiological data of 575 consecutive lung cancer patients with brain metastases. Results: In adenocarcinoma and squamous cell carcinoma, peritumoral brain edema was more pronounced than in small-cell lung cancer (p <0.001 and p = 0.042, respectively). There was a positive correlation between the size of metastasis and the thickness of peritumoral brain edema (p <0.001). It was thicker in supratentorial tumors (p = 0.019), in younger patients (= 50 years) (p = 0.016). The time to development of brain metastasis was shorter in central than in peripheral lung cancer (5.3 vs. 9.0 months, p = 0.035). Early brain metastasis was characteristic for adenocarcinomas. A total of 135 patients had brain only metastases (N0 disease) characterized by peripheral lung cancer predominance (p <0.001) and a longer time to development of brain metastasis (9.2 vs. 4.4 months, p <0.001). OS was longer in the brain only subgroup than in patients with N1-3 diseases (p = 0.001). Conclusions: The clinicopathological characteristics of lung cancer are related to the development and radiographic features of brain metastases. Our results might be helpful in selecting patients who might benefit from prophylactic cranial irradiation. (C) 2016 S. Karger AG, Basel
Species-independent identification of known and novel recurrent genomic entities in multiple cancer patients
Here we present a new method for the identification of recurrent genomic entities that play a causative role in the onset of disease. Our approach is particularly amenable for the analyses high-throughput sequencing data.

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Strategies for structuring interdisciplinary education in Systems Biology: an European perspective

Systems Biology is an approach to biology and medicine that has the potential to lead to a better understanding of how biological properties emerge from the interaction of genes, proteins, molecules, cells and organisms. The approach aims at elucidating how these interactions govern biological function by employing experimental data, mathematical models and computational simulations. As Systems Biology is inherently multidisciplinary, education within this field meets numerous hurdles including departmental barriers, availability of all required expertise locally, appropriate teaching material and example curricula. As university education at the Bachelor's level is traditionally built upon disciplinary degrees, we believe that the most effective way to implement education in Systems Biology would be at the Master's level, as it offers a more flexible framework. Our team of experts and active performers of Systems Biology education suggest here (i) a definition of the skills that students should acquire within a Master's programme in Systems Biology, (ii) a possible basic educational curriculum with flexibility to adjust to different application areas and local research strengths, (iii) a description of possible career paths for students who undergo such an education, (iv) conditions that should improve the recruitment of students to such programmes and (v) mechanisms for collaboration and excellence spreading among education professionals. With the growing interest of industry in applying Systems Biology approaches in their fields, a concerted action between academia and industry is needed to build this expertise. Here we present a reflection of the European situation and expertise, where most of the challenges we discuss are universal, anticipating that our suggestions will be useful internationally. We believe that one of the overriding goals of any Systems Biology education should be a student’s ability to phrase and communicate research questions in such a manner that they can be solved by the integration of experiments and modelling, as well as to communicate and collaborate productively across different experimental and theoretical disciplines in research and development.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Regulatory Genomics, Chalmers University of Technology, German Cancer Research Center (DKFZ), University of Ljubljana, University of Milano Bicocca, Norwegian University of Science and Technology, University of Warwick, CNRS-UPEC, Imperial College London, University College Dublin, Pompeu Fabra University, Humboldt-Universität zu Berlin, SystemsX.ch, LifeGlimmer GmbH, University of Heidelberg, University of Latvia, ETH Zurich, Vrije Universiteit Amsterdam, Universite Libre de Bruxelles, University of Gothenburg, Wageningen University & Research, University of Barcelona
Number of pages: 7
Publication date: 2016
Main Research Area: Technical/natural sciences

Publication information
Journal: Npj Systems Biology and Applications
Volume: 2
Article number: 16011
Susceptibility to Lower Respiratory Infections in Childhood is Associated with Perturbation of the Cytokine Response to Pathogenic Airway Bacteria

BACKGROUND: Neonatal colonization of the airways with respiratory pathogens is associated with increased risk of lower respiratory infections (LRI) in early childhood. Therefore, we hypothesized that children developing LRI have an aberrant immune response to pathogenic bacteria in infancy. OBJECTIVE: To characterize in vitro the early life systemic immune response to pathogenic bacteria and study the possible association with incidence of LRI during the first 3 years of life. METHODS: The Copenhagen Prospective Study on Asthma in Childhood2000 (COPSAC2000) is a clinical birth cohort study of 411 children born of mothers with asthma. LRI incidence was prospectively captured from 6-monthly planned visits and visits at acute respiratory episodes. The in vitro systemic immune response to H. influenzae, M. catarrhalis and S. pneumoniae was characterized by the production of TNF-α, IFN-γ, IL-2, IL-5, IL-10, IL-13, and IL-17 in peripheral blood mononuclear cells isolated at age 6 months from 291 infants. Data were analyzed by Poisson regression against incidence of LRI in infancy. RESULTS: A multivariable model including all cytokine responses from the three different bacterial stimulations significantly identified children at risk of LRI (p=0.006). The immune response pattern associated with LRI was characterized by perturbed production of several cytokines rather than production of one specific cytokine, and was independent of concurrent asthma. TNF-α and IL-5 were key drivers but did not explain the entire variation in LRI susceptibility. CONCLUSIONS: Children at risk of future LRI present a perturbed systemic immune response upon exposure to common airway pathogens in early life.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Copenhagen
Authors: Vissing, N. H. (Ekstern), Larsen, J. M. (Intern), Rasmussen, M. A. (Ekstern), Chawes, B. L. K. (Ekstern), Thysen, A. H. (Intern), Bennelykke, K. (Ekstern), Pedersen, S. B. (Intern), Bisgaard, H. F. (Ekstern)
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Main Research Area: Technical/natural sciences

Publication information
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BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.09 SJR 1.486 SNIP 1.03
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 1.435 SNIP 1.051 CiteScore 2.1
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 1.801 SNIP 1.169 CiteScore 2.48
Synthesis and biological evaluations of cytotoxic and antiangiogenic triterpenoids-jacaranone conjugates

Background: The development of antiangiogenic agents arises as a more effective and selective therapeutic approach for the treatment of cancer. In addition to reduced acute toxicity, the efficacy of chemotherapy could be improved when administered in combination specific antiangiogenic with cytotoxic agents. The conjugation or hybridization of bifunctional molecules is one of the alternative rational design strategies for co-administration of anticancer drugs. Objective and Methods: The goal of this work is to prepare the conjugates of an antiangiogenic triterpene, 3-oxo oleanolic acid, and structurally related triterpenoids with a cytotoxic semibenzoquinone, jacaranone. The cytotoxic, antiproliferative and antiangiogenic activities of segments and conjugates were determined. The possible targets of conjugates 6a-6h were predicted using Similarity Ensemble Approach (SEA). Results: The results showed that these conjugates are more potent in both cytotoxic and antiangiogenic assays than their corresponding parent molecules, and are also selectively more active against melanoma cells B16 and metastatic B16BL6 than the two other cancer cell lines (A549 and MCF-7) tested. The predicted antiangiogenesis related targets could involve glycogen phosphorylase, neuraminidase, interferon gamma, and tubulin beta chain. Conclusion: The bifunctional conjugates could be useful as dual acting antitumor/antigiogenic agents.

General information

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Chinese Academy of Medical Sciences, Hong Kong Baptist University, Nankai University
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Number of pages: 11
Pages: 775-785
Publication date: 2016
Targeting the DCIR Receptor with a TLR7 Agonist Specifically Activates Monocytes and DCs

General information
State: Published
Organisations: Department of Micro- and Nanotechnology, Colloids and Biological Interfaces, Department of Systems Biology, Center for Biological Sequence Analysis, Disease Systems Immunology, Telormedix SA
Authors: Klauber, T. C. B. (Intern), Laursen, J. M. (Intern), Maj, R. (Ekstern), Pedersen, S. B. (Intern), Jensen, S. S. (Intern), Andresen, T. L. (Intern)
Publication date: 2016
Event: Abstract from The 43rd Annual Meeting & Exposition of the Controlled Release Society, Seattle, WA, United States.
Main Research Area: Technical/natural sciences
Electronic versions:
CRS2016_Abstract_Thomas_Klauber.pdf
T-cell recognition is shaped by epitope sequence conservation in the host proteome and microbiome

Several mechanisms exist to avoid or suppress inflammatory T-cell immune responses that could prove harmful to the host due to targeting self-antigens or commensal microbes. We hypothesized that these mechanisms could become evident when comparing the immunogenicity of a peptide from a pathogen or allergen with the conservation of its sequence in the human proteome or the healthy human microbiome. Indeed, performing such comparisons on large sets of validated T-cell epitopes, we found that epitopes that are similar with self-antigens above a certain threshold showed lower immunogenicity, presumably as a result of negative selection of T cells capable of recognizing such peptides. Moreover, we also found a reduced level of immune recognition for epitopes conserved in the commensal microbiome, presumably as a result of peripheral tolerance. These findings indicate that the existence (and potentially the polarization) of T-cell responses to a given epitope is influenced and to some extent predictable based on its similarity to self-antigens and commensal antigens.
The elusive endogenous adipogenic PPARγ agonists: Lining up the suspects

The nuclear receptor peroxisome proliferator-activated receptor γ (PPARγ) is the key decisive factor controlling the development of adipocytes. Ligand-mediated activation of PPARγ occurs early during adipogenesis and is thought to prime adipose conversion. Although several fatty acids and their derivatives are known to bind to and activate PPARγ, the identity of the ligand(s) responsible for initiating adipocyte differentiation is still a matter of debate. Here we review recent data on pathways involved in ligand production as well as possible endogenous, adipogenic PPARγ agonists.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Copenhagen, Agricultural Research Service
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Volume: 61
ISSN (Print): 0163-7827
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BFI (2017): BFI-level 2
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): SJR 4.59 SNIP 3.359 CiteScore 11.67
The hunt for fatal myocardial infarction biomarkers: predictive circulating microRNAs

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Integrative Systems Biology, University of Copenhagen, National Research Council of Italy
Authors: Russo, F. (Ekstern), Rizzo, M. (Ekstern), Belling, K. (Ekstern), Brunak, S. (Intern), Folkersen, L. (Intern)
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Publication date: 2016
Main Research Area: Technical/natural sciences

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Scopus rating (2015): SJR 0.111 SNIP 0.019

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Publication: Research - peer-review > Review – Annual report year: 2016
The Length Distribution of Class I-Restricted T Cell Epitopes Is Determined by Both Peptide Supply and MHC Allele-Specific Binding Preference

HLA class I-binding predictions are widely used to identify candidate peptide targets of human CD8+ T cell responses. Many such approaches focus exclusively on a limited range of peptide lengths, typically 9 aa and sometimes 9-10 aa, despite multiple examples of dominant epitopes of other lengths. In this study, we examined whether epitope predictions can be improved by incorporating the natural length distribution of HLA class I ligands. We found that, although different HLA alleles have diverse length-binding preferences, the length profiles of ligands that are naturally presented by these alleles are much more homogeneous. We hypothesized that this is due to a defined length profile of peptides available for HLA binding in the endoplasmic reticulum. Based on this, we created a model of HLA allele-specific ligand length profiles and demonstrate how this model, in combination with HLA-binding predictions, greatly improves comprehensive identification of CD8+ T cell epitopes.

General information
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Oklahoma, La Jolla Institute for Allergy & Immunology
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Journal: Journal of Immunology
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BFI (2017): BFI-level 2
Web of Science (2017): Indexed Yes
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Scopus rating (2016): CiteScore 4.79 SJR 3.368 SNIP 1.177
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 3.568 SNIP 1.267 CiteScore 5.05
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 3.716 SNIP 1.279 CiteScore 5.03
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 3.844 SNIP 1.345 CiteScore 5.61
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 3.929 SNIP 1.356 CiteScore 5.82
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
The limits and potential of paleogenomic techniques for reconstructing grapevine domestication

In ancient DNA (aDNA) research, evolutionary and archaeological questions are often investigated using the genomic sequences of organelles: mitochondrial and chloroplast DNA. Organellar genomes are found in multiple copies per living cell, increasing their chance of recovery from archaeological samples, and are inherited from one parent without genetic recombination, simplifying analyses. While mitochondrial genomes have played a key role in many mammalian aDNA projects, including research focused on prehistoric humans and extinct hominins, it is unclear how useful plant chloroplast genomes (plastomes) may be at elucidating questions related to plant evolution, crop domestication, and the prehistoric movement of botanical products through trade and migration. Such analyses are particularly challenging for plant species whose genomes have highly repetitive sequences and that undergo frequent genomic reorganization, notably species with high retrotransposon activity. To address this question, we explored the research potential of the grape (Vitis vinifera L.) plastome using targeted-enrichment methods and high-throughput DNA sequencing on a collection of archaeological grape pip and vine specimens from sites across Eurasia dating ca. 4000 BCE-1500 CE. We demonstrate that due to unprecedented numbers of sequence insertions into the nuclear and mitochondrial genomes, the grape plastome provides limited intraspecific phylogenetic resolution. Nonetheless, we were able to assign archaeological specimens in the Italian peninsula, Sardinia, UK, and Armenia from pre-Roman to medieval times as belonging to all three major chlorotypes A, C, and D found in modern varieties of Western Europe. Analysis of nuclear genomic DNA from these samples reveals a much greater potential for understanding ancient viticulture, including domestication events, genetic introgression from local wild populations, and the origins and histories of varietal lineages.
The Mouse Intestinal Bacterial Collection (miBC) provides host-specific insight into cultured diversity and functional potential of the gut microbiota

Intestinal bacteria influence mammalian physiology, but many types of bacteria are still uncharacterized. Moreover, reference strains of mouse gut bacteria are not easily available, although mouse models are extensively used in medical research. These are major limitations for the investigation of intestinal microbiomes and their interactions with diet and host. It is thus important to study in detail the diversity and functions of gut microbiota members, including those colonizing the mouse intestine. To address these issues, we aimed at establishing the Mouse Intestinal Bacterial Collection (miBC), a public repository of bacterial strains and associated genomes from the mouse gut, and studied host-specificity of colonization and sequence-based relevance of the resource. The collection includes several strains representing novel species, genera and even one family. Genomic analyses showed that certain species are specific to the mouse intestine and that a minimal consortium of 18 strains covered 50-75% of the known functional potential of metagenomes. The present work will sustain future research on microbiota-host interactions in health and disease, as it will facilitate targeted colonization and molecular studies. The resource is available at www.dsmz.de/miBC.
The stepwise evolution of the exome during acquisition of docetaxel resistance in breast cancer cells

Background: Resistance to taxane-based therapy in breast cancer patients is a major clinical problem that may be addressed through insight of the genomic alterations leading to taxane resistance in breast cancer cells. In the current study we used whole exome sequencing to discover somatic genomic alterations, evolving across evolutionary stages during the acquisition of docetaxel resistance in breast cancer cell lines. Results: Two human breast cancer in vitro models (MCF-7 and MDA-MB-231) of the step-wise acquisition of docetaxel resistance were developed by exposing cells to 18 gradually increasing concentrations of docetaxel. Whole exome sequencing performed at five successive stages during this process was used to identify single point mutational events, insertions/deletions and copy number alterations associated with the acquisition of docetaxel resistance. Acquired coding variation undergoing positive selection and harboring characteristics likely to be functional were further prioritized using network-based approaches. A number of genomic changes were found to be undergoing evolutionary selection, some of which were likely to be functional. Of the five stages of progression toward resistance, most resistance relevant genomic variation appeared to arise midway towards fully resistant cells corresponding to passage 31 (5 nM docetaxel) for MDA-MB-231 and passage 16 (1.2 nM docetaxel) for MCF-7, and where the cells also exhibited a period of reduced growth rate or arrest, respectively. MCF-7 cell acquired several copy number gains on chromosome 7, including ABC transporter genes, including ABCB1 and ABCB4, as well as DMRT1, CLDN12, CROT, and SRI. For MDA-MB-231 numerous copy number losses on chromosome X involving more than 30 genes was observed. Of these genes, CASK, POLA1, PRDX4, MED14 and PIGA were highly prioritized by the applied network-based gene ranking approach. At higher docetaxel concentration MCF-7 subclones exhibited a copy number loss in EZF4, and the gene encoding this important transcription factor was down-regulated in MCF-7 resistant cells. Conclusions: Our study of the evolution of acquired docetaxel resistance identified several genomic changes that might explain development of docetaxel resistance. Interestingly, the most relevant resistance-associated changes appeared to originate midway through the evolution towards fully resistant cell lines. Our data suggest that no single genomic event sufficiently predicts resistance to docetaxel, but require genomic alterations affecting multiple pathways that in concert establish the final resistance stage.

General information
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Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Functional Human Variation, Sino-Danish Breast Cancer Research Centre
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Article number: 442
ISSN (Print): 1471-2164
Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 4.05 SJR 2.065 SNIP 1.122
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.287 SNIP 1.172 CiteScore 4.3
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.297 SNIP 1.205 CiteScore 4.18
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 2.141 SNIP 1.174 CiteScore 4.39
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
Tools and data services registry: a community effort to document bioinformatics resources

Life sciences are yielding huge data sets that underpin scientific discoveries fundamental to improvement in human health, agriculture, and the environment. In support of these discoveries, a plethora of databases and tools are deployed, in technically complex and diverse implementations, across a spectrum of scientific disciplines. The corpus of documentation of these resources is fragmented across the Web, with much redundancy, and has lacked a common standard of information. The outcome is that scientists must often struggle to find, understand, compare and use the best resources for the task at hand. Here we present a community-driven curation effort, supported by ELIXIR—the European infrastructure for biological information—that aspires to a comprehensive and consistent registry of information about bioinformatics resources. The sustainable upkeep of this Tools and Data Services Registry is assured by a curation effort driven by and tailored to local needs, and shared amongst a network of engaged partners. As of September 2015, the registry includes 1633 resources, with depositions from 91 individual registrations including 40 institutional providers and 51 individuals. With community support, the registry can become a standard for dissemination of information about bioinformatics resources.
General information

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Institut Pasteur, University of Copenhagen, University of Manchester, Palacky University, European Bioinformatics Institute, Centre for Ecology and Hydrology, National Institute for Agronomic Research, University of Bologna, University of Roma ‘Tor Vergata’, VIB - Flanders Institute for Biotechnology, CRS4-Bioinformatics Laboratory, University of Milano Bicocca, Swiss Institute of Bioinformatics, Bielefeld University, Albert Ludwigs Universität Freiburg, Technical University of Munich, French Institute of Bioinformatics, University of Lubljana, Chinese University of Hong Kong, University of Padua, Bioinformatics Research Centre, Daresbury Laboratory, University of Lübeck, University of Tartu, Imperial College London, IRCCS AOU San Martino-IST, University of Southern Denmark, Wellcome Trust Centre for Human Genetics, Central European Institute of Technology, Fundación Centro Nacional de Investigaciones Cardiovasculares, Sapienza University of Rome, University of Milan, Radboud University Nijmegen, Masaryk University, University of Bergen


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BFI (2018): BFI-level 2
BFI (2017): BFI-level 2
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 9.28 SJR 7.397 SNIP 2.657
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 7.239 SNIP 2.639 CiteScore 9.48
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 6.576 SNIP 2.568 CiteScore 8.74
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 6.582 SNIP 2.266 CiteScore 8.46
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 6.13 SNIP 2.392 CiteScore 8.62
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 5.758 SNIP 2.172 CiteScore 7.86
Tracking the elusive cytotoxic T cell response in pigs

Quantitative and qualitative assessment of antigen-specific cytotoxic T cell (CTL) responses in pigs is not a straightforward process. Through the years we have developed a series of reagents, tools and protocols to characterize peptide-specific CTL responses in pigs.

The most common recombinant SLA heavy chains were produced and peptide binding motifs were determined by assays measuring the affinity and stability of the peptide-SLA complex (pSLA) interaction. These results have been used to train neural networks to predict the binding of any pSLA (http://www.cbs.dtu.dk/services/). Recombinant SLA molecules complexed with verified binding peptides can be assembled to SLA multimers for staining of peptide-specific CTLs, and measured by flow cytometry, as we have shown with FMDV and influenza. This, however, requires SLA-matched pigs for which we have developed two methods: a sequence-based, high-resolution SLA genotyping method by standard PCR for specific detection of eight in-house SLA molecules; and a next-generation sequencing method for parallel detection of up to 50 samples of barcoded cDNA PCR products spanning exon 2 and 3. The latter for a wider characterization of expressed alleles in candidate pigs.

The in vivo generation of CTL responses to antigens following peptide immunizations is thought to require cross-presentation in appropriate dendritic cells (DC). In mice this was linked to targeting of CD103+DCs recruited after intraperitoneal immunizations. We have therefore developed a protocol for intraperitoneal delivery of peptides formulated in poly(l:C)/MMG-decorated liposomes (CAF09) to investigate the influence of peptide dose on the generation of CTL vs. antibody responses. Finally, the induced CTL killing was assessed by an in vivo cytotoxicity assay, where purified autologous PBMCs, fluorescently labeled and pulsed with target peptides, were reinjected into the donor. The in vivo
killing of peptide-pulsed cells was measured by flow cytometry relative to non-pulsed PBMCs at different time points after cell transfer.

**General information**

State: Published
Organisations: National Veterinary Institute, Section for Immunology and Vaccinology, Section for Virology, Section for Bacteriology, Pathology and Parasitology, Department of Systems Biology, Center for Biological Sequence Analysis, Department of Bio and Health Informatics, University of Copenhagen, United States Department of Agriculture
Number of pages: 1
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Main Research Area: Technical/natural sciences
Electronic versions: Jungersen_et_al_IVIS_Abstract.pdf
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**Transcriptional interactions suggest niche segregation among microorganisms in the human gut**

The human gastrointestinal (GI) tract is the habitat for hundreds of microbial species, of which many cannot be cultivated readily, presumably because of the dependencies between species 1. Studies of microbial co-occurrence in the gut have indicated community substructures that may reflect functional and metabolic interactions between cohabitating species 2,3. To move beyond species co-occurrence networks, we systematically identified transcriptional interactions between pairs of coexisting gut microbes using metagenomics and microarray-based metatranscriptomics data from 233 stool samples from Europeans. In 102 significantly interacting species pairs, the transcriptional changes led to a reduced expression of orthologous functions between the coexisting species. Specific species-species transcriptional interactions were enriched for functions important for H₂ and CO₂ homeostasis, butyrate biosynthesis, ATP-binding cassette (ABC) transporters, flagella assembly and bacterial chemotaxis, as well as for the metabolism of carbohydrates, amino acids and cofactors. The analysis gives the first insight into the microbial community-wide transcriptional interactions, and suggests that the regulation of gene expression plays an important role in species adaptation to coexistence and that niche segregation takes place at the transcriptional level.

**General information**

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Integrative Systems Biology, Drug Resistance and Community Dynamics, Novo Nordisk Foundation Center for Biosustainability, DTU Multi Assay Core, Research Groups, Bacterial Synthetic Biology, Metagenomics, University Hospital Vall d’Hebron, INRA Institut National de La Recherche Agronomique, University of Copenhagen, Université Paris-Saclay, European Molecular Biology Laboratory
Publication date: 2016
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**Publication information**

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BFI (2017): BFI-level 1
Web of Science (2017): Indexed yes
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Original language: English
Microbial ecology, Microbiome, Systems analysis
DOIs: 10.1038/nmicrobiol.2016.152
Source: FindIt
Tumor suppressor microRNAs are downregulated in myelodysplastic syndrome with spliceosome mutations

Spliceosome mutations are frequently observed in patients with myelodysplastic syndromes (MDS). However, it is largely unknown how these mutations contribute to the disease. MicroRNAs (miRNAs) are small noncoding RNAs, which have been implicated in most human cancers due to their role in post transcriptional gene regulation. The aim of this study was to analyze the impact of spliceosome mutations on the expression of miRNAs in a cohort of 34 MDS patients. In total, the expression of 76 miRNAs, including mirtrons and splice site overlapping miRNAs, was accurately quantified using reverse transcriptase quantitative PCR. The majority of the studied miRNAs have previously been implicated in MDS. Stably expressed miRNA genes for normalization of the data were identified using GeNorm and NormFinder algorithms. High-resolution melting assays covering all mutational hotspots within SF3B1, SRSF2, and U2AF1 (U2AF35) were developed, and all detected mutations were confirmed by Sanger sequencing. Overall, canonical miRNAs were downregulated in spliceosome mutated samples compared to wild-type (P = 0.002), and samples from spliceosome mutated patients clustered together in hierarchical cluster analyses. Among the most downregulated miRNAs were several tumor-suppressor miRNAs, including several let-7 family members, miR-423, and miR-103a. Finally, we observed that the predicted targets of the most downregulated miRNAs were involved in apoptosis, hematopoiesis, and acute myeloid leukemia among other cancer- and metabolic pathways. Our data indicate that spliceosome mutations may play an important role in MDS pathophysiology by affecting the expression of tumor suppressor miRNA genes involved in the development and progression of MDS.
Glacier melting and altered precipitation patterns influence Arctic freshwater and coastal ecosystems. Arctic rivers are central to Arctic water ecosystems by linking glacier meltwaters and precipitation with the ocean through transport of particulate matter and microorganisms. However, the impact of different water sources on the microbial communities in Arctic rivers and estuaries remains unknown. In this study we used 16S rRNA gene amplicon sequencing to assess a small river and its estuary on the Disko Island, West Greenland (69°N). Samples were taken in August when there is maximum precipitation and temperatures are high in the Disko Bay area. We describe the bacterial community through a river into the estuary, including communities originating in a glacier and a proglacial lake. Our results show that water from the glacier and lake transports distinct communities into the river in terms of diversity and community composition. Bacteria of terrestrial origin were among the dominating OTUs in the main river, while the glacier and lake supplied the river with water containing fewer terrestrial organisms. Also, more psychrophilic taxa were found in the community supplied by the lake. At the river mouth, the presence of dominant bacterial taxa from the lake and glacier was unnoticeable, but these taxa increased their abundances again further into the estuary. On average 23% of the estuary community consisted of indicator OTUs from different sites along the river. Environmental variables showed only weak correlations with community composition, suggesting that hydrology largely influences the observed patterns.
Using expected sequence features to improve basecalling accuracy of amplicon pyrosequencing data

Amplicon pyrosequencing targets a known genetic region and thus inherently produces reads highly anticipated to have certain features, such as conserved nucleotide sequence, and in the case of protein coding DNA, an open reading frame. Pyrosequencing errors, consisting mainly of nucleotide insertions and deletions, are on the other hand likely to disrupt open reading frames. Such an inverse relationship between errors and expectation based on prior knowledge can be used advantageously to guide the process known as basecalling, i.e. the inference of nucleotide sequence from raw sequencing data. The new basecalling method described here, named Multipass, implements a probabilistic framework for working with the raw flowgrams obtained by pyrosequencing. For each sequence variant Multipass calculates the likelihood and nucleotide sequence of several most likely sequences given the flowgram data. This probabilistic approach enables integration of basecalling into a larger model where other parameters can be incorporated, such as the likelihood for observing a full-length open reading frame at the targeted region. We apply the method to 454 amplicon pyrosequencing data obtained from a malaria virulence gene family, where Multipass generates 20 % more error-free sequences than current state of the art methods, and provides sequence characteristics that allow generation of a set of high confidence error-free sequences. This novel method can be used to increase accuracy of existing and future amplicon sequencing data, particularly where extensive prior knowledge is available about the obtained sequences, for example in analysis of the immunoglobulin VDJ region where Multipass can be combined with a model for the known recombining germline genes. Multipass is available for Roche 454 data at http://www.cbs.dtu.dk/services/MultiPass-1.0 , and the concept can potentially be implemented for other sequencing technologies as well.
Using registries to integrate bioinformatics tools and services into workbench environments

The diversity and complexity of bioinformatics resources presents significant challenges to their localisation, deployment and use, creating a need for reliable systems that address these issues. Meanwhile, users demand increasingly usable and integrated ways to access and analyse data, especially within convenient, integrated "workbench" environments.

Resource descriptions are the core element of registry and workbench systems, which are used to both help the user find and comprehend available software tools, data resources, and Web Services, and to localise, execute and combine them. The descriptions are, however, hard and expensive to create and maintain, because they are volatile and require an
exhaustive knowledge of the described resource, its applicability to biological research, and the data model and syntax used to describe it. We present here the Workbench Integration Enabler, a software component that will ease the integration of bioinformatics resources in a workbench environment, using their description provided by the existing ELIXIR Tools and Data Services Registry.

**General information**

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Institut Pasteur, University of Bergen
Authors: Ménager, H. (Ekstern), Kalaš, M. (Ekstern), Rapacki, K. (Intern), Ison, J. (Intern)
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BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.587 SNIP 1.587 CiteScore 1.59
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.469 SNIP 1.6 CiteScore 1.5
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 0.585 SNIP 1.884 CiteScore 1.62
ISI indexed (2013): ISI indexed no
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 0.5 SNIP 1.313 CiteScore 1.28
ISI indexed (2012): ISI indexed no
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 0.638 SNIP 1.574 CiteScore 1.65
ISI indexed (2011): ISI indexed no
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 0.69 SNIP 2.116
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 0.776 SNIP 1.885
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 1.139 SNIP 2.269
Scopus rating (2007): SJR 0.715 SNIP 1.593
Scopus rating (2006): SJR 0.698 SNIP 1.696
Scopus rating (2005): SJR 0.576 SNIP 1.27
Scopus rating (2004): SJR 0.584 SNIP 0.912
Scopus rating (2003): SJR 1.146 SNIP 1.628
Scopus rating (2002): SJR 0.976 SNIP 1.681
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Scopus rating (2000): SJR 0.862 SNIP 2.813
Scopus rating (1999): SJR 0.444 SNIP 2.276
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Whole genome sequencing as a tool for phylogenetic analysis of clinical strains of Mitis group streptococci

Identification of Mitis group streptococci (MGS) to the species level is challenging for routine microbiology laboratories. Correct identification is crucial for the diagnosis of infective endocarditis, identification of treatment failure, and/or infection relapse. Eighty MGS from Danish patients with infective endocarditis were whole genome sequenced. We compared the phylogenetic analyses based on single genes (recA, sodA, gdh), multigene (MLSA), SNPs, and core-genome sequences. The six phylogenetic analyses generally showed a similar pattern of six monophyletic clusters, though a few differences were observed in single gene analyses. Species identification based on single gene analysis showed their limitations when more strains were included. In contrast, analyses incorporating more sequence data, like MLSA, SNPs and core-genome analyses, provided more distinct clustering. The core-genome tree showed the most distinct clustering.
Whole genome sequencing for childhood cancer in Denmark

The talk will describe our involvement in the Danish project STAGING, “Sequencing Three Actionable Genomes – Implications & National Guidelines”, an interdisciplinary, multi-tiered 3-year study of 600 consecutive childhood cancer patients and their families, with extensive genomic sequencing of host, tumour and gut microbiome’s genomes. In Europe, cancer accounts for approximately 25% of all deaths in children >1 year. Most cured patients are burdened by late effects, including risk of second cancer and debilitating toxicities. Recent advancements in genetic sequencing technology and reduction in costs have led to new strategies for identification of cancer predisposition and targeted treatment. STAGING is a nation-wide programme offering full, up-front genetic testing for childhood cancer patients and implements the findings into health care. Paediatric oncology provides a unique proof-of-principle framework for such a program, since it is one of the best organized medical specialties with nation-wide strategies for diagnostics, therapy, deep response phenotyping, and follow-up.

General information
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Organisations: Center for Biological Sequence Analysis, Functional Human Variation, Department of Bio and Health Informatics, Disease Intelligence and Molecular Evolution
Authors: Gupta, R. (Intern)
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Links:
http://www.sustain.dtu.dk/

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wKinMut-2: Identification and Interpretation of Pathogenic Variants in Human Protein Kinases

Most genomic alterations are tolerated while only a minor fraction disrupts molecular function sufficiently to drive disease. Protein kinases play a central biological function and the functional consequences of their variants are abundantly characterized. However, this heterogeneous information is often scattered across different sources, which makes the integrative analysis complex and laborious. wKinMut-2 constitutes a solution to facilitate the interpretation of the consequences of human protein kinase variation. Nine methods predict their pathogenicity, including a kinase-specific random forest approach. To understand the biological mechanisms causative of human diseases and cancer, information from pertinent reference knowledgebases and the literature is automatically mined, digested and homogenized. Variants are visualized in their structural contexts and residues affecting catalytic and drug-binding are identified. Known protein-
protein interactions are reported. Altogether, this information is intended to assist the generation of new working hypothesis to be corroborated with ulterior experimental work. The wKinMut-2 system, along with a user manual and examples is freely accessible at http://kinmut2.bioinfo.cnio.es, the code for local installations at https://github.com/Rbbt-Workflows/KinMut2.

**General information**

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Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Integrative Systems Biology, Spanish National Cancer Research Centre  
Authors: Vazquez, M. (Ekstern), Pons, T. (Ekstern), Brunak, S. (Intern), Valencia, A. (Ekstern), Gonzalez-Izarzugaza, J. M. (Intern)  
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BFI (2014): BFI-level 2  
Scopus rating (2014): SJR 3.521 SNIP 1.788 CiteScore 4.91  
BFI (2013): BFI-level 2  
Scopus rating (2013): SJR 3.169 SNIP 1.774 CiteScore 5.21  
ISI indexed (2013): ISI indexed yes  
BFI (2012): BFI-level 2  
Scopus rating (2012): SJR 3.04 SNIP 1.9 CiteScore 5.4  
ISI indexed (2012): ISI indexed yes  
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Scopus rating (2011): SJR 3.185 SNIP 1.988 CiteScore 5.45  
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BFI (2009): BFI-level 2  
Scopus rating (2009): SJR 2.877 SNIP 1.914  
BFI (2008): BFI-level 2  
Scopus rating (2008): SJR 2.395 SNIP 1.788  
Scopus rating (2007): SJR 2.122 SNIP 1.846  
Scopus rating (2006): SJR 2.113 SNIP 1.922  
Scopus rating (2005): SJR 2.217 SNIP 2.059  
Web of Science (2005): Indexed yes  
Scopus rating (2004): SJR 1.718 SNIP 1.944  
Scopus rating (2003): SJR 1.204 SNIP 1.851  
Scopus rating (2002): SJR 1.271 SNIP 1.646  
Web of Science (2002): Indexed yes  
Scopus rating (2001): SJR 1.351 SNIP 1.399
A catalog of the mouse gut metagenome

We established a catalog of the mouse gut metagenome comprising ~2.6 million nonredundant genes by sequencing DNA from fecal samples of 184 mice. To secure high microbiome diversity, we used mouse strains of diverse genetic backgrounds, from different providers, kept in different housing laboratories and fed either a low-fat or high-fat diet. Similar to the human gut microbiome, >99% of the cataloged genes are bacterial. We identified 541 metagenomic species and defined a core set of 26 metagenomic species found in 95% of the mice. The mouse gut microbiome is functionally similar to its human counterpart, with 95.2% of its Kyoto Encyclopedia of Genes and Genomes (KEGG) orthologous groups in common. However, only 4.0% of the mouse gut microbial genes were shared (95% identity, 90% coverage) with those of the human gut microbiome. This catalog provides a useful reference for future studies.
Accurate pan-specific prediction of peptide-MHC class II binding affinity with improved binding core identification

A key event in the generation of a cellular response against malicious organisms through the endocytic pathway is binding of peptidic antigens by major histocompatibility complex class II (MHC class II) molecules. The bound peptide is then presented on the cell surface where it can be recognized by T helper lymphocytes. NetMHCIIpan is a state-of-the-art method for the quantitative prediction of peptide binding to any human or mouse MHC class II molecule of known sequence. In this paper, we describe an updated version of the method with improved peptide binding register identification. Binding register prediction is concerned with determining the minimal core region of nine residues directly in contact with the MHC binding cleft, a crucial piece of information both for the identification and design of CD4+ T cell antigens. When applied to a set of 51 crystal structures of peptide-MHC complexes with known binding registers, the new method NetMHCIIpan-3.1 significantly outperformed the earlier 3.0 version. We illustrate the impact of accurate binding core identification for the interpretation of T cell cross-reactivity using tetramer double staining with a CMV epitope and its variants mapped to the epitope binding core. NetMHCIIpan is publicly available at http://www.cbs.dtu.dk/services/NetMHCIIpan-3.1.

General information
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Universidad Nacional de San Martin, La Jolla Institute for Allergy & Immunology, University of Copenhagen
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A computational method for identification of vaccine targets from protein regions of conserved human leukocyte antigen binding

Background: Computational methods for T cell-based vaccine target discovery focus on selection of highly conserved peptides identified across pathogen variants, followed by prediction of their binding of human leukocyte antigen molecules. However, experimental studies have shown that T cells often target diverse regions in highly variable viral pathogens and this diversity may need to be addressed through redefinition of suitable peptide targets. Methods: We have developed a method for antigen assessment and target selection for polyvalent vaccines, with which we identified immune epitopes from variable regions, where all variants bind HLA. These regions, although variable, can thus be considered stable in terms of HLA binding and represent valuable vaccine targets. Results: We applied this method to predict CD8+ T-cell targets in influenza A H7N9 hemagglutinin and significantly increased the number of potential vaccine targets compared to the number of targets discovered using the traditional approach where low-frequency peptides are excluded. Conclusions: We developed a webserver with an intuitive visualization scheme for summarizing the T cell-based antigenic potential of any given protein or proteome using human leukocyte antigen binding predictions and made a web-accessible software implementation freely available at http://met-hilab.cbs.dtu.dk/blockcons/.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Technical University of Denmark, University of Copenhagen, Dana-Farber Cancer Institute
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Web of Science (2015): Indexed yes
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Web of Science (2014): Indexed yes
Scopus rating (2013): SJR 2.166 SNIP 1.037 CiteScore 4.26
Scopus rating (2012): SJR 1.891 SNIP 0.964 CiteScore 4
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A_computational_method_for_identification_of_vaccine_targets_from_protein_regions_of_conserved_human_leukocyte_antigen_binding.pdf
DOIs:
Acquisition of docetaxel resistance in breast cancer cells reveals upregulation of \( ABCB1 \) expression as a key mediator of resistance accompanied by discrete upregulation of other specific genes and pathways.

The microtubule-targeting taxanes are important in breast cancer therapy, but no predictive biomarkers have yet been identified with sufficient scientific evidence to allow clinical routine use. The purposes of the present study were to develop a cell-culture-based discovery platform for docetaxel resistance and thereby identify key molecular mechanisms and predictive molecular characteristics to docetaxel resistance. Two docetaxel-resistant cell lines, MCF\(^{RES} \) and MDA\(^{RES} \), were generated from their respective parental cell lines MCF-7 and MDA-MB-231 by stepwise selection in docetaxel dose increments over 15 months. The cell lines were characterized regarding sensitivity to docetaxel and other chemotherapeutics and subjected to transcriptome-wide mRNA microarray profiling. MCF\(^{RES} \) and MDA\(^{RES} \) exhibited a biphasic growth inhibition pattern at increasing docetaxel concentrations. Gene expression analysis singled out \( ABCB1 \), which encodes permeability glycoprotein (Pgp), as the top upregulated gene in both MCF\(^{RES} \) and MDA\(^{RES} \). Functional validation revealed Pgp as a key resistance mediator at low docetaxel concentrations (first-phase response), whereas additional resistance mechanisms appeared to be prominent at higher docetaxel concentrations (second-phase response). Additional resistance mechanisms were indicated by gene expression profiling, including genes in the interferon-inducible protein family in MCF7RES and cancer testis antigen family in MDA\(^{RES} \). Also, upregulated expression of various ABC transporters, ECM-associated proteins, and lysosomal proteins was identified in both resistant cell lines. Finally, MCF7RES and MDA\(^{RES} \) presented with crossresistance to epirubicin, but only MDA\(^{RES} \) showed cross-resistance to oxaliplatin. In conclusion, Pgp was identified as a key mediator of resistance to low docetaxel concentrations with other resistance mechanisms prominent at higher docetaxel concentrations. Supporting Pgp upregulation as one major mechanism of taxane resistance and cell-line-specific alterations as another, both MCF\(^{RES} \) and MDA\(^{RES} \) were crossresistant to epirubicin (Pgp substrate), but only MDA\(^{RES} \) was cross-resistant to oxaliplatin (non-Pgp substrate).
A global reference for human genetic variation

The 1000 Genomes Project set out to provide a comprehensive description of common human genetic variation by applying whole-genome sequencing to a diverse set of individuals from multiple populations. Here we report completion of the project, having reconstructed the genomes of 2,504 individuals from 26 populations using a combination of low-coverage whole-genome sequencing, deep exome sequencing, and dense microarray genotyping. We characterized a broad spectrum of genetic variation, in total over 88 million variants (84.7 million single nucleotide polymorphisms (SNPs), 3.6 million short insertions/deletions (indels), and 60,000 structural variants), all phased onto high-quality haplotypes. This resource includes >99% of SNP variants with a frequency of >1% for a variety of ancestries. We describe the distribution of genetic variation across the global sample, and discuss the implications for common disease studies.
Airway Mucosal Immune-suppression in Neonates of Mothers Receiving A(H1N1)pnd09 Vaccination During Pregnancy

Background: It is recommended to vaccinate pregnant women against influenza. A possible impact on the immune expression of the fetus has never been studied. We aim to study the immune signature in the upper airways and the incidence of infections in neonates born to mothers receiving Influenza A(H1N1) pnd09 vaccination during pregnancy.

Methods: One hundred and fifty-six women from the unselected Copenhagen Prospective Study on Asthma in Childhood (COPSAC 2010) received Influenza A(H1N1) pnd09-vaccination during the 2009 pandemic. Fifty-one mothers received the vaccine during pregnancy and 105 after pregnancy; 332 neonates of nonvaccinated mothers were included as secondary controls. Nasal mucosal lining fluid was sampled in 488 neonates and assessed for interleukin (IL)-12p70, IP-10, interferon-gamma (IFN)-gamma, tumor necrosis factor-alpha (TNF)-alpha, MIP-1 beta, MCP-1, MCP-4, IL-4, IL-5, IL-13, eotaxin-1, eotaxin-3, TARC, MDC, IL-17, IL-1 beta, IL-8, transforming growth factor beta (TGF)-beta 1, IL-10 and IL-2. Infections were monitored the first year of life by daily diary cards and clinical controls. Results: Neonates of mothers vaccinated during pregnancy had significant up-regulation of TGF-beta 1 [ratio = 1.52 (1.22-1.90), P = 0.0002], and corresponding down-regulation (P <0.05) of IL-12p70, IFN-gamma, IL-5, eotaxin-1, TARC, MDC, IL-8 in comparison to those vaccinated after pregnancy. The lag-time from vaccination during pregnancy to assessment of the immune signature showed significant and positive association to up-regulation of TGF-beta 1 levels (P = 0.0003) and significant negative association to other mediators. The study was not powered to study differences in the incidence of infections in early infancy which did not differ between the study groups. Conclusion: Influenza A(H1N1) pnd09 vaccination during pregnancy up-regulates TGF-beta 1 and down-regulates key mediators of the protective immunity.

General Information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Copenhagen
Authors: Pedersen, S. B. (Intern), Bischoff, A. L. (Ekstern), Folsgaard, N. V. (Ekstern), Vissing, N. H. (Ekstern), Birch, S. (Ekstern), Bisgaard, H. (Ekstern)
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Scopus rating (2016): CiteScore 2.09 SJR 1.486 SNIP 1.03
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 1.435 SNIP 1.051 CiteScore 2.1
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 1.801 SNIP 1.169 CiteScore 2.48
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 1.619 SNIP 1.24 CiteScore 2.81
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 1.821 SNIP 1.37 CiteScore 3.23
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 1.745 SNIP 1.373 CiteScore 3.08
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 1.677 SNIP 1.383
Web of Science (2010): Indexed yes
AllelicImbalance: An R/bioconductor package for detecting, managing, and visualizing allele expression imbalance data from RNA sequencing

Background: One aspect in which RNA sequencing is more valuable than microarray-based methods is the ability to examine the allelic imbalance of the expression of a gene. This process is often a complex task that entails quality control, alignment, and the counting of reads over heterozygous single-nucleotide polymorphisms. Allelic imbalance analysis is subject to technical biases, due to differences in the sequences of the measured alleles. Flexible bioinformatics tools are needed to ease the workflow while retaining as much RNA sequencing information as possible throughout the analysis to detect and address the possible biases. Results: We present AllelicImbalance, a software program that is designed to detect, manage, and visualize allelic imbalances comprehensively. The purpose of this software is to allow users to pose genetic questions in any RNA sequencing experiment quickly, enhancing the general utility of RNA sequencing. The visualization features can reveal notable, non-trivial allelic imbalance behavior over specific regions, such as exons. Conclusions: The software provides a complete framework to perform allelic imbalance analyses of aligned RNA sequencing data, from detection to visualization, within the robust and versatile management class, ASEset.
Systemic low-grade inflammation has been demonstrated in a range of the frequent noncommunicable diseases (NCDs) as a possible shared mechanism, but is largely unexplored in relation to allergic sensitization. Therefore, we aimed to
investigate the possible association between systemic low-grade inflammation and childhood allergic sensitization.

**General information**

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Copenhagen
Authors: Chawes, B. L. K. (Ekstern), Stokholm, J. (Ekstern), Malby-Schoos, A. (Ekstern), Kreiner-Moller, L. (Ekstern), Pedersen, S. B. (Intern), Bisgaard, H. F. (Ekstern)
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  - Scopus rating (2016): CiteScore 6.23 SJR 2.724 SNIP 2.475
  - Web of Science (2016): Indexed yes
  - BFI (2015): BFI-level 1
  - Scopus rating (2015): SJR 3.13 SNIP 2.127 CiteScore 5.73
  - Web of Science (2015): Indexed yes
  - BFI (2014): BFI-level 1
  - Scopus rating (2014): SJR 2.464 SNIP 2.121 CiteScore 5.51
  - Web of Science (2014): Indexed yes
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  - Scopus rating (2013): SJR 2.195 SNIP 1.902 CiteScore 4.91
  - ISI indexed (2013): ISI indexed yes
  - Web of Science (2013): Indexed yes
  - BFI (2012): BFI-level 1
  - Scopus rating (2012): SJR 2.008 SNIP 1.818 CiteScore 4.81
  - ISI indexed (2012): ISI indexed yes
  - Web of Science (2012): Indexed yes
  - BFI (2011): BFI-level 1
  - Scopus rating (2011): SJR 2.328 SNIP 1.781 CiteScore 4.89
  - ISI indexed (2011): ISI indexed yes
  - BFI (2010): BFI-level 1
  - Scopus rating (2010): SJR 1.826 SNIP 1.845
  - Web of Science (2010): Indexed yes
  - BFI (2009): BFI-level 1
  - Scopus rating (2009): SJR 1.681 SNIP 0.958
  - Web of Science (2009): Indexed yes
  - BFI (2008): BFI-level 2
  - Scopus rating (2008): SJR 1.433 SNIP 1.937
  - Web of Science (2008): Indexed yes
  - Scopus rating (2007): SJR 1.374 SNIP 1.862
  - Web of Science (2007): Indexed yes
  - Scopus rating (2006): SJR 1.523 SNIP 2.691
  - Web of Science (2006): Indexed yes
A modern approach for epitope prediction: identification of foot-and-mouth disease virus peptides binding bovine leukocyte antigen (BoLA) class I molecules

Major histocompatibility complex (MHC) class I molecules regulate adaptive immune responses through the presentation of antigenic peptides to CD8+ T cells. Polymorphisms in the peptide binding region of class I molecules determine peptide binding affinity and stability during antigen presentation, and different antigen peptide motifs are associated with specific genetic sequences of class I molecules. Understanding bovine leukocyte antigen (BoLA), peptide-MHC class I binding specificities may facilitate development of vaccines or reagents for quantifying the adaptive immune response to intracellular pathogens, such as foot-and-mouth disease virus (FMDV). Six synthetic BoLA class I (BoLA-I) molecules were produced, and the peptide binding motif was generated for five of the six molecules using a combined approach of positional scanning combinatorial peptide libraries (PSCPLs) and neural network-based predictions (NetMHCpan). The updated NetMHCpan server was used to predict BoLA-I binding peptides within the P1 structural polyprotein sequence of FMDV (strain A24 Cruzeiro) for BoLA-1*01901, BoLA-2*00801, BoLA-2*01201, and BoLA-4*02401. Peptide binding affinity and stability were determined for these BoLA-I molecules using the luminescent oxygen channeling immunoassay (LOCI) and scintillation proximity assay (SPA). The functional diversity of known BoLA alleles was predicted using the MHCluster tool, and functional predictions for peptide motifs were compared to observed data from this and prior studies. The results of these analyses showed that BoLA alleles cluster into three distinct groups with the potential to define “BoLA supertypes.” This streamlined approach identifies potential T cell epitopes from pathogens, such as FMDV, and provides insight into T cell immunity following infection or vaccination.

General information
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Organisations: Department of Chemical and Biochemical Engineering, Department of Systems Biology, Center for Biological Sequence Analysis, University of Vermont, University of Copenhagen, Agricultural Research Service
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Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.2 SJR 1.231 SNIP 0.703
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.551 SNIP 0.819 CiteScore 2.47
Analysis artefacts of the INS-IGF2 fusion transcript

Background: In gene expression analysis, overlapping genes, splice variants, and fusion transcripts are potential sources of data analysis artefacts, depending on how the observed intensity is assigned to one, or more genes. We here exemplify this by an in-depth analysis of the INS-IGF2 fusion transcript, which has recently been reported to be among the highest expressed transcripts in human pancreatic beta cells and its protein indicated as a novel autoantigen in Type 1 Diabetes.

Results: Through RNA sequencing and variant specific qPCR analyses we demonstrate that the true abundance of INS-IGF2 is >20,000 fold lower than INS in human beta cells, and we suggest an explanation to the nature of the artefacts which have previously led to overestimation of the gene expression level in selected studies. We reinvestigated the previous reported findings of detection of INS-IGF2 using antibodies both in Western blotting and immunohistochemistry. We found that the one available commercial antibody (BO1P) raised against recombinant INS-IGF2 show strong cross-
reaction to native proinsulin, and we did not detect INS-IGF2 protein in the human beta cell line EndoC-βH1. Furthermore, using highly sensitive proteomics analysis we could not demonstrate INS-IGF2 protein in samples of human islets nor in EndoC-βH1. Conclusions: Sequence features, such as fusion transcripts spanning multiple genes can lead to unexpected results in gene expression analysis, and care must be taken in generating and interpreting the results. For the specific case of INS-IGF2 we conclude that the abundance of the fusion transcript/protein is exceedingly lower than previously reported, and that current immuno-reagents available for detecting INS-IGF2 protein have a strong cross-reaction to native human proinsulin. Finally, we were unable to detect INS-IGF2 protein by proteomics analysis.

General information
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Novo Nordisk A/S, Intomics A/S
Authors: Wernersson, R. (Intern), Frogne, T. (Ekstern), Rescan, C. (Ekstern), Hansson, L. (Ekstern), Bruun, C. (Ekstern), Grønborg, M. (Ekstern), Jensen, J. N. (Ekstern), Madsen, O. D. (Ekstern)
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Main Research Area: Technical/natural sciences
A novel genomic alteration of LSAMP associates with aggressive prostate cancer in African American men

Evaluation of cancer genomes in global context is of great interest in light of changing ethnic distribution of the world population. We focused our study on men of African ancestry because of their disproportionately higher rate of prostate cancer (CaP) incidence and mortality. We present a systematic whole genome analyses, revealing alterations that differentiate African American (AA) and Caucasian American (CA) CaP genomes. We discovered a recurrent deletion on chromosome 3q13.31 centering on the LSAMP locus that was prevalent in tumors from AA men (cumulative analyses of 435 patients: whole genome sequence, 14; FISH evaluations, 101; and SNP array, 320 patients). Notably, carriers of this deletion experienced more rapid disease progression. In contrast, PTEN and ERG common driver alterations in CaP were significantly lower in AA prostate tumors compared to prostate tumors from CA. Moreover, the frequency of inter-chromosomal rearrangements was significantly higher in AA than CA tumors. These findings reveal differentially distributed somatic mutations in CaP across ancestral groups, which have implications for precision medicine strategies.

General information
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Cancer Systems Biology, Uniformed Services University of the Health Sciences, Genomatix Software GmbH, Xiamen University, Technical University of Denmark, CytoTest Inc., The Joint Pathology Center, National Cancer Institute, Harvard Medical School, University of Heidelberg
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A_novel_genomic ALTERATION_of_LSAMP_ASSOCIATES_withAggressive_Prostate_Cancer_in_African_American_men.pdf
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A novel in vitro wound biofilm model used to evaluate low-frequency ultrasonic-assisted wound debridement

Objective: Bacterial biofilms remain difficult to treat. The biofilm mode of growth enables bacteria to survive antibiotic treatment and the inflammatory reaction. Low-frequency ultrasound has recently been shown to improve healing in a variety of settings. It is hypothesised that ultrasound disrupts the biofilm leaving bacteria more vulnerable to antiseptic or antibiotic treatment. The objective of this study is to develop a realistic model to elucidate the effect of ultrasound on biofilms.

Method: A novel in vitro wound biofilm model was developed. Biofilms of Staphylococcus aureus were casted in a semi-solid agar gel composed of either tryptic soy broth (TSB) or a wound simulating media (WSM; composed of Bolton broth with blood and plasma), to resemble the non-surface attached aggregates. The model was used to evaluate the antibiofilm effect of an ultrasonic-assisted wound debridement device (UA W) in the presence of saline irrigation and treatment with a polyhexamethylene biguanide (PHMB)-containing antiseptic. Confocal microscopy was used to evaluate the effect of treatments on biofilm disruption and cell viability counting measured the antibacterial effects.

Results: Confocal microscopy showed that application of 10 seconds of moderate-intensity UA W could effectively disrupt semi-solid biofilms grown on both media settings. This treatment only had a small effect on the cell viability. A 24-hour treatment with PHMB was able to reduce the number of bacteria but not eradicate the biofilm in both media settings. Interestingly, the efficacy of the PHMB antiseptic was significantly higher when applied on biofilms grown in the more complex WSM media. However, we found a significant improvement in reducing the number of viable bacteria grown on both media when applying UA W before administration of the PHMB solution. Applying UA W in the presence of PHMB further improved the efficacy.

Conclusion: Using a realistic in vitro biofilm wound model, we show combining UA W with a PHMB-containing antiseptic has potential as an antibiofilm strategy in wound care.
Applying genetics in inflammatory disease drug discovery

Recent groundbreaking work in genetics has identified thousands of small-effect genetic variants throughout the genome that are associated with almost all major diseases. These genome-wide association studies (GWAS) are often proposed as a source of future medical breakthroughs. However, with several notable exceptions, the journey from a small-effect genetic variant to a functional drug has proven arduous, and few examples of actual contributions to drug discovery exist. Here, we discuss novel approaches of overcoming this hurdle by using instead public genetics resources as a pragmatic guide alongside existing drug discovery methods. Our aim is to evaluate human genetic confidence as a rationale for drug target selection.

General information
State: Published
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Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.085 SNIP 1.596 CiteScore 5.62
Web of Science (2015): Indexed yes
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Scopus rating (2014): SJR 1.84 SNIP 1.61 CiteScore 5.61
A proteomic study of the regulatory role for STAT-1 in cytokine-induced beta-cell death

PURPOSE: Signal transducer and activator of transcription 1 (STAT-1) plays a crucial role in cytokine-induced beta-cell destruction. However, its precise downstream pathways have not been completely clarified. We performed a proteome analysis of cytokine-exposed C57Bl/6 and STAT-1-/- mouse islets and prioritized proteins for their potential in relation to type 1 diabetes (T1D).

EXPERIMENTAL DESIGN: Differential proteins were identified using a combination of 2D-DIGE and MALDI-TOF/TOF analysis and were subjected to ingenuity pathway analysis (IPA). Protein-protein interaction networks were created and a phenome-interactome ranking of the differential proteins based on their assignment to T1D was performed.

RESULTS: Numerous STAT-1-regulated proteins were identified and divided in different groups according to their biological function. The largest group of proteins was the one involved in protein synthesis and processing. Network analysis revealed a complex interaction between proteins from different functional groups and IPA analysis confirmed the protective effect of STAT-1 deletion on cytokine-induced beta-cell death. Finally, a central role in this STAT-1-regulated mechanism was assigned to small ubiquitin-related modifier 4 (SUMO4).

CONCLUSIONS AND CLINICAL RELEVANCE: These findings confirm a central role for STAT-1 in pancreatic islet inflammation induced destruction and most importantly elucidate the underlying proteomic pathways involved.
Archival Bone Marrow Samples: Suitable for Multiple Biomarker Analysis?

Archival samples represent a significant potential for genetic studies, particularly in severe diseases with risk of lethal outcome, such as in cancer. In this pilot study, we aimed to evaluate the usability of archival bone marrow smears and biopsies for DNA extraction and purification, whole genome amplification (WGA), multiple marker analysis including 10 short tandem repeats, and finally a comprehensive genotyping of 33,683 single nucleotide polymorphisms (SNPs) with multiplexed targeted next-generation sequencing. A total of 73 samples from 21 bone marrow smears and 13 bone marrow biopsies from 18 Danish and Norwegian childhood acute lymphoblastic leukemia patients were included and compared with corresponding blood samples. Samples were grouped according to the age of sample and whether WGA was performed or not. We found that measurements of DNA concentration after DNA extraction was dependent on detection method and that spectrophotometry overestimated DNA amount compared with fluorometry. In the short tandem repeat analysis, detection rate dropped slightly with longer fragments. After WGA, this drop was more pronounced. Samples stored for 0 to 3 years showed better results compared with samples stored for 4 to 10 years. Acceptable call rates for SNPs were detected for 7 of 42 archival samples. In conclusion, archival bone marrow samples are suitable for DNA extraction and multiple marker analysis, but WGA was less successful, especially when longer fragments were
analyzed. Multiple SNP analysis seems feasible, but the method has to be further optimized.
A redox-dependent dimerization switch regulates activity and tolerance for reactive oxygen species of barley seed glutathione peroxidase

Monomeric and dimeric forms of recombinant barley (Hordeum vulgare subsp. vulgare) glutathione peroxidase 2 (HvGpx2) are demonstrated to display distinctly different functional properties in vitro. Monomeric HvGpx2 thus has five fold higher catalytic efficiency than the dimer towards tert-butyl hydroperoxide, but is more sensitive to inactivation by hydrogen peroxide. Treatment of the monomer with hydrogen peroxide results in dimer formation. This observed new behavior of a plant glutathione peroxidase suggests a mechanism involving a switch from a highly catalytically competent monomer to a less active, but more oxidation-resistant dimer.

General information

State: Published
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Scopus rating (2016): CiteScore 3.4 SJR 1.159 SNIP 1.158
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.156 SNIP 1.284 CiteScore 3.19
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.052 SNIP 1.157 CiteScore 2.86
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.052 SNIP 1.376 CiteScore 3.24
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.167 SNIP 1.35 CiteScore 3.07
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.183 SNIP 1.269 CiteScore 3.1
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.033 SNIP 1.062
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.131 SNIP 1.168
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 0.884 SNIP 0.99
Scopus rating (2007): SJR 0.92 SNIP 0.926
Scopus rating (2006): SJR 0.828 SNIP 0.77
Scopus rating (2005): SJR 0.824 SNIP 0.893
Scopus rating (2004): SJR 0.773 SNIP 0.699
A retrospective metagenomics approach to studying Blastocystis

Blastocystis is a common single-celled intestinal parasitic genus, comprising several subtypes. Here, we screened data obtained by metagenomic analysis of faecal DNA for Blastocystis by searching for subtype-specific genes in coabundance gene groups, which are groups of genes that covary across a selection of 316 human faecal samples, hence representing genes originating from a single subtype. The 316 faecal samples were from 236 healthy individuals, 13 patients with Crohn's disease (CD) and 67 patients with ulcerative colitis (UC). The prevalence of Blastocystis was 20.3% in the healthy individuals and 14.9% in patients with UC. Meanwhile, Blastocystis was absent in patients with CD. Individuals with intestinal microbiota dominated by Bacteroides were much less prone to having Blastocystis-positive stool (Matthew's correlation coefficient = -0.25, P < 0.0001) than individuals with Ruminococcus- and Prevotella-driven enterotypes. This is the first study to investigate the relationship between Blastocystis and communities of gut bacteria using a metagenomics approach. The study serves as an example of how it is possible to retrospectively investigate microbial eukaryotic communities in the gut using metagenomic datasets targeting the bacterial component of the intestinal microbiome and the interplay between these microbial communities.

General information
State: Published
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Scopus rating (2016): CiteScore 13.54
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Scopus rating (2013): CiteScore 13.78
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Automated benchmarking of peptide-MHC class I binding predictions

Motivation: Numerous in silico methods predicting peptide binding to major histocompatibility complex (MHC) class I molecules have been developed over the last decades. However, the multitude of available prediction tools makes it non-trivial for the end-user to select which tool to use for a given task. To provide a solid basis on which to compare different prediction tools, we here describe a framework for the automated benchmarking of peptide-MHC class I binding prediction tools. The framework runs weekly benchmarks on data that are newly entered into the Immune Epitope Database (IEDB), giving the public access to frequent, up-to-date performance evaluations of all participating tools. To overcome potential selection bias in the data included in the IEDB, a strategy was implemented that suggests a set of peptides for which different prediction methods give divergent predictions as to their binding capability. Upon experimental binding validation, these peptides entered the benchmark study.

Results: The benchmark has run for 15 weeks and includes evaluation of 44 datasets covering 17 MHC alleles and more than 4000 peptide-MHC binding measurements. Inspection of the results allows the end-user to make educated selections between participating tools. Of the four participating servers, NetMHCpan performed the best, followed by ANN, SMM and finally ARB.

Availability and implementation: Up-to-date performance evaluations of each server can be found online at http://tools.iedb.org/auto_bench/mhci/weekly. All prediction tool developers are invited to participate in the benchmark. Sign-up instructions are available at http://tools.iedb.org/auto_bench/mhci/join.
Porcine Reproductive and Respiratory Syndrome Virus (PRRSV) causes one of the most important diseases in all swine producing countries. The infection has a high impact on animal welfare, food safety and production economics. PRRSV possesses multiple immunoevasive strategies, from suppression of the host cell antiviral machinery, to the deceptive induction of a non-neutralizing antibody response through decoy antigen presentation. This, combined with a very high mutation rate, has hampered the development of safe and effective vaccines.
With the overall aim to design a vaccine that induces an effective CTL response against PRRSV, we have taken a bioinformatics approach to identify common PRRSV epitopes predicted to react broadly with predominant swine MHC (SLA) alleles. First, the genomic integrity and sequencing method was examined for 334 available complete PRRSV type 2 genomes leaving 104 strains of high quality. For each strain, a library of all possible 9- and 10-mer peptides was generated considering the known ribosomal frame shift sites and sites for post translational cleavage.

All peptides were in silico analyzed for binding affinity to either of five common SLA class I alleles. A quantitative rank score was generated for each peptide by combining two algorithms based on the NetMHCpan neural network and lab determined SLA binding affinity of each amino acid at any position in the peptide, respectively.

Peptides with a rank score above a predefined threshold were further analyzed by the PopCover algorithm, providing a final list of 54 epitopes prioritized according to maximum coverage of PRRSV strains and SLA alleles. This bioinformatics approach provides a rational strategy for selecting peptides for a CTL-activating vaccine with broad coverage of both virus and swine diversity. The immunogenicity of the selected peptides is in the process of being verified in vivo.

**General information**

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Organisations: National Veterinary Institute, Section for Virology, Center for Biological sequence analysis, Department of Systems Biology, Center for Biological Sequence Analysis, Immunological Bioinformatics, Section for Immunology and Virology
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Breast milk IL-1β level associates with development of eczema during early childhood

We recently demonstrated a dual effect of breastfeeding with increased risk of eczema and decreased risk of wheezing in early childhood. We hypothesized that maternal immune constitution characterized by breast milk mediators may explain such association.

**General information**

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Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 3.13 SNIP 2.127 CiteScore 5.73
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.464 SNIP 2.121 CiteScore 5.51
CAUSEL: an epigenome- and genome-editing pipeline for establishing function of noncoding GWAS variants.

The vast majority of disease-associated single-nucleotide polymorphisms (SNPs) mapped by genome-wide association studies (GWASs) are located in the non-protein-coding genome, but establishing the functional and mechanistic roles of these sequence variants has proven challenging. Here we describe a general pipeline in which candidate functional SNPs are first evaluated by fine mapping, epigenomic profiling, and epigenome editing, and then interrogated for causal function by using genome editing to create isogenic cell lines followed by phenotypic characterization. To validate this approach, we analyzed the 6q22.1 prostate cancer risk locus and identified rs339331 as the top-scoring SNP. Epigenome editing confirmed that the rs339331 region possessed regulatory potential. By using transcription activator-like effector nuclease (TALEN)-mediated genome editing, we created a panel of isogenic 22Rv1 prostate cancer cell lines representing all three genotypes (TT, TC, CC) at rs339331. Introduction of the 'T' risk allele increased transcription of the regulatory factor 6 (RFX6) gene, increased homeobox B13 (HOXB13) binding at the rs339331 region, and increased deposition of the enhancer-associated H3K4me2 histone mark at the rs339331 region compared to lines homozygous for the 'C' protective allele. The cell lines also differed in cellular morphology and adhesion, and pathway analysis of differentially expressed genes suggested an influence of androgens. In summary, we have developed and validated a widely accessible approach that can be used to establish functional causality for noncoding sequence variants identified by GWASs.
Changing the way science is taught through gamified laboratories

A large proportion of high school and college students indicate that they have little interest in science, and many graduate with marginal science competencies. However, laboratory exercises, usually the most engaging part of science courses, tend to be expensive, time consuming and occasionally constrained by safety concerns. Combining gamification elements with simulations may provide an opportunity for great gains in learning effectiveness and motivation of biotech students. An advanced laboratory simulation platform based on mathematical algorithms supporting open-ended investigations was developed and combined with gamification elements such as an immersive 3D universe, storytelling, conversations with fictional characters and a scoring system. Two gamified laboratory simulations were tested: a crime-scene lab and a genetic engineering lab (http://www.labster.com/biolabs/). A study testing the crime-scene case in an introductory, college-level, life science course was conducted revealed that a gamified laboratory simulation can significantly increase both learning outcomes and motivation levels when compared with, and particularly when combined with, traditional teaching.

Chronic obstructive pulmonary disease and asthma-associated Proteobacteria, but not commensal Prevotella spp., promote Toll-like receptor 2-independent lung inflammation and pathology

Recent studies of healthy human airways have revealed colonization by a distinct commensal bacterial microbiota containing Gram-negative Prevotella spp. However, the immunological properties of these bacteria in the respiratory system inflammation remain unknown. Here we compare the innate respiratory immune response to three Gram-negative commensal Prevotella strains (Prevotella melaninogenica, Prevotella nanceiensis and Prevotella salivae) and three Gram-negative pathogenic Proteobacteria known to colonize lungs of patients with chronic obstructive pulmonary disease (COPD) and asthma (Haemophilus influenzae B, non-typeable Haemophilus influenzae and Moraxella catarrhalis). The commensal Prevotella spp. and pathogenic Proteobacteria were found to exhibit intrinsic differences in innate inflammatory capacities on murine lung cells in vitro. In vivo in mice, non-typeable H.influenzae induced severe Toll-like receptor 2 (TLR2)-independent COPD-like inflammation characterized by predominant airway neutrophilia, expression of a neutrophilic cytokine/chemokine profile in lung tissue, and lung immunopathology. In comparison, P.nanceiensis induced a diminished neutrophilic airway inflammation and no detectable lung pathology. Interestingly, the inflammatory airway response to the Gram-negative bacteria P.nanceiensis was completely TLR2-dependent. These findings demonstrate weak inflammatory properties of Gram-negative airway commensal Prevotella spp. that may make colonization by these bacteria tolerable by the respiratory immune system.
Clonal status of actionable driver events and the timing of mutational processes in cancer evolution

Deciphering whether actionable driver mutations are found in all or a subset of tumor cells will likely be required to improve drug development and precision medicine strategies. We analyzed nine cancer types to determine the subclonal frequencies of driver events, to time mutational processes during cancer evolution, and to identify drivers of subclonal expansions. Although mutations in known driver genes typically occurred early in cancer evolution, we also identified later subclonal “actionable” mutations, including BRAF (V600E), IDH1 (R132H), PIK3CA (E545K), EGFR (L858R), and KRAS (G12D), which may compromise the efficacy of targeted therapy approaches. More than 20% of IDH1 mutations in glioblastomas, and 15% of mutations in genes in the PI3K (phosphatidylinositol 3-kinase)–AKT–mTOR (mammalian target of rapamycin) signaling axis across all tumor types were subclonal. Mutations in the RAS–MEK (mitogen-activated protein kinase kinase) signaling axis were less likely to be subclonal than mutations in genes associated with PI3K-AKT-mTOR signaling. Analysis of late mutations revealed a link between APOBEC-mediated mutagenesis and the acquisition of subclonal driver mutations and uncovered putative cancer genes involved in subclonal expansions, including CTNNA2 and ATXN1. Our results provide a pan-cancer census of driver events within the context of intratumor heterogeneity and reveal patterns of tumor evolution across cancers. The frequent presence of subclonal driver mutations suggests the need to stratify targeted therapy response according to the proportion of tumor cells in which the driver is identified.
Convolutional LSTM Networks for Subcellular Localization of Proteins

Machine learning is widely used to analyze biological sequence data. Non-sequential models such as SVMs or feed-forward neural networks are often used although they have no natural way of handling sequences of varying length. Recurrent neural networks such as the long short term memory (LSTM) model on the other hand are designed to handle sequences. In this study we demonstrate that LSTM networks predict the subcellular location of proteins given only the protein sequence with high accuracy (0.902) outperforming current state of the art algorithms. We further improve the performance by introducing convolutional filters and experiment with an attention mechanism which lets the LSTM focus on specific parts of the protein. Lastly we introduce new visualizations of both the convolutional filters and the attention mechanisms and show how they can be used to extract biologically relevant knowledge from the LSTM networks.

General information
State: Published
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Convolutional LSTM Networks for Subcellular Localization of Proteins

Machine learning is widely used to analyze biological sequence data. Non-sequential models such as SVMs or feed-forward neural networks are often used although they have no natural way of handling sequences of varying length. Recurrent neural networks such as the long short term memory (LSTM) model on the other hand are designed to handle sequences. In this study we demonstrate that LSTM networks predict the subcellular location of proteins given only the protein sequence with high accuracy (0.902) outperforming current state of the art algorithms. We further improve the performance by introducing convolutional filters and experiment with an attention mechanism which lets the LSTM focus on specific parts of the protein. Lastly we introduce new visualizations of both the convolutional filters and the attention mechanisms and show how they can be used to extract biologically relevant knowledge from the LSTM networks.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Functional Human Variation, Department of Applied Mathematics and Computer Science, Cognitive Systems, University of Copenhagen
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Creation of Functional Viruses from Non-Functional cDNA Clones Obtained from an RNA Virus Population by the Use of Ancestral Reconstruction

RNA viruses have the highest known mutation rates. Consequently it is likely that a high proportion of individual RNA virus genomes, isolated from an infected host, will contain lethal mutations and be non-functional. This is problematic if the aim is to clone and investigate high-fitness, functional cDNAs and may also pose problems for sequence-based analysis of viral evolution. To address these challenges we have performed a study of the evolution of classical swine fever virus (CSFV) using deep sequencing and analysis of 84 full-length cDNA clones, each representing individual genomes from a moderately virulent isolate. In addition to here being used as a model for RNA viruses generally, CSFV has high socioeconomic importance and remains a threat to animal welfare and pig production. We find that the majority of the investigated genomes are non-functional and only 12% produced infectious RNA transcripts. Full length sequencing of cDNA clones and deep sequencing of the parental population identified substitutions important for the observed phenotypes. The investigated cDNA clones were furthermore used as the basis for inferring the sequence of functional viruses. Since each unique clone must necessarily be the descendant of a functional ancestor, we hypothesized that it should be possible to produce functional clones by reconstructing ancestral sequences. To test this we used phylogenetic methods to infer two ancestral sequences, which were then reconstructed as cDNA clones. Viruses rescued from the reconstructed cDNAs were tested in cell culture and pigs. Both reconstructed ancestral genomes proved functional, and displayed distinct phenotypes in vitro and in vivo. We suggest that reconstruction of ancestral viruses is a useful tool for experimental and computational investigations of virulence and viral evolution. Importantly, ancestral reconstruction can be done even on the basis of a set of sequences that all correspond to non-functional variants.

General information
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Organisations: National Veterinary Institute, Section for Virology, Department of Systems Biology, Center for Biological Sequence Analysis, Molecular Evolution, Friedrich Loeffler Institute, University of Glasgow
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Scopus rating (2016): CiteScore 3.11 SJR 1.201 SNIP 1.092
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Cyclebase 3.0: a multi-organism database on cell-cycle regulation and phenotypes

The eukaryotic cell division cycle is a highly regulated process that consists of a complex series of events and involves thousands of proteins. Researchers have studied the regulation of the cell cycle in several organisms, employing a wide range of high-throughput technologies, such as microarray-based mRNA expression profiling and quantitative proteomics. Due to its complexity, the cell cycle can also fail or otherwise change in many different ways if important genes are knocked out, which has been studied in several microscopy-based knockdown screens. The data from these many large-scale efforts are not easily accessed, analyzed and combined due to their inherent heterogeneity. To address this, we have created Cyclebase-available at http://www.cyclebase.org-an online database that allows users to easily visualize and download results from genome-wide cell-cycle-related experiments. In Cyclebase version 3.0, we have updated the content of the database to reflect changes to genome annotation, added new mRNA and protein expression data, and integrated cell-cycle phenotype information from high-content screens and model-organism databases. The new version of Cyclebase also features a new web interface, designed around an overview figure that summarizes all the cell-cycle-related data for a gene.

General information
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Number of pages: 5
Danger in the reef: proteome, toxicity, and neutralization of the venom of the olive sea snake, *Aipysurus laevis*

Four specimens of the olive sea snake, *Aipysurus laevis*, were collected off the coast of Western Australia, and the venom proteome was characterized and quantitatively estimated by RP-HPLC, SDS-PAGE, and MALDI-TOF-TOF analyses. *A. laevis* venom is remarkably simple and consists of phospholipases A2 (71.2%), three-finger toxins (3FTx; 25.3%), cysteine-rich secretory proteins (CRISP; 2.5%), and traces of a complement control module protein (CCM; 0.2%). Using a Toxicity Score, the most lethal components were determined to be short neurotoxins. Whole venom had an intravenous LD50 of 0.07 mg/kg in mice and showed a high phospholipase A2 activity, but no proteinase activity in vitro. Preclinical assessment of neutralization and ELISA immunoprofiling showed that BioCSL Sea Snake Antivenom was effective in cross-neutralizing *A. laevis* venom with an ED50 of 821 μg venom per mL antivenom, with a binding preference towards short neurotoxins, due to the high degree of conservation between short neurotoxins from *A. laevis* and *Enhydrina schistosa* venom. Our results point towards the possibility of developing recombinant antibodies or synthetic inhibitors against *A. laevis* venom due to its simplicity.

**General information**

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Copenhagen, Universidad de Costa Rica, Royal Danish Academy of Fine Arts, National Aquarium of Denmark, University of Adelaide
Authors: Laustsen, A. H. (Intern), Gutiérrez, J. M. (Ekstern), Redsted Rasmussen, A. (Ekstern), Engmark, M. (Intern), Gravlund, P. (Ekstern), Sanders, K. L. (Ekstern), Lohse, B. (Ekstern), Lomonte, B. (Ekstern)
Number of pages: 10
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Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.33 SJR 0.752 SNIP 1.056
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.903 SNIP 1.05 CiteScore 2.47
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.972 SNIP 1.104 CiteScore 2.48
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.008 SNIP 1.244 CiteScore 2.9
ISI indexed (2013): ISI indexed yes
Dataset for the proteomic inventory and quantitative analysis of the breast cancer hypoxic secretome associated with osteotropism

The cancer secretome includes all of the macromolecules secreted by cells into their microenvironment. Cancer cell secretomes are significantly different to that of normal cells reflecting the changes that normal cells have undergone during their transition to malignancy. More importantly, cancer secretomes are known to be active mediators of both local and distant host cells and play an important role in the progression and dissemination of cancer. Here we have quantitatively profiled both the composition of breast cancer secretomes associated with osteotropism, and their modulation under normoxic and hypoxic conditions. We detect and quantify 162 secretome proteins across all conditions which show differential hypoxic induction and association with osteotropism. Mass Spectrometry proteomics data have been deposited to the ProteomeXchange Consortium with the dataset identifier PXD000397 and the complete proteomic, bioinformatic and biological analyses are reported in Cox et al. (2015) [1].

General information
State: Published
Organisations: Department of Systems Biology, Cellular Signal Integration, University of Copenhagen, University of Sheffield
Authors: Cox, T. (Ekstern), Schoof, E. (Intern), Gartland, A. (Ekstern), Erler, J. (Ekstern), Linding, R. (Intern)
Number of pages: 5
Pages: 621-625
Publication date: 2015
Main Research Area: Technical/natural sciences

Publication information
Journal: Data in Brief
Volume: 5
ISSN (Print): 2352-3409
Defining the microbial effluxome in the content of the host-microbiome interaction

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Peloponnese, Macquarie University, Harvard Medical School, University of New Mexico
Authors: Ioannidis, A. (Ekstern), Magana, M. (Ekstern), Bologa, C. G. (Ekstern), Oprea, T. I. (Intern), Paulsen, I. T. (Ekstern), Tegos, G. P. (Ekstern)
Number of pages: 5
Publication date: 2015
Main Research Area: Technical/natural sciences

Publication information
Journal: Frontiers in Pharmacology
Volume: 6
Article number: 31
ISSN (Print): 1663-9812
Ratings:
Web of Science (2017): Indexed Yes
Scopus rating (2016): SJR 1.685 SNIP 1.082 CiteScore 3.93
Scopus rating (2015): SJR 1.855 SNIP 1.096 CiteScore 4.05
Web of Science (2015): Indexed yes
Scopus rating (2014): SJR 1.549 SNIP 1.089 CiteScore 3.67
Scopus rating (2013): SJR 1.344 SNIP 0.825 CiteScore 3.16
ISI indexed (2013): ISI indexed no
Scopus rating (2012): SJR 0.71 SNIP 0.783 CiteScore 2.06
ISI indexed (2012): ISI indexed no
Scopus rating (2011): SJR 0.166 SNIP 0.325
ISI indexed (2011): ISI indexed no
Original language: English
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Source-ID: 274769952
Publication: Research - peer-review › Comment/debate – Annual report year: 2015

Determination of specificity influencing residues for key transcription factor families

Transcription factors (TFs) are major modulators of transcription and subsequent cellular processes. The binding of TFs to specific regulatory elements is governed by their specificity. Considering the gap between known TFs sequence and specificity, specificity prediction frameworks are highly desired. Key inputs to such frameworks are protein residues that modulate the specificity of TF under consideration. Simple measures like mutual information (MI) to delineate specificity influencing residues (SIRs) from alignment fail due to structural constraints imposed by the three-dimensional structure of protein. Structural restraints on the evolution of the amino-acid sequence lead to identification of false SIRs. In this manuscript we extended three methods (direct information, PSICOV and adjusted mutual information) that have been used
to disentangle spurious indirect protein residue-residue contacts from direct contacts, to identify SIRs from joint alignments of amino-acids and specificity. We predicted SIRs for homeodomain (HD), helix-loop-helix, Lact and GntR families of TFs using these methods and compared to MI. Using various measures, we show that the performance of these three methods is comparable but better than MI. Implication of these methods in specificity prediction framework is discussed. The methods are implemented as an R package and available along with the alignments at http://stormo.wustl.edu/SpecPred.

**General information**
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Washington University School of Medicine
Authors: Patel, R. Y. (Ekstern), Garde, C. (Intern), Stormo, G. D. (Ekstern)
Number of pages: 9
Pages: 115-123
Publication date: 2015
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Journal: Quantitative Biology
Volume: 3
Issue number: 3
ISSN (Print): 2095-4689
Ratings:
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Original language: English
Protein-DNA interactions, Residue co-variance, Motifs, Co-evolution, Feature selection, Direct information, Specificity determinants
DOIs: 10.1007/s40484-015-0045-y
Source: FindIt
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Publication: Research - peer-review

Developing a Molecular Roadmap of Drug-Food Interactions
Recent research has demonstrated that consumption of food—especially fruits and vegetables—can alter the effects of drugs by interfering either with their pharmacokinetic or pharmacodynamic processes. Despite the recognition of such drug-food associations as an important element for successful therapeutic interventions, a systematic approach for identifying, predicting and preventing potential interactions between food and marketed or novel drugs is not yet available.

The overall objective of this work was to sketch a comprehensive picture of the interference of ∼ 4,000 dietary components present in ∼ 1800 plant-based foods with the pharmacokinetics and pharmacodynamics processes of medicine, with the purpose of elucidating the molecular mechanisms involved. By employing a systems chemical biology approach that integrates data from the scientific literature and online databases, we gained a global view of the associations between diet and dietary molecules with drug targets, metabolic enzymes, drug transporters and carriers currently deposited in Drug-Bank. Moreover, we identified disease areas and drug targets that are most prone to the negative effects of drug-food interactions, showcasing a platform for making recommendations in relation to foods that should be avoided under certain medications. Lastly, by investigating the correlation of gene expression signatures of foods and drugs we were able to generate a completely novel drug-diet interactome map.

**General information**
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Hong Kong
Authors: Jensen, K. (Intern), Ni, Y. (Ekstern), Panagiotou, G. (Ekstern), Kouskoumvekaki, I. (Intern)
Number of pages: 15
Publication date: 2015
Main Research Area: Technical/natural sciences

**Publication information**
Journal: PLoS Computational Biology (Online)
Volume: 11
Issue number: 2
ISSN (Print): 1553-7358
Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed yes
Discovery, genotyping and characterization of structural variation and novel sequence at single nucleotide resolution from de novo genome assemblies on a population scale

Comprehensive recognition of genomic variation in one individual is important for understanding disease and developing personalized medication and treatment. Many tools based on DNA re-sequencing exist for identification of single nucleotide polymorphisms, small insertions and deletions (indels) as well as large deletions. However, these approaches consistently display a substantial bias against the recovery of complex structural variants and novel sequence in individual genomes and do not provide interpretation information such as the annotation of ancestral state and formation mechanism. We present a novel approach implemented in a single software package, AsmVar, to discover, genotype and characterize different forms of structural variation and novel sequence from population-scale de novo genome assemblies up to nucleotide resolution. Application of AsmVar to several human de novo genome assemblies captures a wide spectrum of structural variants and novel sequences present in the human population in high sensitivity and specificity. Our method provides a direct solution for investigating structural variants and novel sequences from de novo genome assemblies, facilitating the construction of population-scale pan-genomes. Our study also highlights the usefulness of the de novo assembly strategy for definition of genome structure.
Discovery of Peptidic Anti-cobratoxins by Next Generation Phage Display

Antivenoms are still being produced by animal immunization protocols and are therefore associated with high immunogenicity for human recipients. Here we report the first step towards discovery of synthetic antitoxins that could be used for development of a fully synthetic antivenom against neurotoxin from cobras (Naja genus).

General information
State: Published
Organisations: Department of Systems Biology, Department of Micro- and Nanotechnology, Fluidic Array Systems and Technology, Center for Biological Sequence Analysis, Network Engineering of Eukaryotic Cell Factories, University of Copenhagen, Universidad de Costa Rica
Authors: Laustsen, A. H. (Intern), Lynagh, T. (Forskerdatabase), Kringelum, J. V. (Intern), Christiansen, A. (Intern), Johannesen, J. (Ekstern), Engmark, M. (Intern), Pless, S. A. (Forskerdatabase), Olsen, L. (Ekstern), Fernández, J. (Ekstern), Gutiérrez, J. M. (Ekstern), Lomonte, B. (Ekstern), Lohse, B. (Ekstern)
Number of pages: 1
Publication date: 2015
Event: Poster session presented at PhD Day 2015, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark.
Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota

In recent years, several associations between common chronic human disorders and altered gut microbiome composition and function have been reported. In most of these reports, treatment regimens were not controlled for and conclusions could thus be confounded by the effects of various drugs on the microbiota, which may obscure microbial causes, protective factors or diagnostically relevant signals. Our study addresses disease and drug signatures in the human gut microbiome of type 2 diabetes mellitus (T2D). Two previous quantitative gut metagenomics studies of T2D patients that were unstratified for treatment yielded divergent conclusions regarding its associated gut microbial dysbiosis. Here we show, using 784 available human gut metagenomes, how antidiabetic medication confounds these results, and analyse in detail the effects of the most widely used anti-diabetic drug metformin. We provide support for microbial mediation of the therapeutic effects of metformin through short-chain fatty acid production, as well as for potential microbiota-mediated mechanisms behind known intestinal adverse effects in the form of a relative increase in abundance of Escherichia species. Controlling for metformin treatment, we report a unified signature of gut microbiome shifts in T2D with a depletion of butyrate-producing taxa. These in turn cause functional microbiome shifts, in part alleviated by metformin-induced changes. Overall, the present study emphasizes the need to disentangle gut microbiota signatures of specific human diseases from those of medication.

General information

State: Published

Organizations: Department of Systems Biology, Center for Biological Sequence Analysis, Integrative Systems Biology, European Molecular Biology Laboratory, Katholieke Universiteit, University of Copenhagen, Capital Region of Denmark, BGI-Shenzhen, INRA Institut National de La Recherche Agronomique, University of Southern Denmark


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BFI (2017): BFI-level 2
Web of Science (2017): Indexed Yes
Scopus rating (2016): CiteScore 13.33
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): CiteScore 14.38
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): CiteScore 14.22
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): CiteScore 14.96
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): CiteScore 14.01
Distinct inflammatory and cytopathic characteristics of *Escherichia coli* isolates from inflammatory bowel disease patients

*Escherichia coli* (*E. coli*) may be implicated in the pathogenesis of inflammatory bowel disease (IBD), as implied from a higher prevalence of mucosa-associated *E. coli* in the gut of IBD-affected individuals. However, it is unclear whether different non-diarrheagenic *E. coli* spp. segregate from each other in their ability to promote intestinal inflammation. Herein we compared the inflammation-inducing properties of non-diarrheagenic LF82, 691-04A, *E. coli* Nissle 1917 (ECN) and eleven new intestinal isolates from different locations in five IBD patients and one healthy control. Viable *E. coli* were cultured with human monocyte-derived dendritic cells (moDCs) and monolayers of intestinal epithelial cells (IECs), followed by analysis of secreted cytokines, intracellular levels of reactive oxygen species and cellular death. The IBD-associated *E. coli* LF82 induced the same dose-dependent inflammatory cytokine profile as ECN and ten of the new *E. coli* isolates displayed as high level IL-12p70, IL-1β, IL-23 and TNF-α from moDCs irrespective of their site of isolation (ileum/colon/faeces), disease origin (diseased/non-diseased) or known virulence factors. Contrarily, 691-04A and one new IBD *E. coli* isolate induced a different cellular phenotype with enhanced killing of moDCs and IECs, coupled to elevated IL-18. The cytopathic nature of 691-04A and one other IBD *E. coli* isolate suggests that colonization with specific non-diarrheagenic *E. coli* could promote intestinal barrier leakage and profound intestinal inflammation, while LF82, ECN and the remaining non-diarrheagenic *E. coli* isolates hold notorious pro-inflammatory characteristics that can progress inflammation in case of intestinal barrier leakage.

**General information**

State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Statens Serum Institut, University of Copenhagen
Authors: Jensen, S. R. (Intern), Mirsepasi-Lauridsen, H. C. (Ekstern), Thysen, A. H. (Intern), Brynskov, J. (Ekstern), Krogfelt, K. A. (Ekstern), Petersen, A. M. (Ekstern), Pedersen, A. E. (Ekstern), Brix, S. (Intern)
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Publication date: 2015
Main Research Area: Technical/natural sciences

**Publication information**

Journal: International Journal of Medical Microbiology
Volume: 305
Issue number: 8
ISSN (Print): 1438-4221
Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): SJR 1.686 SNIP 0.863 CiteScore 3.65
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.788 SNIP 0.833 CiteScore 3.31
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.607 SNIP 0.953 CiteScore 3.62
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.908 SNIP 0.912 CiteScore 4.26
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.834 SNIP 0.972 CiteScore 4.17
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.337 SNIP 0.842 CiteScore 3.43
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.155 SNIP 0.859
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.19 SNIP 1.021
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 1.416 SNIP 1.31
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 1.277 SNIP 0.976
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 1.134 SNIP 0.771
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 1.005 SNIP 0.82
Scopus rating (2004): SJR 1.135 SNIP 0.789
Web of Science (2004): Indexed yes
Scopus rating (2003): SJR 1.074 SNIP 0.795
Web of Science (2003): Indexed yes
Scopus rating (2002): SJR 0.642 SNIP 0.636
Scopus rating (2001): SJR 0.485 SNIP 0.471
Web of Science (2001): Indexed yes
Scopus rating (2000): SJR 0.333 SNIP 0.486
Web of Science (2000): Indexed yes
Scopus rating (1999): SJR 0.423 SNIP 0.418
Original language: English
Cell death, Cytokine profile, Dendritic cells, IBD-associated E. coli, Inflammation
Electronic versions:
Distinct_inflammatory_and_cytopathic_characteristics.pdf
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Source: FindIt
Distinct summer and winter bacterial communities in the active layer of Svalbard permafrost revealed by DNA- and RNA-based analyses

The active layer of soil overlaying permafrost in the Arctic is subjected to dramatic annual changes in temperature and soil chemistry, which likely affect bacterial activity and community structure. We studied seasonal variations in the bacterial community of active layer soil from Svalbard (78°N) by co-extracting DNA and RNA from 12 soil cores collected monthly over a year. PCR amplicons of 16S rRNA genes (DNA) and reverse transcribed transcripts (cDNA) were quantified and sequenced to test for the effect of low winter temperature and seasonal variation in concentration of easily degradable organic matter on the bacterial communities. The copy number of 16S rRNA genes and transcripts revealed no distinct seasonal changes indicating potential bacterial activity during winter despite soil temperatures well below -10°C. Multivariate statistical analysis of the bacterial diversity data (DNA and cDNA libraries) revealed a season-based clustering of the samples, and, e.g., the relative abundance of potentially active Cyanobacteria peaked in June and Alphaproteobacteria increased over the summer and then declined from October to November. The structure of the bulk (DNA-based) community was significantly correlated with pH and dissolved organic carbon, while the potentially active (RNA-based) community structure was not significantly correlated with any of the measured soil parameters. A large fraction of the 16S rRNA transcripts was assigned to nitrogen-fixing bacteria (up to 24% in June) and phototrophic organisms (up to 48% in June) illustrating the potential importance of nitrogen fixation in otherwise nitrogen poor Arctic ecosystems and of phototrophic bacterial activity on the soil surface.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Copenhagen, Lawrence Berkeley National Laboratory, Pacific Northwest National Laboratory
Authors: Schostag, M. (Ekstern), Stibal, M. (Ekstern), Jacobsen, C. S. (Ekstern), Bælum, J. (Intern), Tas, N. (Ekstern), Elberling, B. (Ekstern), Jansson, J. K. (Ekstern), Semenchuk, P. (Ekstern), Prieme, A. (Ekstern)
Number of pages: 13
Publication date: 2015
Main Research Area: Technical/natural sciences

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Journal: Frontiers in Microbiology
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Article number: 399
ISSN (Print): 1664-302X
Ratings:
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BFI (2017): BFI-level 1
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 4.16 SJR 1.731 SNIP 1.172
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.878 SNIP 1.208 CiteScore 4.15
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.861 SNIP 1.16 CiteScore 3.76
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.751 SNIP 0.951 CiteScore 3.56
ISI indexed (2013): ISI indexed no
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.415 SNIP 0.725 CiteScore 2.78
ISI indexed (2012): ISI indexed no
Scopus rating (2011): SJR 0.626 SNIP 0.187
Web of Science (2011): Indexed yes
Original language: English
Permafrost active layer, Seasonal variation, Bacterial community structure, 16SrRNA gene, Arctic
Titanium (Ti) is a widely used material for surgical implants; total joint replacements (TJRs), screws and plates for fixing bones and dental implants are forged from Ti. Whilst Ti integrates well into host tissue approximately 10% of TJRs will fail in the lifetime of the patient through a process known as aseptic loosening. These failures necessitate revision arthroplasties which are more complicated and costly than the initial procedure. Finding ways of enhancing early (osseo)integration of TJRs is therefore highly desirable and continues to represent a research priority in current biomaterial design. One way of realising improvements in implant quality is to coat the Ti surface with small biological agents known to support human osteoblast formation and maturation at Ti surfaces. Lysophosphatidic acid (LPA) and certain LPA analogues offer potential solutions as Ti coatings in reducing aseptic loosening. Herein we present evidence for the successful bio-functionalisation of Ti using LPA. This modified Ti surface heightened the maturation of human osteoblasts, as supported by increased expression of alkaline phosphatase. These functionalised surfaces also deterred the attachment and growth of Staphylococcus aureus, a bacterium often associated with implant failures through sepsis. Collectively we provide evidence for the fabrication of a dual-action Ti surface finish, a highly desirable feature towards the development of next-generation implantable devices.
Early Divergent Strains of Yersinia pestis in Eurasia 5,000 Years Ago

The bacteria Yersinia pestis is the etiological agent of plague and has caused human pandemics with millions of deaths in historic times. How and when it originated remains contentious. Here, we report the oldest direct evidence of Yersinia pestis identified by ancient DNA in human teeth from Asia and Europe dating from 2,800 to 5,000 years ago. By sequencing the genomes, we find that these ancient plague strains are basal to all known Yersinia pestis. We find the origins of the Yersinia pestis lineage to be at least two times older than previous estimates. We also identify a temporal sequence of genetic changes that lead to increased virulence and the emergence of the bubonic plague. Our results show that plague infection was endemic in the human populations of Eurasia at least 3,000 years before any historical recordings of pandemics.

Bibliographical note

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Early Divergent Strains of Yersinia pestis in Eurasia 5,000 Years Ago

The bacteria Yersinia pestis is the etiological agent of plague and has caused human pandemics with millions of deaths in historic times. How and when it originated remains contentious. Here, we report the oldest direct evidence of Yersinia pestis identified by ancient DNA in human teeth from Asia and Europe dating from 2,800 to 5,000 years ago. By sequencing the genomes, we find that these ancient plague strains are basal to all known Yersinia pestis. We find the origins of the Yersinia pestis lineage to be at least two times older than previous estimates. We also identify a temporal sequence of genetic changes that lead to increased virulence and the emergence of the bubonic plague. Our results show that plague infection was endemic in the human populations of Eurasia at least 3,000 years before any historical recordings of pandemics.

General information

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Metagenomics, Molecular Evolution, Eucaryotic Molecular Cell Biology, Integrative Systems Biology, University of Copenhagen, National Academy of Sciences of the Republic of Armenia, South Ural State University, Orenburg Museum of Fine Arts, Yerevan State University, University of Tartu, University of Wroclaw, Peter the Great Museum of Anthropology and Ethnography, University of Cambridge, University of California, University of Gothenburg
Number of pages: 12
Ebolavirus comparative genomics

The 2014 Ebola outbreak in West Africa is the largest documented for this virus. To examine the dynamics of this genome, we compare more than 100 currently available ebolavirus genomes to each other and to other viral genomes. Based on oligomer frequency analysis, the family Filoviridae forms a distinct group from all other sequenced viral genomes. All filovirus genomes sequenced to date encode proteins with similar functions and gene order, although there is considerable divergence in sequences between the three genera *Ebolavirus*, *Cuevavirus* and *Marburgvirus* within the family Filoviridae. Whereas all ebolavirus genomes are quite similar (multiple sequences of the same strain are often identical), variation is most common in the intergenic regions and within specific areas of the genes encoding the glycoprotein (GP), nucleoprotein (NP) and polymerase (L). We predict regions that could contain epitope-binding sites, which might be good vaccine targets. This information, combined with glycosylation sites and experimentally determined epitopes, can identify the most promising regions for the development of therapeutic strategies.

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**General information**

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Oak Ridge National Laboratory, Boozé Allen Hamilton, Molecular Microbiology and Genomics Consultants
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Volume: 479
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BFI (2018): BFI-level 2
BFI (2017): BFI-level 2
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 13.54
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): CiteScore 13.38
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): CiteScore 12.9
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): CiteScore 13.78
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
Environmental genes and genomes: understanding the differences and challenges in the approaches and software for their analyses

DNA-based taxonomic and functional profiling is widely used for the characterization of organismal communities across a rapidly increasing array of research areas that include the role of microbiomes in health and disease, biomonitoring, and estimation of both microbial and metazoan species richness. Two principal approaches are currently used to assign taxonomy to DNA sequences: DNA metabarcoding and metagenomics. When initially developed, each of these approaches mandated their own particular methods for data analysis; however, with the development of high-throughput sequencing (HTS) techniques they have begun to share many aspects in data set generation and processing. In this review we aim to define the current characteristics, goals and boundaries of each field, and describe the different software used for their analysis. We argue that an appreciation of the potential and limitations of each method can help underscore the improvements required by each field so as to better exploit the richness of current HTS-based data sets.
Epitopic Profiling of Antibody Response against Neurotoxins from the Black Mamba (Dendroaspis polyepis)

The black mamba (Dendroaspis Polyepis) is among the most dangerous snakes in the world, with a venom dominated by three-finger toxins and dendrotoxins. Among the three-finger toxins, the α-neurotoxins (α-NT) are the most important, and these are conserved between snake species. Cross-reactivity between three-finger toxins is known to occur, and understanding this phenomenon in depth may help guide future design of antivenoms to obtain optimal specificity against medically important toxins from different snake species. Using a bioinformatic approach, we investigated the cross-
reactivity between three-finger toxins for a rabbit antiserum raised against short neurotoxin 1 from *D. polylepis* (SN1-DP).

**General information**

State: Published

Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Network Engineering of Eukaryotic Cell Factories, Universidad de Costa Rica, University of Copenhagen

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Establishment and characterization of models of chemotherapy resistance in colorectal cancer: Towards a predictive signature of chemoresistance

Current standard treatments for metastatic colorectal cancer (CRC) are based on combination regimens with one of the two chemotherapeutic drugs, irinotecan or oxaliplatin. However, drug resistance frequently limits the clinical efficacy of these therapies. In order to gain new insights into mechanisms associated with chemoresistance, and departing from three distinct CRC cell models, we generated a panel of human colorectal cancer cell lines with acquired resistance to either oxaliplatin or irinotecan. We characterized the resistant cell line variants with regards to their drug resistance profile and transcriptome, and matched our results with datasets generated from relevant clinical material to derive putative resistance biomarkers. We found that the chemoresistant cell line variants had distinctive irinotecan- or oxaliplatin-specific resistance profiles, with non-reciprocal cross-resistance. Furthermore, we could identify several new, as well as some previously described, drug resistance-associated genes for each resistant cell line variant. Each chemoresistant cell line variant acquired a unique set of changes that may represent distinct functional subtypes of chemotherapy resistance. In addition, and given the potential implications for selection of subsequent treatment, we also performed an exploratory analysis, in relevant patient cohorts, of the predictive value of each of the specific genes identified in our cellular models.

**General information**

State: Published

Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Integrative Systems Biology, Functional Human Variation, University of Copenhagen, Aarhus University Hospital, University of Southern Denmark, University of Lausanne, University Hospital Gasthuisberg, University Hospital of Geneva, Masaryk University

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Web of Science (2016): Indexed yes

BFI (2015): BFI-level 1

Scopus rating (2015): SJR 2.84 SNIP 1.308 CiteScore 5.65

Web of Science (2015): Indexed yes

BFI (2014): BFI-level 1
Evidence of interactions between aroma compounds and the CB1 receptor opens new routes for regulation of food intake

**General information**

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Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Integrative Systems Biology, Universite de Bourgogne
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Web of Science (2017): Indexed Yes

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BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.437 SNIP 1.15 CiteScore 2.83
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.618 SNIP 1.109 CiteScore 3.23
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.333 SNIP 1.164 CiteScore 2.65
ISI indexed (2013): ISI indexed yes
Evolutionary Genomics and Conservation of the Endangered Przewalski's Horse

Przewalski's horses (PHs, Equus ferus ssp. przewalskii) were discovered in the Asian steppes in the 1870s and represent the last remaining true wild horses. PHs became extinct in the wild in the 1960s but survived in captivity, thanks to major conservation efforts. The current population is still endangered, with just 2,109 individuals, one-quarter of which are in Chinese and Mongolian reintroduction reserves [1]. These horses descend from a founding population of 12 wild-caught PHs and possibly up to four domesticated individuals [2, 3 and 4]. With a stocky build, an erect mane, and stripped and short legs, they are phenotypically and behaviorally distinct from domesticated horses (DHs, Equus caballus). Here, we sequenced the complete genomes of 11 PHs, representing all founding lineages, and five historical specimens dated to 1878–1929 CE, including the Holotype. These were compared to the hitherto-most-extensive genome dataset characterized for horses, comprising 21 new genomes. We found that loci showing the most genetic differentiation with DHs were enriched in genes involved in metabolism, cardiac disorders, muscle contraction, reproduction, behavior, and signaling pathways. We also show that DH and PH populations split ~45,000 years ago and have remained connected by gene-flow thereafter. Finally, we monitor the genomic impact of ~110 years of captivity, revealing reduced heterozygosity, increased inbreeding, and variable introgression of domestic alleles, ranging from non-detectable to as much as 31.1%. This, together with the identification of ancestry informative markers and corrections to the International Studbook, establishes a framework for evaluating the persistence of genetic variation in future reintroduced populations.

General information

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Metagenomics, University of Copenhagen, University of California, University College London, Hebrew University of Jerusalem, CSIC, San Diego Zoo’s Institute for Conservation Research, Agroscope, University of Bern, Tour du Valat, Leibniz Institute for Zoo and Wildlife Research, Russian Academy of Sciences, EAZA Equid TAG, Martin-Luther University, University of Minnesota
Number of pages: 7
Evolution of substrate recognition sites (SRSs) in cytochromes P450 from Apiaceae exemplified by the CYP71AJ subfamily

Background: Large proliferations of cytochrome P450 encoding genes resulting from gene duplications can be termed as 'blooms', providing genetic material for the genesis and evolution of biosynthetic pathways. Furanocoumarins are allelochemicals produced by many of the species in Apiaceous plants belonging to the Apioideae subfamily of Apiaceae and have been described as being involved in the defence reaction against phytophageous insects. Results: A bloom in the cytochromes P450 CYP71AJ subfamily has been identified, showing at least 2 clades and 6 subclades within the CYP71AJ subfamily. Two of the subclades were functionally assigned to the biosynthesis of furanocoumarins. Six substrate recognition sites (SRS1-6) important for the enzymatic conversion were investigated in the described cytochromes P450 and display significant variability within the CYP71AJ subfamily. Homology models underline a significant modification of the accession to the iron atom, which might explain the difference of the substrate specificity between the cytochromes P450 restricted to furanocoumarins as substrates and the orphan CYP71AJ. Conclusion: Two subclades functionally assigned to the biosynthesis of furanocoumarins and four other subclades were identified and shown to be part of two distinct clades within the CYP71AJ subfamily. The subclades show significant variability within their substrate recognition sites between the clades, suggesting different biochemical functions and providing insights into the evolution of cytochrome P450 'blooms' in response to environmental pressures.
Exposure to perfluorononanoic acid combined with a low-dose mixture of 14 human-relevant compounds disturbs energy/lipid homeostasis in rats

Humans are constantly exposed to a significant number of compounds and many are readily detected in human body fluids. Worryingly, several of these compounds are either suspected to be, or have already been shown to be harmful to humans either individually or in combination. However, the potential consequences of low-dose exposure to complex mixtures remain poorly understood. We have profiled the effects on rat blood plasma and liver homeostasis using metabolomics and transcriptomics following 2-week exposure to either a mixture of 14 common chemicals (Mix), perfluorononanoic acid (PFNA) at low (0.0125 mg/kg/day) or mid (0.25 mg/kg/day) doses, or a combination of Mix and PFNA. In blood plasma, 63 and 64 metabolites were significantly changed upon exposure to Mix alone or PFNA + Mix, respectively. Twelve of the metabolites were identified and comprised mainly lipids, with various lipid classes differentially affected across study groups. In the liver, expression of 182 and 203 genes—mainly related to energy homeostasis and lipid metabolism—were differentially expressed upon exposure to PFNA alone or PFNA + Mix, respectively. In general, Mix alone affected lipid metabolism evident in blood plasma, whereas effects on lipid metabolism in the liver were mainly driven by PFNA. This study verifies that a chemical mixture given at high-end human exposure levels can affect lipid homeostasis and that the combined use of metabolomics and transcriptomics can provide complimentary information allowing for a detailed analysis of affected signaling pathways.
FluKB: A Knowledge-Based System for Influenza Vaccine Target Discovery and Analysis of the Immunological Properties of Influenza Viruses

FluKB is a knowledge-based system focusing on data and analytical tools for influenza vaccine discovery. The main goal of FluKB is to provide access to curated influenza sequence and epitope data and enhance the analysis of influenza sequence diversity and the analysis of targets of immune responses. FluKB consists of more than 400,000 influenza protein sequences, known epitope data (357 verified T-cell epitopes, 685 HLA binders, and 16 naturally processed MHC ligands), and a collection of 28 influenza antibodies and their structurally defined B-cell epitopes. FluKB was built using a modular framework allowing the implementation of analytical workflows and includes standard search tools, such as keyword search and sequence similarity queries, as well as advanced tools for the analysis of sequence variability. The advanced analytical tools for vaccine discovery include visual mapping of T- and B-cell vaccine targets and assessment of neutralizing antibody coverage. FluKB supports the discovery of vaccine targets and the analysis of viral diversity and its implications for vaccine discovery as well as potential T-cell breadth and antibody cross neutralization involving multiple strains. FluKB is a representation of a new generation of databases that integrates data, analytical tools, and analytical workflows that enable comprehensive analysis and automatic generation of analysis reports.
Functional Analysis of a Carotid Intima-Media Thickness Locus Implicates BCAR1 and Suggests a Causal Variant

Carotid intima-media thickness (IMT) is a marker of subclinical atherosclerosis that can predict cardiovascular disease events over traditional risk factors. This study examined the BCAR1-CFDP1-TMEM170A locus on chromosome 16, associated with carotid IMT and coronary artery disease in the IMT and IMT-Progression as Predictors of Vascular Events (IMPROVE) cohort, to identify the functional variant. In analysis of the locus lead single nucleotide polymorphism (SNP: rs4888378, intronic in CFDP1) in Progressione della Lesione Intimale Carotidea (PLIC), the protective AA genotype was associated with slower IMT progression in women (P=0.04) but not in men. Meta-analysis of 5 cohort studies also supported a protective effect of the A allele on common carotid IMT in women only (women: \( \beta = -0.0047, P = 1.63 \times 10^{-4} \); men: \( \beta = -0.0029, P = 0.0678 \)). Two hundred fourteen noncoding variants in strong linkage disequilibrium \( (r^2 \geq 0.8) \) with rs4888378 were identified from 1000 Genome Project. ENCODE regulatory chromatin marks were used to create a shortlist of 6 possible regulatory variants. Electrophoretic mobility shift assays on the shortlist detected allele-specific protein binding to the lead SNP rs4888378; multiplexed competitor electrophoretic mobility shift assays implicated FOXA.
as the protein. Luciferase reporter assays on rs4888378 showed a significant 35% to 92% ($P=0.0057; P=4.0\times10^{-22}$) decrease in gene expression with the A allele. Expression quantitative trait loci analysis confirmed previously reported associations of rs4888378 with BCAR1 in vascular tissues. Molecular studies suggest the lead SNP as a potentially causal SNP at the BCAR1-CFDP1-TMEM170A locus, and expression quantitative trait loci studies implicate BCAR1 as the causal gene. This variant showed stronger effects on common carotid IMT in women, raising questions about the mechanism of the causal SNP on atherosclerosis.

Gene expression analysis identifies global gene dosage sensitivity in cancer

Many cancer-associated somatic copy number alterations (SCNAs) are known. Currently, one of the challenges is to identify the molecular downstream effects of these variants. Although several SCNAs are known to change gene expression levels, it is not clear whether each individual SCNA affects gene expression. We reanalyzed 77,840 expression profiles and observed a limited set of ‘transcriptional components’ that describe well-known biology, explain the vast majority of variation in gene expression and enable us to predict the biological function of genes. On correcting expression profiles for these components, we observed that the residual expression levels (in ‘functional genomic mRNA’ profiling) correlated strongly with copy number. DNA copy number correlated positively with expression levels for 99% of all abundantly expressed human genes, indicating global gene dosage sensitivity. By applying this method to 16,172 patient-derived tumor samples, we replicated many loci with aberrant copy numbers and identified recurrently disrupted genes in genomically unstable cancers.
Genetic studies of body mass index yield new insights for obesity biology

Obesity is heritable and predisposes to many diseases. To understand the genetic basis of obesity better, here we conduct a genome-wide association study and MetaChip meta-analysis of body mass index (BMI), a measure commonly used to define obesity and assess adiposity, in up to 339,224 individuals. This analysis identifies 97 BMI-associated loci (P < 5 x 10^{-8}), 56 of which are novel. Five loci demonstrate clear evidence of several independent association signals, and many loci have significant effects on other metabolic phenotypes. The 97 loci account for similar to 2.7% of BMI variation, and genome-wide estimates suggest that common variation accounts for >20% of BMI variation. Pathway analyses provide strong support for a role of the central nervous system in obesity susceptibility and implicate new genes and pathways, including those related to synaptic function, glutamate signalling, insulin secretion/action, energy metabolism, lipid biology, and adipogenesis.

General information

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, National Cancer Institute, University of North Carolina at Chapel Hill, University of Cambridge, Boston Children's Hospital, University of North Carolina, University of Queensland, Brigham and Women's Hospital, Statens Serum Institut, University of Copenhagen, Karolinska Institutet, University of Michigan, Steno Diabetes Centre
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Web of Science (2017): Indexed Yes
One unreported case of extended-spectrum-beta-lactamase (ESBL)-producing Salmonella enterica serovar Typhi was identified, whole-genome sequence typed, among other analyses, and compared to other available genomes of S. Typhi. The reported strain was similar to a previously published strain harboring blaSHV-12 from the Philippines and likely part of an undetected outbreak, the first of ESBL-producing S. Typhi.
Scopus rating (2003): SJR 1.845 SNIP 1.855
Web of Science (2003): Indexed yes
Scopus rating (2002): SJR 1.947 SNIP 1.722
Web of Science (2002): Indexed yes
Scopus rating (2001): SJR 2.076 SNIP 1.808
Web of Science (2001): Indexed yes
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Web of Science (2000): Indexed yes
Scopus rating (1999): SJR 1.851 SNIP 2.036

Genomic Epidemiology

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Research Group for Genomic Epidemiology, National Food Institute
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Genomic evidence for the Pleistocene and recent population history of Native Americans

How and when the Americas were populated remains contentious. Using ancient and modern genome-wide data, we found that the ancestors of all present-day Native Americans, including Athabascans and Amerindians, entered the Americas as a single migration wave from Siberia no earlier than 23 thousand years ago (ka) and after no more than an 8000-year isolation period in Beringia. After their arrival to the Americas, ancestral Native Americans diversified into two basal genetic branches around 13 ka, one that is now dispersed across North and South America and the other restricted to North America. Subsequent gene flow resulted in some Native Americans sharing ancestry with present-day East Asians (including Siberians) and, more distantly, Australo-Melanesians. Putative "Paleoamerican" relict populations, including the historical Mexican Pericues and South American Fuego-Patagonians, are not directly related to modern Australo-Melanesians as suggested by the Paleoamerican Model.

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Metagenomics, University of Copenhagen, University of California, Wellcome Trust Genome Campus, Pennsylvania State University
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Genomic profiling of thousands of candidate polymorphisms predicts risk of relapse in 778 Danish and German childhood acute lymphoblastic leukemia patients

Childhood acute lymphoblastic leukemia survival approaches 90%. New strategies are needed to identify the 10–15% who evade cure. We applied targeted, sequencing-based genotyping of 25 000 to 34 000 preselected potentially clinically relevant single-nucleotide polymorphisms (SNPs) to identify host genome profiles associated with relapse risk in 352 patients from the Nordic ALL92/2000 protocols and 426 patients from the German Berlin–Frankfurt–Munster (BFM) ALL2000 protocol. Patients were enrolled between 1992 and 2008 (median follow-up: 7.6 years). Eleven cross-validated SNPs were significantly associated with risk of relapse across protocols. SNP and biologic pathway level analyses associated relapse risk with leukemia aggressiveness, glucocorticosteroid pharmacology/response and drug transport/metabolism pathways. Classification and regression tree analysis identified three distinct risk groups defined by end of induction residual leukemia, white blood cell count and variants in myeloperoxidase (MPO), estrogen receptor 1 (ESR1), lamin B1 (LMNB1) and matrix metalloproteinase-7 (MMP7) genes, ATP-binding cassette transporters and glucocorticosteroid transcription regulation pathways. Relapse rates ranged from 4% (95% confidence interval (CI): 1.6–6.3%) for the best group (72% of patients) to 76% (95% CI: 41–90%) for the worst group (5% of patients, P<0.001). Validation of these findings and similar approaches to identify SNPs associated with toxicities may allow future individualized relapse and toxicity risk-based treatments adaptation.
Retrospectively, we investigated the epidemiology of a massive Salmonella enterica serovar Typhi outbreak in Zambia during 2010 to 2012. Ninety-four isolates were susceptibility tested by MIC determinations. Whole-genome sequence typing (WGST) of 33 isolates and bioinformatic analysis identified the multilocus sequence type (MLST), haplotype, plasmid replicon, antimicrobial resistance genes, and genetic relatedness by single nucleotide polymorphism (SNP) analysis and genomic deletions. The outbreak affected 2,040 patients, with a fatality rate of 0.5%. Most (83.0%) isolates were multidrug resistant (MDR). The isolates belonged to MLST ST1 and a new variant of the haplotype, H58B. Most isolates contained a chromosomally translocated region containing seven antimicrobial resistance genes, catA1, blaTEM-1, dfrA7, sul1, sul2, strA, and strB, and fragments of the incompatibility group Q1 (IncQ1) plasmid replicon, the class 1 integron, and the mer operon. The genomic analysis revealed 415 SNP differences overall and 35 deletions among 33 of the isolates subjected to whole-genome sequencing. In comparison with other genomes of H58, the Zambian isolates separated from genomes from Central Africa and India by 34 and 52 SNPs, respectively. The phylogenetic analysis indicates that 32 of the 33 isolates sequenced belonged to a tight clonal group distinct from other H58 genomes included in the study. The small numbers of SNPs identified within this group are consistent with the short-term transmission that can be expected over a period of 2 years. The phylogenetic analysis and deletions suggest that a single MDR clone was responsible for the outbreak, during which occasional other S. Typhi lineages, including sensitive ones, continued to cocirculate. The common view is that the emerging global S. Typhi haplotype, H58B, containing the MDR IncHI1 plasmid is responsible for the majority of typhoid infections in Asia and sub-Saharan Africa; we found that a new variant of the haplotype harboring a chromosomally translocated region containing the MDR islands of IncHI1 plasmid has emerged in Zambia. This could change the perception of the term “classical MDR typhoid” currently being solely associated with the IncHI1 plasmid. It might be more common than presently thought that S. Typhi haplotype H58B harbors the IncHI1 plasmid or a chromosomally translocated MDR region or both.
Germ Cell Cancer and Multiple Relapses: Toxicity and Survival

Purpose: A small number of patients with germ cell cancer (GCC) receive more than one line of treatment for disseminated disease. The purpose of this study was to evaluate late toxicity and survival in an unselected cohort of patients who experienced relapse after receiving first-line treatment for disseminated disease. Methods: From the Danish Testicular Cancer database, we identified all patients who received more than one line of treatment for disseminated disease. Information about late toxicity and mortality was obtained by means of linkage to national registers. Prognostic factors for relapse and death were identified and compared with the International Prognostic Factors Study Group (IPFSG) classification. Results: In total, 268 patients received more than one line of treatment for disseminated GCC. Approximately half of patients (n = 136) died as a result of GCC. The 132 remaining patients, compared with patients treated with only orchietomy, had an increased risk for a second cancer (hazard ratio [HR], 3.2; 95% CI, 1.9 to 5.5), major cardiovascular disease (HR, 1.9; 95% CI, 1.0 to 3.3), pulmonary disease (HR, 2.0; 95% CI, 1.0 to 3.8), GI disease (HR, 7.3; 95% CI, 3.6 to 14.8), renal impairment (HR, 8.3; 95% CI, 3.0 to 23.2), neurologic disorders (HR, 6.3; 95% CI, 3.1 to 12.6), and death as a result of other causes (HR, 2.6; 95% CI, 1.6 to 4.2). In large part, the IPFSG classification was confirmed in our population; however, we could not confirm the primary site and the level of human chorionic gonadotropin as independent factors. We identified increasing age as a possible new prognostic factor for treatment failure after second-line treatment (HR, 1.2 per 10 years; 95% CI, 1.2 to 15). Conclusion: Patients with GCC who survive after more than one line of treatment for disseminated disease have a highly increased risk of late toxicity and death as a result of causes other than GCC. Therefore, they should be candidates for life-long follow-up. The IPFSG classification was confirmed in this unselected population.
Gliadin affects glucose homeostasis and intestinal metagenome in C57BL/6 mice fed a high-fat diet

Dietary gluten and its component gliadin are well-known environmental triggers of celiac disease and important actors in type-1 diabetes, and are reported to induce alterations in the intestinal microbiota. However, research on the impact of gluten on type-2 diabetes in non-celiac subjects is more limited. The aim of this study was to investigate the effect of gliadin on glucose homeostasis and intestinal ecology in the mouse.

Forty male C57BL/6 mice were fed a high-fat diet containing either 4% gliadin or no gliadin for 22 weeks. Gliadin consumption significantly increased the HbA1c level over time, with a borderline significance of higher HOMA-IR (homeostasis model assessment of insulin resistance) after 22 weeks. Sequencing of the V3 region of the bacterial 16S rRNA genes showed that gliadin altered the abundance of 81 bacterial taxa, separating the intestinal microbial profile of the gliadin consuming mice from the control mice in the principal coordinate analysis (PCoA) of weighted UniFrac distance. Moreover, gliadin reduced the ileal gene expression of tight junction protein 1, occludin, cadherin 1, mucin 2 and mucin 3, indicating an impaired intestinal barrier function. No difference was found in body weight gain, feed consumption or circulating cytokines (IL-1β, IL-6, IFN-γ, TNF-α and IL-10).

Our study is the first to show that gliadin as part of a defined synthetic feed exacerbates the glycaemia and alters the intestinal microbiota composition. Comprehensive analyses of metabolites, histological sections and the profile of specific
immune cells are in progress to elucidate the mechanism behind the observed effects.
Glioblastoma adaptation traced through decline of an IDH1 clonal driver and macro-evolution of a double-minute chromosome

**Background:** Glioblastoma (GBM) is the most common malignant brain cancer occurring in adults, and is associated with dismal outcome and few therapeutic options. GBM has been shown to predominantly disrupt three core pathways through somatic aberrations, rendering it ideal for precision medicine approaches.

**Methods:** We describe a 35 year-old female patient with recurrent GBM following surgical removal of the primary tumor, adjuvant treatment with temozolomide, and a 3-year disease-free period. Rapid whole genome sequencing (WGS) of three separate tumour regions at recurrence was performed and interpreted relative to WGS of two regions of the primary tumour.

**Results** We found extensive mutational and copy number heterogeneity within the primary tumour. We identified a TP53 mutation and two focal amplifications involving PDGFRA, KIT and CDK4, on chromosomes 4 and 12. A clonal IDH1 R132H mutation in the primary, a known GBM driver event, was detectable at only very low frequency in the recurrent tumour. After subclonal diversification, evidence was found for a whole genome-doubling event and a translocation between the amplified regions of PDGFRA, KIT and CDK4, encoded within a double minute chromosome also incorporating miR26a-2. The WGS analysis uncovered progressive evolution of the double minute chromosome converging on the KIT/PDGFRA/PI3K/mTOR axis, superseding the IDH1 mutation in dominance in a mutually exclusive manner at recurrence, consequently the patient was treated with imatinib. Despite rapid sequencing and cancer-genome guided therapy against amplified oncogenes, the disease progressed, and the patient died shortly after.

**Conclusions:** This case sheds light on the dynamic evolution of a GBM tumor, defining the origins of the lethal subclone, the macroevolutionary genomic events dominating the disease at recurrence and the loss of a clonal driver. Even in the era of rapid WGS analysis, cases such as this illustrate the significant hurdles for precision medicine success.

**General information**

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Number of pages: 8
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Glioblastoma, Multi-region sequencing, Intra-tumour heterogeneity, Double minute chromosome

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- Glioblastoma_adaptation_traced_through.pdf

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- 10.1093/annonc/mdv127
Global gene expression profiling of brown to white adipose tissue transformation in sheep reveals novel transcriptional components linked to adipose remodeling

Background: Large mammals are capable of thermoregulation shortly after birth due to the presence of brown adipose tissue (BAT). The majority of BAT disappears after birth and is replaced by white adipose tissue (WAT).

Results: We analyzed the postnatal transformation of adipose in sheep with a time course study of the perirenal adipose depot. We observed changes in tissue morphology, gene expression and metabolism within the first two weeks of postnatal life consistent with the expected transition from BAT to WAT. The transformation was characterized by massively decreased mitochondrial abundance and down-regulation of gene expression related to mitochondrial function and oxidative phosphorylation. Global gene expression profiling demonstrated that the time points grouped into three phases: a brown adipose phase, a transition phase and a white adipose phase. Between the brown adipose and the transition phase 170 genes were differentially expressed, and 717 genes were differentially expressed between the transition and the white adipose phase. Thirty-eight genes were shared among the two sets of differentially expressed genes. We identified a number of regulated transcription factors, including NR1H3, MYC, KLF4, ESR1, RELA and BCL6, which were linked to the overall changes in gene expression during the adipose tissue remodeling. Finally, the perirenal adipose tissue expressed both brown and brite/beige adipocyte marker genes at birth, the expression of which changed substantially over time.

Conclusions: Using global gene expression profiling of the postnatal BAT to WAT transformation in sheep, we provide novel insight into adipose tissue plasticity in a large mammal, including identification of novel transcriptional components linked to adipose tissue remodeling. Moreover, our data set provides a useful resource for further studies in adipose tissue plasticity.
Hand eczema and stratum corneum ceramides

Background: Hand eczema (HE) is a multifactorial disease, comprising different aetiological conditions and different morphologies. There are two aetiologically distinct groups of HE recognised: exogenous, such as contact dermatitis (allergic and/or irritant HE) and endogenous, such as the classic hyperkeratotic HE. Differences in the skin barrier properties of these two conditions could theoretically be expected.

Aim: To examine whether differences exist in the lipid profile and the susceptibility of the stratum corneum (SC) in patients with allergic/irritant HE and those with hyperkeratotic HE.

Methods: Using cyanoacrylate, SC samples were taken from 23 patients with allergic/irritant HE and 15 with hyperkeratotic HE for lipid analysis by high-performance thin-layer chromatography (HPTLC). Samples were also taken from adjacent, unaffected skin. Severity of HE was assessed by the Hand Eczema Severity Index (HECSI), and skin barrier susceptibility was assessed by measuring transepidermal water loss (TEWL) after a 24-hour patch test with sodium lauryl sulfate (SLS).
Results: No statistically significant difference was found between groups for the lipid analysis or for skin susceptibility to SLS. We found a significantly higher HECSI score for hyperkeratotic HE compared with irritant or allergic HE (P=0.02).

Conclusions: There appears to be no difference in skin barrier between allergic/irritant HE (exogenous eczema) and hyperkeratotic HE (endogenous eczema) with regard to SC lipids or susceptibility to SLS.
High-throughput epitope identification for snakebite antivenom

Insight into the epitopic recognition pattern for polyclonal antivenoms is a strong tool for accurate prediction of antivenom cross-reactivity and provides a basis for design of novel antivenoms. In this work, a high-throughput approach was applied to characterize linear epitopes in 966 individual toxins from pit vipers (Crotalidae) using the ICP Crotalidae antivenom. Due to an abundance of snake venom metalloproteinases and phospholipase A2s in the venoms used for production of the investigated antivenom, this study focuses on these toxin families.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Regulatory Genomics, Network Engineering of Eukaryotic Cell Factories, Universidad de Costa Rica, University of Copenhagen
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High-throughput sequencing enhanced phage display enables the identification of patient-specific epitope motifs in serum

Phage display is a prominent screening technique with a multitude of applications including therapeutic antibody development and mapping of antigen epitopes. In this study, phages were selected based on their interaction with patient serum and exhaustively characterised by high-throughput sequencing. A bioinformatics approach was developed in order to identify peptide motifs of interest based on clustering and contrasting to control samples. Comparison of patient and control samples confirmed a major issue in phage display, namely the selection of unspecific peptides. The potential of the bioinformatic approach was demonstrated by identifying epitopes of a prominent peanut allergen, Ara h 1, in sera from patients with severe peanut allergy. The identified epitopes were confirmed by high-density peptide micro-arrays. The present study demonstrates that high-throughput sequencing can empower phage display by (i) enabling the analysis of complex biological samples, (ii) circumventing the traditional laborious picking and functional testing of individual phage clones and (iii) reducing the number of selection rounds.

General information
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Organisations: Department of Micro- and Nanotechnology, Fluidic Array Systems and Technology, Department of Systems Biology, Center for Biological Sequence Analysis, National Food Institute, Regulatory Genomics, Roche NimbleGen, Institute of Food Research, Medical University of Vienna
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Identification of Disease Relevant Post Translational Modifications of Proteins in Pulmonary Fibrosis as Novel Biochemical Marker Targets

Idiopathic pulmonary fibrosis (IPF) is the most common interstitial lung disease and is associated with a heterogeneous occurrence of fibrosis but the cause of the disease is still unknown. There is no cure and the two most promising drug candidates (pirfenidone and nintedanib) only provide limited halt in disease progression and outcome. Biopsies are the standard tool in IPF diagnosis but they are time-consuming, highly invasive and often fail to provide a prognosis. Biopsies are also taken too late to provide an early diagnose that can alter outcome. Chest radiography and computed tomography are less invasive but also inadequate in specific diagnose. Thus new lung specific biomarkers are needed for the diagnosis and prognosis of IPF. Novel biomarkers would be best applicable if non-invasive and able to provide information not already accessible by other noninvasive tools such as spirometry, chest radiography and computed tomography. The levels of the two proteinases neutrophil elastase (NE) and matrix metalloproteinase-7 (MMP-7) are elevated in IPF in several studies. We believe that the activity of these proteases may be related to the progression of IPF. In the present work we aimed to discuss and highlight the roles of posttranslational modifications (PTMs) in the progression of IPF with special focus on proteolytic cleavage of lung proteins such as elastin. We also aimed to develop novel non-invasive elastin biomarkers that may contribute with higher sensitivity towards diagnosis of IPF. First, we developed biomarkers for NE-specific degradation of elastin. Monoclonal antibodies (mABs) were raised against immunogenic sites in the human elastin sequence. The mABs were screened for technical performance, specificity towards NE-degraded elastin and clinical relevance. The EL-NE mAB was selected as the best candidate for the quantification of NE-specific degradation of elastin and ELISA assay development was conducted resulting in the EL-NE assay. The assay was specific towards NE-degraded elastin and the EL-NE neo-epitope with limited reactivity towards intact elastin. Second, we developed biomarkers for matrix MMP-7 degradation of elastin. The screening and assay development was conducted using similar methodology to EL-NE. The ELM7 mAB was selected as the best candidate for the quantification of MMP-7-specific degradation of elastin. The assay was specific towards MMP-7-degraded elastin and the ELM7 neo-epitope with limited reactivity towards intact elastin. Finally, we tested the assays for clinical relevance in serum from patients diagnosed with IPF or lung cancer and healthy matched controls. Serum EL-NE- and ELM7 fragment levels were significantly elevated in
IPF- and lung cancer patients compared to matched controls. In conclusion, we have developed two technically stable assays, EL-NE and ELM7, for the quantification of elastin degraded by NE and MMP-7 respectively. Both assays were protease specific. Initial clinical testing suggested clinical relevance of the assays in the quantification of the excessive lung extracellular remodelling occurring in pulmonary disorders, especially IPF.

**General information**

**State:** Published

**Organisations:** Enzyme and Protein Chemistry, Department of Systems Biology, Center for Biological Sequence Analysis, Proteomics Platform, Enzyme and Protein Chemistry, Nordic Bioscience A/S

**Authors:** Kristensen, J. H. (Intern), Hägglund, P. (Intern), Svensson, B. (Intern), Oersnes-Leeming, D. J. (Ekstern)

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**Relations**

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Identification of Disease Relevant Post Translational Modifications of Proteins in Pulmonary Fibrosis as Novel Biochemical Marker Targets

**Publication:** Research › Ph.D. thesis – Annual report year: 2016

**Identification of novel immune and barrier genes in atopic dermatitis by means of laser capture microdissection**

**Background:** The molecular signature of atopic dermatitis (AD) lesions is associated with T(H)2 and T(H)22 activation and epidermal alterations. However, the epidermal and dermal AD transcriptomes and their respective contributions to abnormalities in respective immune and barrier phenotypes are unknown. **Objective:** We sought to establish the genomic profile of the epidermal and dermal compartments of lesional and nonlesional AD skin compared with normal skin.

**Methods:** Laser capture microdissection was performed to separate the epidermis and dermis of lesional and nonlesional skin from patients with AD and normal skin from healthy volunteers, followed by gene expression (microarrays and real-time PCR) and immunostaining studies.

**Results:** Our study identified novel immune and barrier genes, including the IL-34 cytokine and claudins 4 and 8, and showed increased detection of key AD genes usually undetectable on arrays (ie, IL22, thymic stromal lymphopoietin [TSLP], CCL22, and CCL26). Overall, the combined epidermal and dermal transcriptomes enlarged the AD transcriptome, adding 674 upregulated and 405 downregulated differentially expressed genes between lesional and nonlesional skin to the AD transcriptome. We were also able to localize individual transcripts as primarily epidermal (defensin, beta 4A [DEFB4A]) or dermal (IL22, cytotoxic T-lymphocyte antigen 4 [CTLA4], and CCR7) and link their expressions to possible cellular sources. Conclusions: This is the first report that establishes robust epidermal and dermal genomic signatures of lesional and nonlesional AD skin and normal skin compared with whole tissues. These data establish the utility of laser capture microdissection to separate different compartments and cellular subsets in patients with AD, allowing localization of key barrier or immune molecules and enabling detection of gene products usually not detected on arrays.

**General information**

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**Organisations:** Department of Systems Biology, Center for Biological Sequence Analysis, Regulatory Genomics, The Rockefeller University, LEO Pharma A/S


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Identification of possible adverse drug reactions in clinical notes: the case of glucose-lowering medicines

Objective: Through manual review of clinical notes for patients with type 2 diabetes mellitus attending a Danish diabetes center, the aim of the study was to identify adverse drug reactions (ADRs) associated with three classes of glucose-lowering medicines: “Combinations of oral blood-glucose lowering medicines” (A10BD), “dipeptidyl peptidase-4 (DP4) inhibitors” (A10BH), and “other blood glucose lowering medicines” (A10BX). Specifically, we aimed to describe the potential of clinical notes to identify new ADRs and to evaluate if sufficient information can be obtained for causality assessment.

Methods: For observed adverse events (AEs) we extracted time to onset, outcome, and suspected medicine(s). AEs were assessed according to World Health Organization-Uppsala Monitoring Centre causality criteria and analyzed with respect
to suspected medicines, type of ADR (system organ class), seriousness and labeling status.

Findings: A total of 207 patients were included in the study leading to the identification of 163 AEs. 14% were categorized as certain, 60% as probable/likely, and 26% as possible. 15 (9%) ADRs were unlabeled of which two were serious: peripheral edema associated with sitagliptin and stomach ulcer associated with liraglutide. Of the unlabeled ADRs, 13 (87%) were associated with "other blood glucose lowering medications," the remaining 2 (13%) with "DP-4 inhibitors."

Conclusion: Clinical notes could potentially reveal unlabeled ADRs associated with prescribed medicines and sufficient information is generally available for causality assessment. However, manual review of clinical notes is too time-consuming for routine use and hence there is a need for developing information technology (IT) tools for automatic screening of patient records with the purpose to detect information about potentially serious and unlabeled ADRs.
**Lactococcus lactis** Thioredoxin Reductase Is Sensitive to Light Inactivation

Thioredoxin, involved in numerous redox pathways, is maintained in the dithiol state by the nicotinamide adenine dinucleotide phosphate-dependent flavoprotein thioredoxin reductase (TrxR). Here, TrxR from *Lactococcus lactis* is compared with the well-characterized TrxR from *Escherichia coli*. The two enzymes belong to the same class of low-molecular weight thioredoxin reductases and display similar $k_{cat}$ values ($\sim 25 \text{ s}^{-1}$) with their cognate thioredoxin. Remarkably, however, the *L. lactis* enzyme is inactivated by visible light and furthermore reduces molecular oxygen 10 times faster than *E. coli* TrxR. The rate of light inactivation under standardized conditions ($\lambda_{max} = 460 \text{ nm and } 4 \degree \text{C}$) was reduced at lowered oxygen concentrations and in the presence of iodide. Inactivation was accompanied by a distinct spectral shift of the flavin adenine dinucleotide (FAD) that remained firmly bound. High-resolution mass spectrometric analysis of heat-extracted FAD from light-damaged TrxR revealed a mass increment of 13.979 Da, relative to that of unmodified FAD, corresponding to the addition of one oxygen atom and the loss of two hydrogen atoms. Tandem mass spectrometry confined the increase in mass of the isoalloxazine ring, and the extracted modified cofactor reacted with dinitrophenyl hydrazine, indicating the presence of an aldehyde. We hypothesize that a methyl group of FAD is oxidized to a formyl group. The significance of this not previously reported oxidation and the exceptionally high rate of oxygen reduction are discussed in relation to other flavin modifications and the possible occurrence of enzymes with similar properties.

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Individualization of treatments with drugs metabolized by CES1: combining genetics and metabolomics

CES1 is involved in the hydrolysis of ester group-containing xenobiotic and endobiotic compounds including several essential and commonly used drugs. The individual variation in the efficacy and tolerability of many drugs metabolized by CES1 is considerable. Hence, there is a large interest in individualizing the treatment with these drugs. The present review addresses the issue of individualized treatment with drugs metabolized by CES1. It describes the composition of the gene encoding CES1, reports variants of this gene with focus upon those with a potential effect on drug metabolism and provides an overview of the protein structure of this enzyme bringing notice to mechanisms involved in the regulation of enzyme activity. Subsequently, the review highlights drugs metabolized by CES1 and argues that individual differences in the pharmacokinetics of these drugs play an important role in determining drug response and tolerability suggesting prospects for individualized drug therapies. Our review also discusses endogenous substrates of CES1 and assesses the potential of using metabolomic profiling of blood to identify proxies for the hepatic activity of CES1 that predict the rate of drug metabolism. Finally, the combination of genetics and metabolomics to obtain an accurate prediction of the individual response to CES1-dependent drugs is discussed.

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Integrative Systems Biology, Copenhagen University Hospital, University of Copenhagen, Bispebjerg University Hospital, deCODE Genetics, Leiden University, Duke University, Capital Region of Denmark, Gentofte University Hospital, Roskilde University, Oslo University Hospital
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Multiple Chemical Sensitivity (MCS) is a chronic condition characterized by reports of recurrent symptoms in response to low level exposure to various chemical substances. Recent findings suggest that dysregulation of the immune system may play a role in MCS pathophysiology. The aim of this study was to examine baseline and low dose n-butanol-induced upper airway inflammatory response profiles in MCS subjects versus healthy controls. Eighteen participants with MCS and 18 age- and sex-matched healthy controls were enrolled in the study. Epithelial lining fluid was collected from the nasal cavity at three time points: baseline, within 15 minutes after being exposed to 3.7 ppm n-butanol in an exposure chamber and four hours after exposure termination. A total of 19 cytokines and chemokines were quantified. Furthermore, at baseline and during the exposure session, participants rated the perceived intensity, valence and levels of symptoms and autonomic recordings were obtained. The physiological and psychophysical measurements during the n-butanol exposure session verified a specific response in MCS individuals only. However, MCS subjects and healthy controls displayed similar upper airway inflammatory mediator profiles (P>0.05) at baseline. Likewise, direct comparison of mediator levels in the MCS group and controls after n-butanol exposure revealed no significant group differences. We demonstrate no abnormal upper airway inflammatory mediator levels in MCS subjects before or after a symptom-eliciting exposure to low dose n-butanol, implying that upper airways of MCS subjects are functionally intact at the level of cytokine and chemokine production and secretory capacity. This suggests that previous findings of increased cytokine plasma levels in MCS are unlikely to be caused by systemic priming via excessive upper airway inflammatory processes.

Inflammatory Mediator Profiling of n-butanol Exposed Upper Airways in Individuals with Multiple Chemical Sensitivity

Multiple Chemical Sensitivity (MCS) is a chronic condition characterized by reports of recurrent symptoms in response to low level exposure to various chemical substances. Recent findings suggest that dysregulation of the immune system may play a role in MCS pathophysiology. The aim of this study was to examine baseline and low dose n-butanol-induced upper airway inflammatory response profiles in MCS subjects versus healthy controls. Eighteen participants with MCS and 18 age- and sex-matched healthy controls were enrolled in the study. Epithelial lining fluid was collected from the nasal cavity at three time points: baseline, within 15 minutes after being exposed to 3.7 ppm n-butanol in an exposure chamber and four hours after exposure termination. A total of 19 cytokines and chemokines were quantified. Furthermore, at baseline and during the exposure session, participants rated the perceived intensity, valence and levels of symptoms and autonomic recordings were obtained. The physiological and psychophysical measurements during the n-butanol exposure session verified a specific response in MCS individuals only. However, MCS subjects and healthy controls displayed similar upper airway inflammatory mediator profiles (P>0.05) at baseline. Likewise, direct comparison of mediator levels in the MCS group and controls after n-butanol exposure revealed no significant group differences. We demonstrate no abnormal upper airway inflammatory mediator levels in MCS subjects before or after a symptom-eliciting exposure to low dose n-butanol, implying that upper airways of MCS subjects are functionally intact at the level of cytokine and chemokine production and secretory capacity. This suggests that previous findings of increased cytokine plasma levels in MCS are unlikely to be caused by systemic priming via excessive upper airway inflammatory processes.

General information
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Capital Region of Denmark, Umeå University
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Inherited coding variants at the CDKN2A locus influence susceptibility to acute lymphoblastic leukaemia in children

There is increasing evidence from genome-wide association studies for a strong inherited genetic basis of susceptibility to acute lymphoblastic leukaemia (ALL) in children, yet the effects of protein-coding variants on ALL risk have not been systematically evaluated. Here we show a missense variant in CDKN2A associated with the development of ALL at genome-wide significance (rs3731249, $P = 9.4 \times 10^{-23}$, odds ratio = 2.23). Functional studies indicate that this hypomorphic variant results in reduced tumour suppressor function of p16INK4A, increases the susceptibility to leukaemic transformation of haematopoietic progenitor cells, and is preferentially retained in ALL tumour cells. Resequencing the CDKN2A-CDKN2B locus in 2,407 childhood ALL cases reveals 19 additional putative functional germline variants. These results provide direct functional evidence for the influence of inherited genetic variation on ALL risk, highlighting the important and complex roles of CDKN2A-CDKN2B tumour suppressors in leukaemogenesis.
Insights from 20 years of bacterial genome sequencing

Since the first two complete bacterial genome sequences were published in 1995, the science of bacteria has dramatically changed. Using third-generation DNA sequencing, it is possible to completely sequence a bacterial genome in a few hours and identify some types of methylation sites along the genome as well. Sequencing of bacterial genome sequences is now a standard procedure, and the information from tens of thousands of bacterial genomes has had a major impact on our views of the bacterial world. In this review, we explore a series of questions to highlight some insights that comparative genomics has produced. To date, there are genome sequences available from 50 different bacterial phyla and 11 different archaeal phyla. However, the distribution is quite skewed towards a few phyla that contain model organisms. But the breadth is continuing to improve, with projects dedicated to filling in less characterized taxonomic groups. The clustered regularly interspaced short palindromic repeats (CRISPR)-Cas system provides bacteria with immunity against viruses, which outnumber bacteria by tenfold. How fast can we go? Second-generation sequencing has produced a large number of draft genomes (close to 90% of bacterial genomes in GenBank are currently not complete); third-generation sequencing can potentially produce a finished genome in a few hours, and at the same time provide methylation sites along the entire chromosome. The diversity of bacterial communities is extensive as is evident from the genome sequences available from 50 different bacterial phyla and 11 different archaeal phyla. Genome sequencing can help in classifying an organism, and in the case where multiple genomes of the same species are available, it is possible to calculate the pan- and core genomes; comparison of more than 2000 Escherichia coli genomes finds an E. coli core genome of about 3100 gene families and a total of about 89,000 different gene families. Why do we care about bacterial genome sequencing? There are many practical applications, such as genome-scale metabolic modeling, biosurveillance, bioforensics, and infectious disease epidemiology. In the near future, high-throughput sequencing of patient metagenomic samples could revolutionize medicine in terms of speed and accuracy of finding pathogens and knowing how to treat them.
Integration and visualization of non-coding RNA and protein interaction networks

Non-coding RNAs (ncRNAs) fulfill a diverse set of biological functions relying on interactions with other molecular entities. The advent of new experimental and computational approaches makes it possible to study ncRNAs and their associations on an unprecedented scale. We present RAIN (RNA Association and Interaction Networks) - a database that combines ncRNA-ncRNA, ncRNA-mRNA and ncRNA-protein interactions with large-scale protein association networks available in the STRING database. By integrating ncRNA and protein networks, RAIN provides a more complete picture of the cell’s complex interaction network. RAIN aggregates associations and (predicted) interactions of a vast collection of ncRNA classes, including microRNAs and long ncRNAs, collected from a wide range of resources: a) curated knowledge, b) experimentally supported interactions, c) predicted microRNA-target interactions, and d) co-occurrences found by text mining Medline abstracts. Each resource was assigned a reliability score by assessing its agreement with a gold standard set of microRNA-target interactions. RAIN is available at: http://rth.dk/resources/rain
Integrative analysis of kinase networks in TRAIL-induced apoptosis provides a source of potential targets for combination therapy

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is an endogenous secreted peptide and, in preclinical studies, preferentially induces apoptosis in tumor cells rather than in normal cells. The acquisition of resistance in cells exposed to TRAIL or its mimics limits their clinical efficacy. Because kinases are intimately involved in the regulation of apoptosis, we systematically characterized kinases involved in TRAIL signaling. Using RNA interference (RNAi) loss-of-function and cDNA overexpression screens, we identified 169 protein kinases that influenced the dynamics of TRAIL-induced apoptosis in the colon adenocarcinoma cell line DLD-1. We classified the kinases as sensitizers or resisters or modulators, depending on the effect that knockdown and overexpression had on TRAIL-induced apoptosis. Two of these kinases that were classified as resisters were PX domain-containing serine/threonine kinase (PXK) and AP2-associated kinase 1 (AAK1), which promote receptor endocytosis and may enable cells to resist TRAIL-induced apoptosis by enhancing endocytosis of the TRAIL receptors. We assembled protein interaction maps using mass spectrometry-based protein interaction analysis and quantitative phosphoproteomics. With these protein interaction maps, we modeled information flow through the networks and identified apoptosis-modifying kinases that are highly connected to regulated substrates downstream of TRAIL. The results of this analysis provide a resource of potential targets for the development of TRAIL combination therapies to selectively kill cancer cells.

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Web of Science (2017): Indexed Yes
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Scopus rating (2016): SJR 4.632 SNIP 1.495 CiteScore 2.37
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 4.815 SNIP 1.442 CiteScore 2.27
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Scopus rating (2014): SJR 4.401 SNIP 1.328 CiteScore 2.06
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 5.291 SNIP 1.496 CiteScore 2.32
ISI indexed (2013): ISI indexed no
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 5.624 SNIP 1.683 CiteScore 2.43
ISI indexed (2012): ISI indexed no
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 5.563 SNIP 1.524 CiteScore 2.22
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BFI (2010): BFI-level 1
Scopus rating (2010): SJR 3.939 SNIP 1.298
BFI (2009): BFI-level 1
Humans are exposed to various chemical agents through food, cosmetics, pharmaceuticals and other sources. Exposure to chemicals is suspected of playing a main role in the development of some adverse health effects in humans. Additionally, European regulatory authorities have recognized the risk associated with combined exposure to multiple chemicals. Testing all possible combinations of the tens of thousands environmental chemicals is impractical. This PhD project was launched to apply existing computational systems biology methods to toxicological research. In this thesis, I present in three projects three different approaches to using computational toxicology to aid classical toxicological investigations. In project I, we predicted human health effects of five pesticides using publicly available data. We obtained a grouping of the chemical according to their potential human health effects that were in concordance with their effects in experimental animals. In project II, I profiled the effects on rat liver gene expression levels following exposure to a 14-chemical mixture ± the presence of an endocrine disrupting chemical. This project helped us shed light on the mechanism of action of the 14-chemical mixture and the endocrine disrupting chemical. In project III, I modeled a predictive signature for an in vivo endpoint that is sensitive to endocrine disruption. I used publicly available data generated for the purpose of modeling predictive signatures for various in vivo endpoints. From this modeling effort, I have suggested a mechanism of action for a subset of the chemicals that has not previously been associated with endocrine disruption. The use of computational methods in toxicology can aid the classical toxicological tests by suggesting interactions between separate components of a system thereby suggesting new ways of thinking specific toxicological endpoints. Furthermore, computational methods can serve as valuable input for the hypothesis generating phase of the preparations of a research project.
Investigating Antivenom Function and Cross-Reactivity – a Study of Antibodies and Their Targets

Venomous snakebites are regarded as one of the World’s most neglected tropical diseases/conditions with up to 2.5 million victims every year. The best-practice treatment is antivenom derived from the blood of large mammals (typically horses or sheep) immunized with venom of one or more snake species. The active toxin neutralizing components in antivenom are complex mixtures of antibodies (or fragments hereof). The individual antibodies are adapted by the immune system of the production animal to bind specific to parts of each toxin used in the immunization procedure. In many cases antivenom is also able to neutralize some – or even all – toxic effects of snakebites from related snake species.

Investigation of Human Cancers for Retrovirus by Low-Stringency Target Enrichment and High-Throughput Sequencing

Although nearly one fifth of all human cancers have an infectious aetiology, the causes for the majority of cancers remain unexplained. Despite the enormous data output from high-throughput shotgun sequencing, viral DNA in a clinical sample typically constitutes a proportion of host DNA that is too small to be detected. Sequence variation among virus genomes complicates application of sequence-specific, and highly sensitive, PCR methods. Therefore, we aimed to develop and characterize a method that permits sensitive detection of sequences despite considerable variation. We demonstrate that our low-stringency in-solution hybridization method enables detection of <100 viral copies. Furthermore, distantly related proviral sequences may be enriched by orders of magnitude, enabling discovery of hitherto unknown viral sequences by high-throughput sequencing. The sensitivity was sufficient to detect retroviral sequences in clinical samples. We used this method to conduct an investigation for novel retrovirus in samples from three cancer types. In accordance with recent studies our investigation revealed no retroviral infections in human B-cell lymphoma cells, cutaneous T-cell lymphoma or colorectal cancer biopsies. Nonetheless, our generally applicable method makes sensitive detection possible and permits sequencing of distantly related sequences from complex material.
Kinome-wide Decoding of Network-Attacking Mutations Rewiring Cancer Signaling

Cancer cells acquire pathological phenotypes through accumulation of mutations that perturb signaling networks. However, global analysis of these events is currently limited. Here, we identify six types of network-attacking mutations (NAMs), including changes in kinase and SH2 modulation, network rewiring, and the genesis and extinction of phosphorylation sites. We developed a computational platform (ReKINect) to identify NAMs and systematically interpreted the exomes and quantitative (phospho-)proteomes of five ovarian cancer cell lines and the global cancer genome repository. We identified and experimentally validated several NAMs, including PKCγ M501I and PKD1 D665N, which encode specificity switches analogous to the appearance of kinases de novo within the kinome. We discover mutant molecular logic gates, a drift toward phospho-threonine signaling, weakening of phosphorylation motifs, and kinase-inactivating hotspots in cancer. Our method pinpoints functional NAMs, scales with the complexity of cancer genomes and cell signaling, and may enhance our capability to therapeutically target tumor-specific networks.

General information

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Organisations: Department of Systems Biology, Cellular Signal Integration, University of Copenhagen, Yale University School of Medicine, University of Zurich, University of Roma 'Tor Vergata', Tottori University
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Publication information

Journal: Cell
Levels of circulating MMP-7 degraded elastin are elevated in pulmonary disorders

**Objectives:** Elastin is a signature protein of the lungs. Matrix metalloproteinase-7 (MMP-7) is important in lung defence mechanisms and degrades elastin. However, MMP-7 activity in regard to elastin degradation has never been quantified serologically in patients with lung diseases. An assay for the quantification of MMP-7 generated elastin fragments (ELM7) was therefore developed to investigate MMP-7 derived elastin degradation in pulmonary disorders such as idiopathic pulmonary fibrosis (IPF) and lung cancer. **Design and methods:** Monoclonal antibodies (mABs) were raised against eight carefully selected MMP-7 cleavage sites on elastin. After characterisation and validation of the mABs, one mAB targeting the ELM7 fragment was chosen. ELM7 fragment levels were assessed in serum samples from patients diagnosed with IPF (n = 123, baseline samples, CTgov reg. NCT00786201), and lung cancer (n = 40) and compared with age- and sex-matched controls. **Results:** The ELM7 assay was specific towards in vitro MMP-7 degraded elastin and the ELM7 neoepitope but not towards other MMP-7 derived elastin fragments. Serum ELM7 levels were significantly increased in IPF (113%, p < 0.0001) and lung cancer (96%, p < 0.0001) compared to matched controls. **Conclusions:** MMP-7-generated elastin fragments can be quantified in serum and may reflect pathological lung tissue turnover in several important lung diseases.
Lipid hydrolysis products affect the composition of infant gut microbial communities in vitro.

Some lipid hydrolysis products such as medium-chained NEFA (MC-NEFA), sphingosine and monoacylglycerols (MAG) possess antibacterial activity, while others, including oleic acid, are essential for the optimal growth of Lactobacillus species. Thus, changes in the concentrations of NEFA and MAG in the distal ileum and colon can potentially selectively modulate the composition of the gut microbiota, especially in early life when lipid absorption efficacy is reduced. As medium-chained fatty acids are enriched in mothers’ milk, such effects may be highly relevant during gut colonisation. In the present study, we examined the effect of selected NEFA, MAG and sphingosine on the composition of faecal microbial communities derived from infants aged 2–5 months during a 24 h anaerobic in vitro fermentation. We tested lipid mixtures in the concentration range of 0–200 mM, either based on MC-NEFA (10 : 0 to 14 : 0 and MAG 12 : 0) or long-chained NEFA (LC-NEFA; 16 : 0 to 18 : 1 and MAG 16 : 0) with and without sphingosine, representing lipid hydrolysis products characteristic for intestinal hydrolysis of breast milk lipids. Ion Torrent sequencing of the bacterial 16S ribosomal RNA gene revealed that the relative abundance of lactic acid-producing genera, including Lactobacillus and Bifidobacterium, was generally increased in the presence of 50mM or higher concentrations of MC-NEFA. For Bifidobacterium, the same effect was also observed in the presence of a mixture containing LC-NEFA with sphingosine. On the contrary, the relative abundance of Enterobacteriaceae was significantly decreased in the presence of both lipid mixtures. Our findings suggest that the high concentration of medium-chained fatty acids in breast milk might have functional effects on the establishment of the gut microbiota in early life.

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Long-chain polyunsaturated fatty acids in breast-milk and erythrocytes and neurodevelopmental outcomes in Danish late-preterm infants

Background: The supply of long-chain polyunsaturated fatty acids (LC-PUFA) during pregnancy and early lactation has been shown to affect cognitive development in preterm infants, but the effect on early neurodevelopment of late-preterm infants has not yet been examined. Aim: To examine the fatty acid composition of late-preterm human milk and identify...
possible associations between infant LC-PUFA status and perinatal as well as 1-year neurobehavioral outcomes. Methods: Mother’s milk and erythrocytes (RBC) were sampled from 53 Danish late-preterm infants (33-36 weeks of gestation) 1 week and 1 month after delivery, and 3 months corrected age. Fatty acid composition was determined by gas-liquid chromatography. Neurodevelopmental outcomes were assessed by the Nicu Network Neurobehavioral Scale (NNNS) at 1 week and 1 month and the Bayley Scales (BSID-III) at 1 year corrected age. Results: We found that breast-milk content of arachidonic acid (AA) and docosahexaenoic acid (DHA) was similar to reported fatty acid compositions of term human milk. Infant RBC-AA decreased from 1 week to 1 month of age and the size of the decrease was associated with better NNNS-scores at 1 month, specifically on regulation (p=0.03). Infant RBC-AA at 1 month was also associated with a lower 1-year corrected age BSID-III score of receptive language (p=0.05) and fine motor development (p=0.03). Infant RBC-DHA did not decrease significantly after delivery and was not associated with any of the developmental outcomes. Conclusion: Breast-milk LC-PUFA content was reflected in the RBC LC-PUFA status of the infant. Early RBC-AA status was associated with both early and long-term neurobehavioral development, but not in a consistent way.

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Long-term risk of cardiovascular and cerebrovascular disease after removal of the colonic microbiota by colectomy: a cohort study based on the Danish National Patient Register from 1996 to 2014

The hypothesis of the study was that if the gut microbiota is involved in the development of atherosclerotic cardiovascular and cerebrovascular diseases (CVDs), total colectomy may reduce the long-term risk of CVDs. The aim was therefore to investigate the risk of CVD in patients after a total colectomy compared with patients undergoing other types of surgery, which are not expected to alter the gut microbiota or the CVD risk. The Danish National Patient Register including all hospital discharges in Denmark from 1996 to 2014. Patients (n=1530) aged 45 years and above and surviving 1000 days after total colectomy without CVDs were selected and matched with five control patients who were also free of CVD 1000 days after other types of surgery. The five control patients were randomly selected from each of the three surgical groups: orthopaedic surgery, surgery in the gastrointestinal tract leaving it intact and other surgeries not related to the gastrointestinal tract or CVD (n=22 950). The primary outcome was the first occurring CVD event in any of the seven diagnostic domains (hypertensive disorders, acute ischaemic heart diseases, chronic ischaemic heart disease, cardiac arrhythmias, heart failure, cerebrovascular diseases and other arterial diseases) and the secondary outcomes were the first occurring event within each of these domains. Estimated by Cox proportional hazard models, the HRs of the composite CVD end point for patients with colectomy compared with the control patients were not significantly reduced (HR=0.94, 95% confidence limits 0.85 to 1.04). Among the seven CVD domains, only the risk of hypertensive disorders was significantly reduced (HR=0.85, 0.73 to 0.98). Colectomy did not reduce the general risk of CVD, but reduced the risk of hypertensive disorders, most likely due to salt and water depletion induced by colectomy. These results encourage a reappraisal of the associations between gut microbiota and CVD.
LYRA, a webserver for lymphocyte receptor structural modeling.

The accurate structural modeling of B- and T-cell receptors is fundamental to gain a detailed insight in the mechanisms underlying immunity and in developing new drugs and therapies. The LYRA (LYmphocyte Receptor Automated modeling) web server (http://www.cbs.dtu.dk/services/LYRA/) implements a complete and automated method for building of B- and T-cell receptor structural models starting from their amino acid sequence alone. The webserver is freely available and easy to use for non-specialists. Upon submission, LYRA automatically generates alignments using ad hoc profiles, predicts the structural class of each hypervariable loop, selects the best templates in an automatic fashion, and provides within minutes a complete 3D model that can be downloaded or inspected online. Experienced users can manually select or exclude template structures according to case specific information. LYRA is based on the canonical structure method, that in the last 30 years has been successfully used to generate antibody models of high accuracy, and in our benchmarks this approach proves to achieve similarly good results on TCR modeling, with a benchmarked average RMSD accuracy of 1.29 and 1.48 Å for B- and T-cell receptors, respectively. To the best of our knowledge, LYRA is the first automated server for the prediction of TCR structure.
Maternal fatty acid desaturase genotype correlates with infant immune responses at 6 months

Breast milk long-chain PUFA (LCPUFA) have been associated with changes in early life immune responses and may modulate T-cell function in infancy. We studied the effect of maternal fatty acid desaturase (FADS) genotype and breast milk LCPUFA levels on infants' blood T-cell profiles and ex vivo-produced cytokines after anti-CD3/CD28 stimulation of peripheral blood mononuclear cells in 6-month-old infants from the Copenhagen Prospective Study of Asthma in Childhood birth cohort. LCPUFA concentrations of breast milk were assessed at 4 weeks of age, and FADS SNP were determined in both mothers and infants (n 109). In general, breast milk arachidonic acid (AA) levels were inversely correlated with the production of IL-10 (r -0.25; P=0.004), IL-17 (r -0.24; P=0.005), IL-5 (r -0.21; P=0.014) and IL-13 (r -0.17; P=0.047), whereas EPA was positively correlated with the counts of blood regulatory T-cells and cytotoxic T-cells and decreased T-helper cell counts. The minor FADS alleles were associated with lower breast milk AA and EPA, and infants of mothers carrying the minor allele of FADS SNP rs174556 had higher production of IL-10 (r -0.23; P=0.018), IL-17 (r -0.25; P=0.009) and IL-5 (r -0.21; P=0.038) from ex vivo-activated immune cells. We observed no association between T-cell distribution and maternal or infant FADS gene variants. We conclude that increased maternal LCPUFA synthesis and breast milk AA are associated with decreased levels of IL-5, IL-13 (type-2 related), IL-17 (type-17 related) and IL-10 (regulatory immune responses), but not with interferon-γ and TNF-α, which could be due to an effect of the maternal FADS variants on the offspring immune response transferred via breast milk LCPUFA. Copyright © The Authors 2015.
Meta-analysis derived atopic dermatitis (MADAD) transcriptome defines a robust AD signature highlighting the involvement of atherosclerosis and lipid metabolism pathways

Atopic dermatitis (AD) is a common inflammatory skin disease with limited treatment options. Several microarray experiments have been conducted on lesional/LS and non-lesional/NL AD skin to develop a genomic disease phenotype. Although these experiments have shed light on disease pathology, inter-study comparisons reveal large differences in...
resulting sets of differentially expressed genes (DEGs), limiting the utility of direct comparisons across studies. We carried out a meta-analysis combining 4 published AD datasets to define a robust disease profile, termed meta-analysis derived AD (MADAD) transcriptome. This transcriptome enriches key AD pathways more than the individual studies, and associates AD with novel pathways, such as atherosclerosis signaling (IL-37, selectin E/SELE). We identified wide lipid abnormalities and, for the first time in vivo, correlated Th2 immune activation with downregulation of key epidermal lipids (FA2H, FAR2, ELOVL3), emphasizing the role of cytokines on the barrier disruption in AD. Key AD “classifier genes” discriminate lesional from nonlesional skin, and may evaluate therapeutic responses. Our meta-analysis provides novel and powerful insights into AD disease pathology, and reinforces the concept of AD as a systemic disease.
Meta-genomic analysis of toilet waste from long distance flights; a step towards global surveillance of infectious diseases and antimicrobial resistance

Human populations worldwide are increasingly confronted with infectious diseases and antimicrobial resistance spreading faster and appearing more frequently. Knowledge regarding their occurrence and worldwide transmission is important to control outbreaks and prevent epidemics. Here, we performed shotgun sequencing of toilet waste from 18 international airplanes arriving in Copenhagen, Denmark, from nine cities in three world regions. An average of 18.6 Gb (14.8 to 25.7 Gb) of raw Illumina paired end sequence data was generated, cleaned, trimmed and mapped against reference sequence databases for bacteria and antimicrobial resistance genes. An average of 106.839 (0.06%) reads were assigned to resistance genes with genes encoding resistance to tetracycline, macrolide and beta-lactam resistance genes as the most abundant in all samples. We found significantly higher abundance and diversity of genes encoding antimicrobial resistance, including critical important resistance (e.g. blaCTX-M) carried on airplanes from South Asia compared to North America. Presence of *Salmonella enterica* and norovirus were also detected in higher amounts from South Asia, whereas *Clostridium difficile* was most abundant in samples from North America. Our study provides a first step towards a potential novel strategy for global surveillance enabling simultaneous detection of multiple human health threatening genetic elements, infectious agents and resistance genes.
Metagenomic heterogeneity explains dual immune effects of endotoxins

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Microbial Biofilm as a Smart Material

Microbial biofilm colonies will in many cases form a smart material capable of responding to external threats dependent on their size and internal state. The microbial community accordingly switches between passive, protective, or attack modes of action. In order to decide which strategy to employ, it is essential for the biofilm community to be able to sense its own size. The sensor designed to perform this task is termed a quorum sensor, since it only permits collective behaviour once a sufficiently large assembly of microbes have been established. The generic quorum sensor construct involves two genes, one coding for the production of a diffusible signal molecule and one coding for a regulator protein dedicated to sensing the signal molecules. A positive feedback in the signal molecule production sets a well-defined condition for switching into the collective mode. The activation of the regulator involves a slow dimerization, which allows low-pass filtering of the activation of the collective mode. Here, we review and combine the model components that form the basic quorum sensor in a number of Gram-negative bacteria, e.g., *Pseudomonas aeruginosa*.
miR-18b overexpression identifies mantle cell lymphoma patients with poor outcome and improves the MIPI-B prognosticator

Recent studies show that mantle cell lymphoma (MCL) express aberrant microRNA (miRNA) profiles; however, the clinical effect of miRNA expression has not previously been examined and validated in large prospective homogeneously treated cohorts. We performed genome-wide miRNA microarray profiling of 74 diagnostic MCL samples from the Nordic MCL2 trial (screening cohort). Prognostic miRNAs were validated in diagnostic MCL samples from 94 patients of the independent Nordic MCL3 trial (validation cohort). Three miRNAs (miR-18b, miR-92a, and miR-378d) were significantly differentially expressed in patients who died of MCL in both cohorts. MiR-18b was superior to miR-92a and miR-378d in predicting high risk. Thus, we generated a new biological MCL International Prognostic Index (MIPI-B)-miR prognosticator, combining expression levels of miR-18b with MIPI-B data. Compared to the MIPI-B, this prognosticator improved identification of high-risk patients with regard to cause-specific, overall, and progression-free survival. Transfection of 2 MCL cell lines with miR-18b decreased their proliferation rate without inducing apoptosis, suggesting that miR-18b may render MCL cells resistant to chemotherapy by decelerating cell proliferation. We conclude that overexpression of miR-18b identifies patients with poor prognosis in 2 large prospective MCL cohorts and adds prognostic information to the MIPI-B. MiR-18b may reduce the proliferation rate of MCL cells as a mechanism of chemoresistance.
Molecular Analysis of Asymptomatic Bacteriuria Escherichia coli Strain VR50 Reveals Adaptation to the Urinary Tract by Gene Acquisition

Urinary tract infections (UTIs) are among the most common infectious diseases of humans, with Escherichia coli responsible for >80% of all cases. One extreme of UTI is asymptomatic bacteriuria (ABU), which occurs as an asymptomatic carrier state that resembles commensalism. To understand the evolution and molecular mechanisms that underpin ABU, the genome of the ABU E. coli strain VR50 was sequenced. Analysis of the complete genome indicated that it most resembles E. coli K-12, with the addition of a 94-kb genomic island (GI-VR50-pheV), eight prophages, and multiple plasmids. GI-VR50-pheV has a mosaic structure and contains genes encoding a number of UTI-associated virulence factors, namely, Afa (afimbrial adhesin), two autotransporter proteins (Ag43 and Sat), and aerobactin. We demonstrated that the presence of this island in VR50 confers its ability to colonize the murine bladder, as a VR50 mutant with GI-VR50-pheV deleted was attenuated in a mouse model of UTI in vivo. We established that Afa is the island-encoded factor responsible for this phenotype using two independent deletion (Afa operon and AfaE adhesin) mutants. E. coli VR50afa and VR50afaE displayed significantly decreased ability to adhere to human bladder epithelial cells. In the mouse model of UTI, VR50afa and VR50afaE displayed reduced bladder colonization compared to wild-type VR50, similar to the colonization level of the GI-VR50-pheV mutant. Our study suggests that E. coli VR50 is a commensal-like strain that has acquired fitness factors that facilitate colonization of the human bladder.

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Mucosal-associated invariant T (MAIT) cells express a semi-invariant T cell receptor (TCR) that detects microbial metabolites presented by the nonpolymorphic major histocompatibility complex (MHC)-like molecule MR1. The highly conserved nature of MR1 in conjunction with biased MAIT TCRα chain usage is widely thought to indicate limited ligand presentation and discrimination within a pattern-like recognition system. Here, we evaluated the TCR repertoire of MAIT cells responsive to three classes of microbes. Substantial diversity and heterogeneity were apparent across the functional MAIT cell repertoire as a whole, especially for TCRβ chain sequences. Moreover, different pathogen-specific responses were characterized by distinct TCR usage, both between and within individuals, suggesting that MAIT cell adaptation was a direct consequence of exposure to various exogenous MR1-restricted epitopes. In line with this interpretation, MAIT cell clones with distinct TCRs responded differentially to a riboflavin metabolite. These results suggest that MAIT cells can discriminate between pathogen-derived ligands in a clonotype-dependent manner, providing a basis for adaptive memory via recruitment of specific repertoires shaped by microbial exposure.
MTR-18 Predictive Biomarkers Of Bevacizumab Response In Recurrent Glioblastoma Patients

Bevacizumab (BEV) plus chemotherapy has shown activity in recurrent glioblastoma (GBM). However, the prognosis varies and only one third of patients have a durable clinical response to BEV combination therapy. Recent findings from a randomized phase-3 study (AVAglio) indicate that patients with the proneural GBM subtype have a survival benefit when treated with BEV in combination with standard treatment. However, no validated biomarkers able to predict BEV response have been identified and the biology reflecting a clinical BEV response is poorly understood. The primary objective of this study was to evaluate the predictive and prognostic value of GBM subtypes in recurrent GBM patients treated with BEV therapy. The secondary objective was to identify biomarkers able to predict response to BEV therapy in recurrent GBM patients.

METHODS: A total of 90 recurrent GBM patients treated with BEV combination treatment according to previously published protocols were included. Inclusion criteria: BEV plus irinotecan treatment in the period between May 2005-2011; available GBM tissue (according to WHO); response evaluable (RANO). RNA was extracted from laser microdissected tumor tissue and analyzed by the NanoString platform covering 800 genes. Raw data was assigned to molecular subtypes for each of the samples using the PAMR classifier model, previously trained on the AVAglio dataset. By performing a t-test, comparing gene profiles of patients responding versus progressing on BEV novel candidate biomarkers were identified. Candidate biomarkers were analyzed by logistic regression and Cox regression modelling response and survival endpoints, respectively. Biomarkers associated with response were added to a prognostic model consisting of three independent prognostic factors: Corticosteroid use, neurocognitive deficit and multifocal disease. RESULTS: Molecular subtypes were not associated with response or survival. However, two independent predictive biomarkers (gene1 down-regulated and gene2 up-regulated in responders, respectively) of BEV response and survival were identified. Results will be presented.
Multidimensional Clusters of CD4+ T Cell Dysfunction Are Primarily Associated with the CD4/CD8 Ratio in Chronic HIV Infection

HIV infection provokes a myriad of pathological effects on the immune system where many markers of CD4+ T cell dysfunction have been identified. However, most studies to date have focused on single/double measurements of immune dysfunction, while the identification of pathological CD4+ T cell clusters that is highly associated to a specific biomarker for HIV disease remain less studied. Here, multi-parametric flow cytometry was used to investigate immune activation, exhaustion, and senescence of diverse maturation phenotypes of CD4+ T cells. The traditional method of manual data analysis was compared to a multidimensional clustering tool, FLOw Clustering with K (FLOCK) in two cohorts of 47 untreated HIV-infected individuals and 21 age and sex matched healthy controls. In order to reduce the subjectivity of FLOCK, we developed an "artificial reference", using 2% of all CD4+ gated T cells from each of the HIV-infected individuals. Principle component analyses demonstrated that using an artificial reference lead to a better separation of the HIV-infected individuals from the healthy controls as compared to using a single HIV-infected subject as a reference or analyzing data manually. Multiple correlation analyses between laboratory parameters and pathological CD4+ clusters revealed that the CD4/CD8 ratio was the preeminent surrogate marker of CD4+ T cells dysfunction using all three methods. Increased frequencies of an early-differentiated CD4+ T cell cluster with high CD38, HLA-DR and PD-1 expression were best correlated (Rho = -0.80, P value = 1.96x10^-11) with HIV disease progression as measured by the CD4/CD8 ratio. The novel approach described here can be used to identify cell clusters that distinguish healthy from HIV infected subjects and is biologically relevant for HIV disease progression. These results further emphasize that a simple measurement of the CD4/CD8 ratio is a useful biomarker for assessment of combined CD4+ T cell dysfunction in chronic HIV disease.
Multilocus Heterozygosity and Coronary Heart Disease: Nested Case-Control Studies in Men and Women

Background: Generalized allelic heterozygosity has been proposed to improve reproductive fitness and has been associated with higher blood pressure, but its association with chronic disease is not well characterized.

Methods: Using the Affymetrix Genome-Wide Human 6.0 array, we performed whole genome scans in parallel case-
control studies of coronary heart disease (CHD) nested in the Health Professionals Follow-up Study and Nurses’ Health Study. We examined ∼ 700,000 single nucleotide polymorphisms (SNPs) in 435 men with incident CHD and 878 matched controls and 435 women with incident CHD with 931 matched controls. We examined the relationship of genome-wide heterozygosity with risk of incident of CHD and with baseline levels of cardiovascular risk factors.

Results: In both cohorts, approximately 227650 (SD 2000) SNPs were heterozygous. The number of heterozygous SNPs was not related to risk of CHD in either men or women (adjusted odds ratios per 2000 heterozygous SNPs 1.01 [95% confidence interval, 0.91-1.13] in women and 0.94 [0.84-1.06] in men). We also found no consistent associations of genome-wide heterozygosity with levels of lipids, inflammatory markers, adhesion molecules, homocysteine, adiponectin, or body-mass index.

Conclusions: In these parallel nested case-control studies, we found no relationship of multilocus heterozygosity with risk of CHD or its major risk factors. Studies in other populations are needed to rule out associations with lower levels of heterozygosity.

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Scopus rating (2014): SJR 1.545 SNIP 1.141 CiteScore 3.54
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ISI indexed (2012): ISI indexed yes
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BFI (2010): BFI-level 1
Scopus rating (2010): SJR 2.631 SNIP 1.161
Web of Science (2010): Indexed yes
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Multi-omic profiling of EPO-producing Chinese hamster ovary cell panel reveals metabolic adaptation to heterologous protein production

Chinese hamster ovary (CHO) cells are the preferred production host for many therapeutic proteins. The production of heterologous proteins in CHO cells imposes a burden on the host cell metabolism and impact cellular physiology on a global scale. In this work, a multi-omics approach was applied to study the production of erythropoietin (EPO) in a panel of CHO-K1 cells under growth-limited and unlimited conditions in batch and chemostat cultures. Physiological characterization of the EPO-producing cells included global transcriptome analysis, targeted metabolome analysis, including intracellular pools of glycolytic intermediates, NAD(P)H/NAD(P)+, adenine nucleotide phosphates (ANP), and extracellular concentrations of sugars, organic acids, and amino acids. Potential impact of EPO expression on the protein secretory pathway was assessed at multiple stages using quantitative PCR (qPCR), reverse transcription PCR (qRT-PCR), Western blots (WB), and global gene expression analysis to assess EPO gene copy numbers, EPO gene expression, intracellular EPO retention, and differentially expressed genes functionally related to secretory protein processing, respectively. We found no evidence supporting the existence of production bottlenecks in energy metabolism (i.e., glycolytic metabolites, NAD(P)H/NAD(P)+ and ANPs) in batch culture or in the secretory protein production pathway (i.e., gene dosage, transcription and post-translational processing of EPO) in chemostat culture at specific productivities up to 5 pg/cell/day. Time-course analysis of high- and low-producing clones in chemostat culture revealed rapid adaptation of transcription levels of amino acid catabolic genes in favor of EPO production within nine generations. Interestingly, the adaptation was followed by an increase in specific EPO productivity.
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Neonates with reduced neonatal lung function have systemic low-grade inflammation

Background: Children and adults with asthma and impaired lung function have been reported to have low-grade systemic inflammation, but it is unknown whether this inflammation starts before symptoms and in particular whether low-grade inflammation is present in asymptomatic neonates with reduced lung function. Objective We sought to investigate the possible association between neonatal lung function and biomarkers of systemic inflammation.

Methods: Plasma levels of high-sensitivity C-reactive protein (hs-CRP), IL-1β, IL-6, TNF-α, and CXCL8 (IL-8) were measured at age 6 months in 300 children of the Copenhagen Prospective Study on Asthma in Childhood 2000 birth cohort who had completed neonatal lung function testing at age 4 weeks. Associations between neonatal lung function indices and inflammatory biomarkers were investigated by conventional statistics and unsupervised principal component analysis.

Results: The neonatal forced expiratory volume at 0.5 seconds was inversely associated with hs-CRP (β-coefficient, −0.12; 95% CI, −0.21 to −0.04; P < .01) and IL-6 (β-coefficient, −0.10; 95% CI, −0.18 to −0.01; P = .03) levels. The multivariate principal component analysis approach, including hs-CRP, IL-6, TNF-α, and CXCL8, confirmed a uniform upregulated inflammatory profile in children with reduced forced expiratory volume at 0.5 seconds (P = .02). Adjusting for body mass index at birth, maternal smoking, older children in the home, neonatal bacterial airway colonization, infections 14 days before, and asthmatic symptoms, as well as virus-induced wheezing, at any time before biomarker assessment at age 6 months did not affect the associations. Conclusion: Diminished neonatal lung function is associated with upregulated systemic inflammatory markers, such as hs-CRP.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Copenhagen
Authors: Chawes, B. L. (Ekstern), Stokholm, J. (Ekstern), Bennelykke, K. (Ekstern), Pedersen, S. B. (Intern), Bisgaard, H. F. (Ekstern)
Number of pages: 8
Pages: 1450-1456
Publication date: 2015
Main Research Area: Technical/natural sciences

Publication information
Journal: Journal of Allergy and Clinical Immunology
Volume: 135
Issue number: 6
ISSN (Print): 0091-6749
Ratings:
BFI (2018): BFI-level 2
New genetic loci link adipose and insulin biology to body fat distribution

Body fat distribution is a heritable trait and a well-established predictor of adverse metabolic outcomes, independent of overall adiposity. To increase our understanding of the genetic basis of body fat distribution and its molecular links to cardiometabolic traits, here we conduct genome-wide association meta-analyses of traits related to waist and hip circumferences in up to 224,459 individuals. We identify 49 loci (33 new) associated with waist-to-hip ratio adjusted for body mass index (BMI), and an additional 19 loci newly associated with related waist and hip circumference measures (P < 5 × 10⁻⁸). In total, 20 of the 49 waist-to-hip ratio adjusted for BMI loci show significant sexual dimorphism, 19 of which display a stronger effect in women. The identified loci were enriched for genes expressed in adipose tissue and for putative regulatory elements in adipocytes. Pathway analyses implicated adipogenesis, angiogenesis, transcriptional
regulation and insulin resistance as processes affecting fat distribution, providing insight into potential pathophysiological mechanisms.

**General information**

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Integrative Systems Biology, Umeå University, University of Regensburg, University of North Carolina, University of Oxford, University of Michigan, University of Tartu, Karolinska Institutet, University of North Carolina at Chapel Hill, Steno Diabetes Centre
Number of pages: 10
Pages: 187-96
Publication date: 2015
Main Research Area: Technical/natural sciences

**Publication information**

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Volume: 518
Issue number: 7538
ISSN (Print): 0028-0836
Ratings:
BFI (2018): BFI-level 3
BFI (2017): BFI-level 2
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 13.33
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): CiteScore 14.38
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): CiteScore 14.22
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): CiteScore 14.96
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): CiteScore 14.01
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): CiteScore 13.96
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 2
Web of Science (2008): Indexed yes
Web of Science (2007): Indexed yes
Web of Science (2006): Indexed yes
Web of Science (2005): Indexed yes
Web of Science (2004): Indexed yes
Web of Science (2003): Indexed yes
New insights on single-stranded versus double-stranded DNA library preparation for ancient DNA

An innovative single-stranded DNA (ssDNA) library preparation method has sparked great interest among ancient DNA (aDNA) researchers, especially after reports of endogenous DNA content increases >20-fold in some samples. To investigate the behavior of this method, we generated ssDNA and conventional double-stranded DNA (dsDNA) libraries from 23 ancient and historic plant and animal specimens. We found ssDNA library preparation substantially increased endogenous content when dsDNA libraries contained...
Novel variation and de novo mutation rates in population-wide de novo assembled Danish trios

Building a population-specific catalogue of single nucleotide variants (SNVs), indels and structural variants (SVs) with frequencies, termed a national pan-genome, is critical for further advancing clinical and public health genetics in large cohorts. Here we report a Danish pan-genome obtained from sequencing 10 trios to high depth (50). We report 536k novel SNVs and 283k novel short indels from mapping approaches and develop a population-wide de novo assembly approach to identify 132k novel indels larger than 10 nucleotides with low false discovery rates. We identify a higher proportion of indels and SVs than previous efforts showing the merits of high coverage and de novo assembly approaches. In addition, we use trio information to identify de novo mutations and use a probabilistic method to provide direct estimates of 1.27e8 and 1.5e9 per nucleotide per generation for SNVs and indels, respectively.
NutriChem: a systems chemical biology resource to explore the medicinal value of plant-based foods

There is rising evidence of an inverse association between chronic diseases and diets characterized by rich fruit and vegetable consumption. Dietary components may act directly or indirectly on the human genome and modulate multiple processes involved in disease risk and disease progression. However, there is currently no exhaustive resource on the health benefits associated to specific dietary interventions, or a resource covering the broad molecular content of food. Here we present the first release of NutriChem, available at http://cbs.dtu.dk/services/NutriChem-1.0, a database generated by text mining of 21 million MEDLINE abstracts for information that links plant-based foods with their small molecule components and human disease phenotypes. NutriChem contains text-mined data for 18478 pairs of 1772 plant-based foods and 7898 phytochemicals, and 6242 pairs of 1066 plant-based foods and 751 diseases. In addition, it includes predicted associations for 548 phytochemicals and 252 diseases. To the best of our knowledge this database is the only resource linking the chemical space of plant-based foods with human disease phenotypes and provides a foundation for understanding mechanistically the consequences of eating behaviors on health.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Hong Kong
Authors: Jensen, K. (Intern), Panagiotou, G. (Ekstern), Kouskoumvekaki, I. (Intern)
Number of pages: 6
Pages: D940-D945
Oxidative stress response pathways: Fission yeast as archetype

Schizosaccharomyces pombe is a popular model eukaryotic organism to study diverse aspects of mammalian biology, including responses to cellular stress triggered by redox imbalances within its compartments. The review considers the current knowledge on the signaling pathways that govern the transcriptional response of fission yeast cells to elevated levels of hydrogen peroxide. Particular attention is paid to the mechanisms that yeast cells employ to promote cell survival in conditions of intermediate and acute oxidative stress. The role of the Sty1/Spc1/Phh1 mitogen-activated protein kinase in regulating gene expression at multiple levels is discussed in detail.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Technical University of Denmark
Authors: Papadakis, M. A. (Ekstern), Workman, C. (Intern)
Number of pages: 16
Pages: 520-535
Publication date: 2015
Main Research Area: Technical/natural sciences

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Journal: Critical Reviews in Microbiology
Volume: 41
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ISSN (Print): 1040-841X
Ratings:
BFI (2018): BFI-level 2
BFI (2017): BFI-level 2
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): SJR 1.681 SNIP 1.778 CiteScore 4.78
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 1.999 SNIP 1.927 CiteScore 5.59
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 1.802 SNIP 1.803 CiteScore 4.99
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 2.125 SNIP 2.385 CiteScore 6.5
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.593 SNIP 2.575 CiteScore 5.81
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.942 SNIP 2.164 CiteScore 6.65
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.811 SNIP 1.816
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.108 SNIP 1.831
BFI (2008): BFI-level 1
P0525 : N-Acetylated alpha smooth muscle actin levels are increased in hepatic fibrosis but decreased in hepatocellular carcinoma

Alpha Smooth Muscle Actin (a-SMA) is upregulated together with extracellular matrix (ECM) during activation of Hepatic Stellate Cells (HSCs) in fibrosis. Histone deacetylase (HDAC) remove acetylations and regulate the expression of genes, which is associated with cancers. There is a close relationship between cirrhosis and hepatocellular carcinoma (HCC), and markers enabling identification of patients in risk of developing HCC with cirrhosis is a major unmet clinical need. We developed an ELISA for the assessment of acetylated a-SMA (Acetylated a-SMA) in serum. The objective was to investigate the ability of this marker to non-invasively diagnose hepatic fibrosis and assess the influence of HDAC in hepatocellular carcinoma (HCC).

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Nordic Bioscience A/S, Nordic Bioscience AS
Authors: Nielsen, M. (Ekstern), Nielsen, S. H. (Intern), Hansen, N. (Intern), Kristensen, J. H. (Intern), Karsdal, M. (Ekstern), Leeming, D. J. (Ekstern)
Pages: S512
Publication date: 2015
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Main Research Area: Technical/natural sciences

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Journal: Journal of Hepatology
Volume: 62
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Ratings:
BFI (2018): BFI-level 2
BFI (2017): BFI-level 2
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): SJR 4.796 SNIP 2.82 CiteScore 7.43
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 4.7 SNIP 3.137 CiteScore 7.56
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 4.09 SNIP 2.818 CiteScore 7.18
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 3.693 SNIP 2.684 CiteScore 6.86
ISI indexed (2013): ISI indexed yes
Pan-cancer analysis of genomic scar signatures associated with homologous recombination deficiency suggests novel indications for existing cancer drugs

Ovarian and triple-negative breast cancers with BRCA1 or BRCA2 loss are highly sensitive to treatment with PARP inhibitors and platinum-based cytotoxic agents and show an accumulation of genomic scars in the form of gross DNA copy number aberrations. Cancers without BRCA1 or BRCA2 loss but with accumulation of similar genomic scars also show increased sensitivity to platinum-based chemotherapy. Therefore, reliable biomarkers to identify DNA repair-deficient cancers prior to treatment may be useful for directing patients to platinum chemotherapy and possibly PARP inhibitors. Recently, three SNP array-based signatures of chromosomal instability were published that each quantitate a distinct type of genomic scar considered likely to be caused by improper DNA repair. They measure telomeric allelic imbalance (named NtAI), large scale transition (named LST), and loss of heterozygosity (named HRD-LOH), and it is suggested that these signatures may act as biomarkers for the state of DNA repair deficiency in a given cancer. We explored the pan-cancer distribution of scores of the three signatures utilizing a panel of 5371 tumors representing 15 cancer types from The Cancer Genome Atlas, and found a good correlation between scores of the three signatures (Spearman’s ρ 0.73-0.87). In addition we found that cancer types ordinarily receiving platinum as standard of care have higher median scores of all three signatures. Interestingly, we also found that smaller subpopulations of high-scoring tumors exist in most cancer types, including those for which platinum chemotherapy is not standard therapy. Within several cancer types that are not ordinarily treated with platinum chemotherapy, we identified tumors with high levels of the three genomic biomarkers. These tumors represent identifiable subtypes of patients which may be strong candidates for clinical trials with PARP inhibitors or platinum-based chemotherapeutic regimens.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Cancer Systems Biology, Dana-Farber Cancer Institute, Brigham and Women's Hospital
Pan-genome Analysis of Human Gastric Pathogen H. pylori: Comparative Genomics and Pathogenomics Approaches to Identify Regions Associated with Pathogenicity and Prediction of Potential Core Therapeutic Targets

Helicobacter pylori is a human gastric pathogen implicated as the major cause of peptic ulcer and second leading cause of gastric cancer (similar to 70%) around the world. Conversely, an increased resistance to antibiotics and hindrances in the development of vaccines against H. pylori are observed. Pan-genome analyses of the global representative H. pylori isolates consisting of 39 complete genomes are presented in this paper. Phylogenetic analyses have revealed close relationships among geographically diverse strains of H. pylori. The conservation among these genomes was further analyzed by pan-genome approach; the predicted conserved gene families (1,193) constitute similar to 77% of the average H. pylori genome and 45% of the global gene repertoire of the species. Reverse vaccinology strategies have been adopted to identify and narrow down the potential core-immunogenic candidates. Total of 28 nonhost homolog proteins were characterized as universal therapeutic targets against H. pylori based on their functional annotation and protein-protein interaction. Finally, pathogenomics and genome plasticity analysis revealed 3 highly conserved and 2 highly variable putative pathogenicity islands in all of the H. pylori genomes been analyzed.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Federal University of Minas Gerais, National University of Sciences and Technology, Khyber Medical University, Federal University of Pará, Institute of Integrative Omics and Applied Biotechnology
Number of pages: 17
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Volume: 2015
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BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.32 SJR 0.843 SNIP 0.875
Pathway and network analysis of cancer genomes

Genomic information on tumors from 50 cancer types cataloged by the International Cancer Genome Consortium (ICGC) shows that only a few well-studied driver genes are frequently mutated, in contrast to many infrequently mutated genes that may also contribute to tumor biology. Hence there has been large interest in developing pathway and network analysis methods that group genes and illuminate the processes involved. We provide an overview of these analysis techniques and show where they guide mechanistic and translational investigations.

General information

State: Published
Organisations: Department of Systems Biology, Cellular Signal Integration, University of Toronto, Ontario Institute for Cancer Research, Oregon Health and Science University, National Cancer Center, Spanish National Cancer Research Centre, Wellcome Trust Sanger Institute, Pompeu Fabra University, University of Queensland, Memorial Sloan-Kettering Cancer Center
Authors: Creixell, P. (Intern), Reimand, J. (Ekstern), Haider, S. (Ekstern), Wu, G. (Ekstern), Shibata, T. (Ekstern), Vazquez, M. (Ekstern), Mustonen, V. (Ekstern), Gonzalez-Perez, A. (Ekstern), Pearson, J. (Ekstern), Sander, C. (Ekstern), Linding, R. (Intern)
Number of pages: 7
Pages: 615-621
Publication date: 2015
Main Research Area: Technical/natural sciences
Population genetic differentiation of height and body mass index across Europe

Across-nation differences in the mean values for complex traits are common (1-8), but the reasons for these differences are unknown. Here we find that many independent loci contribute to population genetic differences in height and body mass index (BMI) in 9,416 individuals across 14 European countries. Using discovery data on over 250,000 individuals and unbiased effect size estimates from 17,500 sibling pairs, we estimate that 24% (95% credible interval (CI) = 9%, 41%) and 8% (95% CI = 4%, 16%) of the captured additive genetic variance for height and BMI, respectively, reflect population genetic differences. Population genetic divergence differed significantly from that in a null model (height, P < 3.94 x 10^-8; BMI, P < 5.95 x 10^-4), and we find an among-population genetic correlation for tall and slender individuals (r = -0.80, 95% CI = -0.95, -0.60), consistent with correlated selection for both phenotypes. Observed differences in height among populations reflected the predicted genetic means (r = 0.51; P < 0.001), but environmental differences across Europe masked genetic differentiation for BMI (P < 0.58).
Population genomics of Bronze Age Eurasia

The Bronze Age of Eurasia (around 3000-1000 BC) was a period of major cultural changes. However, there is debate about whether these changes resulted from the circulation of ideas or from human migrations, potentially also facilitating the spread of languages and certain phenotypic traits. We investigated this by using new, improved methods to sequence low-coverage genomes from 101 ancient humans from across Eurasia. We show that the Bronze Age was a highly dynamic period involving large-scale population migrations and replacements, responsible for shaping major parts of present-day demographic structure in both Europe and Asia. Our findings are consistent with the hypothesized spread of Indo-European languages during the Early Bronze Age. We also demonstrate that light skin pigmentation in Europeans was already present at high frequency in the Bronze Age, but not lactose tolerance, indicating a more recent onset of positive selection on lactose tolerance than previously thought.
Predicting facial characteristics from complex polygenic variations

Research into the importance of the human genome in the context of facial appearance is receiving increasing attention and has led to the detection of several Single Nucleotide Polymorphisms (SNPs) of importance. In this work we attempt a holistic approach predicting facial characteristics from genetic principal components across a population of 1,266 individuals. For this we perform a genome-wide association analysis to select a large number of SNPs linked to specific facial traits, recode these to genetic principal components and then use these principal components as predictors for facial traits in a linear regression. We show in this proof-of-concept study for facial trait prediction from genome-wide SNP data that some facial characteristics can be modeled by genetic information: facial width, eyebrow width, distance between eyes, and features involving mouth shape are predicted with statistical significance (p < 0.03).

General information
State: Published
Organisations: Department of Applied Mathematics and Computer Science, Image Analysis & Computer Graphics, Department of Systems Biology, Center for Biological Sequence Analysis, Behavioral Phenomics, Novo Nordisk Foundation Center for Biosustainability, Boston Children’s Hospital, deCODE Genetics
Number of pages: 6
Prediction of Antibody Epitopes

Antibodies recognize their cognate antigens in a precise and effective way. In order to do so, they target regions of the antigenic molecules that have specific features such as large exposed areas, presence of charged or polar atoms, specific secondary structure elements, and lack of similarity to self-proteins. Given the sequence or the structure of a protein of interest, several methods exploit such features to predict the residues that are more likely to be recognized by an immunoglobulin. Here, we present two methods (BepiPred and DiscoTope) to predict linear and discontinuous antibody epitopes from the sequence and/or the three-dimensional structure of a target protein.

General information
State: Published
Organisations: Immunological Bioinformatics, Department of Systems Biology, Center for Biological Sequence Analysis
Authors: Nielsen, M. (Intern), Marcatili, P. (Intern)
Host publication information
Title of host publication: Peptide Antibodies
Volume: 1348
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Chapter: 4
Series: Methods in Molecular Biology
ISSN: 1064-3745
Main Research Area: Technical/natural sciences
Discontinuous epitope, Epitope, Linear epitope, Prediction
DOIs:
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Source: FindIt
Source-ID: 2282468768
Publication: Research - peer-review › Book chapter – Annual report year: 2015

Pre-labor cesarean section bypasses natural immune cell maturation

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, University of Copenhagen
Authors: Thysen, A. H. (Intern), Larsen, J. M. (Intern), Rasmussen, M. A. (Ekstern), Stokholm, J. (Ekstern), Bennelykke, K. (Ekstern), Bisgaard, H. F. (Ekstern), Brix, S. (Intern)
Pages: 1123-1125.e6
Publication date: 2015
Main Research Area: Technical/natural sciences

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Journal: Journal of Allergy and Clinical Immunology
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Web of Science (2017): Indexed yes
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Scopus rating (2016): CiteScore 6.87 SJR 5.33 SNIP 2.886
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 5.611 SNIP 2.826 CiteScore 6.62
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 4.869 SNIP 2.943 CiteScore 6.61
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 4.966 SNIP 3.04 CiteScore 7.1
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 4.669 SNIP 2.844 CiteScore 6.94
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 5.221 SNIP 2.69 CiteScore 6.8
ISI indexed (2011): ISI indexed yes
Protein raftophilicity. How bioinformatics can help membranologists

Protein raftophilicity is the affinity of proteins for lipid ‘rafts’. Rafts denote nano- and submicro-sized biomembrane domains that are enriched in cholesterol and sphingolipids. These domains are considered relevant for maintaining specialized structures that constitute suitable sites for bioprocesses. Protein raftophilicity depends on features such as lipidation and GPI-anchoring. Can this affinity be inferred solely by knowing such features, without knowing the physical and physico-chemical properties of biomembranes? We tried to answer the question by an artificial neural network (ANN)-based bioinformatics approach. The ANN was trained to recognize feature-based patterns in proteins that are considered to be associated with lipid rafts. The trained ANN was then used to predict protein raftophilicity. We found that, in the case of α-helical membrane proteins, their hydrophobic length does not affect their raftophilicity. This is in agreement with confocal microscopy experiments on DOPC/SM/cholesterol bilayers with reconstituted model peptides, P-23 and P-29.

General information

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Functional Human Variation
Authors: Nielsen, H. (Intern), Sperotto, M. M. (Intern)
Number of pages: 1
Publication date: 2015
Event: Abstract from First Annual Danish Bioinformatics Conference, Odense, Denmark.
Main Research Area: Technical/natural sciences
Electronic versions:

Reads2Type: a web application for rapid microbial taxonomy identification

Identification of bacteria may be based on sequencing and molecular analysis of a specific locus such as 16S rRNA, or a set of loci such as in multilocus sequence typing. In the near future, healthcare institutions and routine diagnostic microbiology laboratories may need to sequence the entire genome of microbial isolates. Therefore we have developed Reads2Type, a web-based tool for taxonomy identification based on whole bacterial genome sequence data. Raw sequencing data provided by the user are mapped against a set of marker probes that are derived from currently available bacteria complete genomes. Using a dataset of 1003 whole genome sequenced bacteria from various sequencing platforms, Reads2Type was able to identify the species with 99.5 % accuracy and on the minutes time scale. In comparison with other tools, Reads2Type offers the advantage of not needing to transfer sequencing files, as the entire computational analysis is done on the computer of whom utilizes the web application. This also prevents data privacy issues to arise. The Reads2Type tool is available at http://www.cbs.dtu.dk/~dhany/reads2type.html.
Reappearance of Salmonella serovar Choleraesuis var. Kunzendorf in Danish pig herds

Salmonella enterica serovar Choleraesuis is a porcine adapted serovar which may cause serious outbreaks in pigs. Here we describe outbreaks of salmonellosis due to S. Choleraesuis in four Danish pig farms in 2012–2013 by clinic, serology, and microbiology and compare the isolates to those of a previous outbreak in 1999–2000. The infection was in some herds associated with high mortality and a moderate to high sero-prevalence was found. In 2012–2013 the disease contributed to increased mortality but occurred concomitant with other disease problems in the herds, which likely delayed the diagnosis by up to several months. Nine isolates from the four farms in 2012–2013 and 14 isolates obtained from the outbreak in Denmark in 1999–2000 were subjected to typing using pulsed-field gel electrophoresis (PFGE). Seven isolates were selected for whole genome sequencing (WGS). The PFGE results of 23 isolates displayed five different profiles. The isolates from 2012 to 2013 revealed two distinct profiles, both different from the isolates recovered in 1999–2000. Two of the 2012–2013 farms shared PFGE profiles and had also transported pigs between them. The profile found in the two other 2012–2013 farms was indistinguishable but no epidemiological connection between these farms was found. Analysis of the number of single nucleotide polymorphisms (SNPs) from the WGS data indicated that the isolates from the farms in 2012–2013 were more closely related to each other than to isolates from the outbreak in 1999. It was therefore concluded that the infection was a new introduction and not a persistent infection since the outbreak in 1999. It may further be suggested that there were two or three independent rather than a single introduction. The re-introduction of S. Choleraesuis in Denmark emphasizes the importance of strict hygiene measures in the herds. Further investigations using WGS are now in progress on a larger collection of isolates to study clonality at European level and trace the origin of the infections.
Reduced ex vivo stimulated IL-6 response in infants randomized to fish oil from 9 to 18 months, especially among PPARG2 and COX2 wild types

We investigated whether n-3 LCPUFA affected immune function in late infancy and explored effect-modification by single nucleotide polymorphisms (SNPs) and links to intestinal microbiota. Infants (n=105) were randomized to fish oil (FO, 1.2 g/d n-3 LCPUFA) or sunflower oil (SO)-supplements from age 9-18 months. Immune function was assessed by ex vivo cytokine production in stimulated blood and plasma immunoglobulin E (IgE). We genotyped functional SNPs in PPARG2...
and COX2 and analyzed fecal microbiota by 16S-rRNA terminal restriction fragment length polymorphism. FO compared to SO reduced Lactobacillus paracasei-stimulated IL-6 at 18 months (P=0.03, n=104). This effect was most pronounced among infants wild-type for PPARG2-Pro12Ala and/or COX2-T8473C (P<0.05). Predominant bacterial fragments were associated with 18 months IgE in all infants (P=0.004) (bp100) and with IL-6 production among infants weaned before 9 months (P=0.047) (bp102). Thus, FO reduced IL-6 in a genotype-modified manner. The microbiota was partly linked to IL-6 and IgE, not directly to FO.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Copenhagen, National Research Center for Working Environment
Authors: Harslof, L. B. S. (Ekstern), Damsgaard, C. T. (Ekstern), Andersen, A. D. (Ekstern), Aakjaer, D. L. (Ekstern), Michaelesen, K. F. (Ekstern), Hellgren, L. I. (Intern), Frekjaer, H. (Ekstern), Vogel, U. (Ekstern), Lauritzen, L. (Ekstern)
Number of pages: 7
Pages: 21-27
Publication date: 2015
Main Research Area: Technical/natural sciences

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Journal: Prostaglandins, Leukotrienes & Essential Fatty Acids
Volume: 94
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Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): SJR 1.345 SNIP 1.055 CiteScore 3.17
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.217 SNIP 0.984 CiteScore 2.92
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.095 SNIP 0.804 CiteScore 2.54
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.066 SNIP 0.935 CiteScore 2.94
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.172 SNIP 1.155 CiteScore 3.19
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.33 SNIP 1.042 CiteScore 3.42
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.052 SNIP 0.916
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 0.906 SNIP 0.91
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 1.079 SNIP 0.865
Scopus rating (2007): SJR 1.069 SNIP 0.92
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 1.067 SNIP 0.873
Scopus rating (2005): SJR 0.992 SNIP 0.739
Scopus rating (2004): SJR 0.965 SNIP 0.695
Scopus rating (2003): SJR 0.694 SNIP 0.601
Scopus rating (2002): SJR 0.52 SNIP 0.485
Scopus rating (2001): SJR 0.669 SNIP 0.613
Scopus rating (2000): SJR 0.515 SNIP 0.583
Relationship of postoperative thrombocytosis and survival of patients with colorectal cancer

Introduction: Thrombocytosis accompanying solid tumors and predicting the prognosis of malignant tumors has been the subject of intensive research lately. Reports so far have evaluated the role of preoperative platelet count. In our present study we looked at the effect of tumor removal on platelet count and the predictive power of postoperative thrombocytosis on the survival of patients with colorectal cancer (CRC).

Methods: We retrospectively evaluated the clinical and histopathological data of 336 patients operated due to CRC between 2001 and 2011. Thrombocytosis was defined as a platelet count exceeding 400 × 10^3/μL. Preoperative platelet count was compared with the value measured 1 month postoperatively. Results: The platelet count significantly decreased after the removal of the primary tumor (paired Wilcoxon test p <0.001). In univariate analysis reoperative thrombocytosis was a significant marker of overall survival (OS) with HR 2.2, p <0.001 while the postoperative thrombocytosis was nearly significant with HR = 1.59, p = 0.087. In multivariate setting, when corrected for location, stage, tumor size and controlling for gender and age (>65 years vs. ≤65 years), both pre- and postoperative thrombocytosis were significant independent prognostic markers with HR 1.80, p = 0.20 and HR = 1.98, p = 0.018, respectively. Discussion and conclusion: Although the pathomechanism of thrombocytosis related to solid tumors is not known the decrease of platelet count after the removal of the primary tumor raises the possibility that the tumor may play an active role in the development of thrombocytosis. Furthermore, the observation of postoperative thrombocytosis with significant worse outcome underlines the predictive power of elevated platelet count.
Renal impairment and late toxicity in germ-cell cancer survivors

Background Treatment with bleomycin–etoposide–cisplatin (BEP) impairs renal function and increases the risk of late cardiovascular disease (CVD) and death. We investigated the influence of BEP on glomerular filtration rate (GFR) and assessed the importance of GFR changes on CVD and death in a large cohort of germ-cell cancer survivors.

Patients and methods BEP-treated patients (N = 1206) were identified in the Danish DaTeCa database, and merged with national registers to identify late toxicity. GFR were measured (51Cr-EDTA clearance) before and after treatment and at 1, 3 and 5-year follow-up. The influence of BEP on GFR was evaluated with a linear mixed model. Risk factors for late toxicity were identified by a landmark analysis adjusting for covariates. The cohort was compared with the background population with standardized hospitalization/mortality rates.

Results GFR changed (ΔGFR) −11.3%, −15.4% and −25.9% after three, four and five+ cycles of BEP. For patients with impaired renal function before treatment the changes were 4.3%, 0.0% and −12.8%, respectively. During follow-up a significant rebound of GFR was documented. Compared with the background population, all patients, irrespective of renal function, had an increased risk of CVD and death. This risk depended on chronic kidney disease stage before treatment but not after treatment. ΔGFR had no influence on risk of late toxicity [death: hazard ratio (HR) 1.06, P = 0.50; CVD: HR 0.97, P = 0.61].

Conclusions Renal function after BEP is closely related to number of cycles, but the changes in GFR are partly reversible and have no impact on risk of CVD or death.
The qac genes of Staphylococcus species encode multidrug efflux pumps: membrane proteins that export toxic molecules and thus increase tolerance to a variety of compounds such as disinfecting agents, including quaternary ammonium compounds (for which they are named), intercalating dyes and some antibiotics. In Staphylococcus species, six different plasmid-encoded Qac efflux pumps have been described, and they belong to two major protein families. QacA and QacB are members of the Major Facilitator Superfamily, while QacC, QacG, QacH, and QacJ all belong to the Small Multidrug Resistance (SMR) family. Not all SMR proteins are called Qac and the reverse is also true, which has caused confusion in the literature and in gene annotations. The discovery of qac genes and their presence in various staphylococcal populations is briefly reviewed. A sequence comparison revealed that some of the PCR primers described in the literature for qac detection may miss particular qac genes due to lack of DNA conservation. Despite their resemblance in substrate specificity, the Qac proteins belonging to the two protein families have little in common. QacA and QacB are highly conserved in Staphylococcus species, while qacA was also detected in Enterococcus faecalis, suggesting that these plasmid-born genes have spread across bacterial genera. Nevertheless, these qacA and qacB genes are quite dissimilar to their closest homologues in other organisms. In contrast, SMR-type Qac proteins display considerable sequence
variation, despite their short length, even within the Staphylococcus genus. Phylogenetic analysis of these genes identified similarity to a large number of other SMR members, found in staphylococci as well as in other genera. A number of phylogenetic trees of SMR Qac proteins are presented here, starting with genes present in S. aureus and S. epidermidis, and extending this to related genes found in other species of this genus, and finally to genes found in other genera.

**General information**

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Molecular Microbiology and Genomics Consultants, University of Copenhagen
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10.1556/eujmi-d-14-00038
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RNA sequencing atopic dermatitis transcriptome profiling provides insights into novel disease mechanisms with potential therapeutic implications

Background: Genomic profiling of lesional and nonlesional skin of patients with atopic dermatitis (AD) using microarrays has led to increased understanding of AD and identification of novel therapeutic targets. However, the limitations of microarrays might decrease detection of AD genes. These limitations might be lessened with next-generation RNA sequencing (RNA-seq).

Objective: We sought to define the lesional AD transcriptome using RNA-seq and compare it using microarrays performed on the same cohort.

Methods: RNA-seq and microarrays were performed to identify differentially expressed genes (criteria: fold change, ≥2.0; false discovery rate ≤0.05) in lesional versus nonlesional skin from 18 patients with moderate-to-severe AD, with real-time PCR (RT-PCR) and immunohistochemistry used for validation.

Results: Both platforms showed robust disease transcriptomes and correlated well with RT-PCR. The common AD transcriptome identified by using both techniques contained 217 genes, including inflammatory (S100A8/A9/A12, CXCL1, and 2′-5′-oligoadenylate synthetase-like [OASL]) and barrier (MKi67, keratin 16 [K16], and claudin 8 [CLDN8]) AD-related genes. Although fold change estimates determined by using RNA-seq showed somewhat better agreement with RT-PCR (intraclass correlation coefficient, 0.57 and 0.70 for microarrays and RNA-seq vs RT-PCR, respectively), bias was not eliminated. Among genes uniquely identified by using RNA-seq were triggering receptor expressed on myeloid cells 1 (TREM-1) signaling (eg, CCL2, CCL3, and single immunoglobulin domain IL1R1 related [SIGIRR]) and IL-36 isoform genes. TREM-1 is a surface receptor implicated in innate and adaptive immunity that amplifies infection-related inflammation.

Conclusions: This is the first report of a lesional AD phenotype using RNA-seq and the first direct comparison between platforms in this disease. Both platforms robustly characterize the AD transcriptome. Through RNA-seq, we unraveled novel disease pathology, including increased expression of the novel TREM-1 pathway and the IL-36 cytokine in patients with AD.

**General information**

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Regulatory Genomics, ZymoGenetics, The Rockefeller University
Selecting key toxins for focused development of elapid snake antivenoms and inhibitors guided by a Toxicity Score

For more than 100 years, antivenoms have been produced by traditional methods of immunization of large mammals with mixtures of snake venoms (World Health Organization, 2010 and Gutiérrez et al., 2011). With the introduction of proteomic and transcriptomic tools in the molecular analysis of both venoms (venomics) (Calvete, 2014) and antivenoms (antivenomics) (Calvete, 2011 and Calvete et al., 2014), in combination with the toxicological assessment of venoms, a more in-depth understanding of venom composition and antivenom efficacy is being built. As retrieved from current public databases on Elapidae, values for Median Lethal Dose (LD50) are known for 203 toxins, belonging to seven protein subfamilies, originating from 40 species (Fig. 1). Furthermore, the number of elapids for which venom-wide proteomics or transcriptomics studies have been reported has now reached 49 out of 355 described species (our unpublished data; http://www.reptile-database.org). Information is now available for a considerable number of species of high medical relevance.

General information
State: Published
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Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.33 SJR 0.752 SNIP 1.056
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.903 SNIP 1.05 CiteScore 2.47
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.972 SNIP 1.104 CiteScore 2.48
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.008 SNIP 1.244 CiteScore 2.9
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.022 SNIP 1.352 CiteScore 2.85
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 0.899 SNIP 1.06 CiteScore 2.54
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 0.866 SNIP 1.138
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 0.745 SNIP 0.979
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 0.887 SNIP 1.068
Web of Science (2008): Indexed yes
Sequenza: allele-specific copy number and mutation profiles from tumor sequencing data

Background: Exome or whole genome deep sequencing of tumor DNA along with paired normal DNA can potentially provide a detailed picture of the somatic mutations that characterize the tumor. However, analysis of such sequence data can be complicated by the presence of normal cells in the tumor specimen, by intratumor heterogeneity, and by the sheer size of the raw data. In particular, determination of copy number variations from exome sequencing data alone has proven difficult; thus SNP arrays have often been used for this task. Recently, algorithms to estimate absolute, but not allele-specific, copy number profiles from tumor sequencing data have been described.

Materials and Methods: We developed Sequenza, a software package that uses paired tumor-normal DNA sequencing data to estimate tumor cellularity and ploidy, and to calculate allele-specific copy number profiles and mutation profiles. We applied Sequenza, as well as two previously published algorithms, to exome sequence data from 30 tumors from The Cancer Genome Atlas. We assessed the performance of these algorithms by comparing their results to those generated using matched SNP arrays and processed by the ASCAT algorithm.

Results: Comparison between Sequenza/exome and SNP/ASCAT revealed strong correlation in cellularity (Pearson’s r = 0.90) and ploidy estimates (r = 0.42, or r = 0.94 after manual inspecting alternative solutions). This performance was noticeably superior to previously published algorithms. In addition, in artificial data simulating normal-tumor admixtures, Sequenza detected the correct ploidy in samples with tumor content as low as 30%.

Conclusions: The agreement between Sequenza and SNP array-based copy number profiles suggests that exome sequencing alone is sufficient not only for identifying small scale mutations but also for estimating cellularity and inferring DNA copy number aberrations.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Cancer Systems Biology
Authors: Favero, F. (Intern), Joshi, T. (Intern), Marquard, A. M. (Intern), Birkbak, N. J. (Intern), Krzystanek, M. (Intern), Li, Q. (Intern), Szallasi, Z. I. (Intern), Eklund, A. C. (Intern)
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BFI (2018): BFI-level 2
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Web of Science (2017): Indexed Yes
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Scopus rating (2016): CiteScore 8.09 SJR 4.929 SNIP 3.072
Web of Science (2016): Indexed yes
Serological assessment of neutrophil elastase activity on elastin during lung ECM remodeling

Background: During the pathological destruction of lung tissue, neutrophil elastase (NE) degrades elastin, one of the major constituents of lung parenchyma. However there are no non-invasive methods to quantify NE degradation of elastin. We selected specific elastin fragments generated by NE for antibody generation and developed an ELISA assay (EL-NE) for the quantification of NE-degraded elastin.

Methods: Monoclonal antibodies were developed against 10 NE-specific cleavage sites on elastin. One EL-NE assay was tested for analyte stability, linearity and intra-and inter-assay variation. The NE specificity was demonstrated using elastin cleaved in vitro with matrix metalloproteinases (MMPs), cathepsin G (CatG), NE and intact elastin. Clinical relevance was assessed by measuring levels of NE-generated elastin fragments in serum of patients diagnosed with idiopathic pulmonary fibrosis (IPF, n = 10) or lung cancer (n = 40).

Results: Analyte recovery of EL-NE for human serum was between 85% and 104%, the analyte was stable for four
freeze/thaw cycles and after 24 h storage at 4 degrees C. EL-NE was specific for NE-degraded elastin. Levels of NE-generated elastin fragments for elastin incubated in the presence of NE were 900% to 4700% higher than those seen with CatG or MMP incubation or in intact elastin. Serum levels of NE-generated elastin fragments were significantly increased in patients with IPF (137%, $p = 0.002$) and in patients with lung cancer (510%, $p < 0.001$) compared with age-and sex-matched controls.

Conclusions: The EL-NE assay was specific for NE-degraded elastin. The EL-NE assay was able to specifically quantify NE-degraded elastin in serum. Serum levels of NE-degraded elastin might be used to detect excessive lung tissue degradation in lung cancer and IPF.

General information
State: Published
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BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.76 SJR 1.128 SNIP 1.131
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.078 SNIP 1.026 CiteScore 2.69
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.142 SNIP 1.145 CiteScore 2.97
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.111 SNIP 1.177 CiteScore 3.24
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.246 SNIP 1.448 CiteScore 3.41
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.257 SNIP 1.252 CiteScore 3.08
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 0.996 SNIP 1.011
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 0.883 SNIP 1.138
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 1.007 SNIP 0.806
Scopus rating (2007): SJR 0.577 SNIP 0.705
Scopus rating (2006): SJR 0.666 SNIP 0.594
Scopus rating (2005): SJR 0.279 SNIP 0.402
Scopus rating (2004): SJR 0.243 SNIP 0.346
Scopus rating (2003): SJR 0.211 SNIP 0.111
Scopus rating (2002): SJR 0.263 SNIP 0.085
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Serological_assessment_of_neutrophil.pdf
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SETD2 loss-of-function promotes renal cancer branched evolution through replication stress and impaired DNA repair

Defining mechanisms that generate intratumour heterogeneity and branched evolution may inspire novel therapeutic approaches to limit tumour diversity and adaptation. SETD2 (Su(var), Enhancer of zeste, Trithorax-domain containing 2) trimethylates histone-3 lysine-36 (H3K36me3) at sites of active transcription and is mutated in diverse tumour types, including clear cell renal carcinomas (ccRCCs). Distinct SETD2 mutations have been identified in spatially separated regions in ccRCC, indicative of intratumour heterogeneity. In this study, we have addressed the consequences of SETD2 loss-of-function through an integrated bioinformatics and functional genomics approach. We find that bi-allelic SETD2 aberrations are not associated with microsatellite instability in ccRCC. SETD2 depletion in ccRCC cells revealed aberrant and reduced nucleosome compaction and chromatin association of the key replication proteins minichromosome maintenance complex component (MCM7) and DNA polymerase δ hindering replication fork progression, and failure to load lens epithelium-derived growth factor and the Rad51 homologous recombination repair factor at DNA breaks. Consistent with these data, we observe chromosomal breakpoint locations are biased away from H3K36me3 sites in SETD2 wild-type ccRCCs relative to tumours with bi-allelic SETD2 aberrations and that H3K36me3-negative ccRCCs display elevated DNA damage in vivo. These data suggest a role for SETD2 in maintaining genome integrity through nucleosome stabilization, suppression of replication stress and the coordination of DNA repair.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Cancer Systems Biology, UCL Cancer Institute, Paul O'Gorman Building, Cancer Research UK, London Research Institute, Danish Cancer Society, Palacky University, Wellcome Trust Sanger Institute, Queen Mary University of London, Royal Marsden Hospital
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BFI (2016): BFI-level 1
Scopus rating (2016): SJR 3.383 SNIP 1.685 CiteScore 6.59
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 3.948 SNIP 1.743 CiteScore 6.77
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 4.371 SNIP 1.691 CiteScore 6.83
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 4.758 SNIP 1.754 CiteScore 7.39
Type 1 diabetes (T1D) is a polygenic autoimmune disease that is often present with autoantibodies directed against pancreatic islet proteins. Many genetic susceptibility loci are shared with other autoimmune or immune-mediated diseases that also cosegregate in families with T1D. The aim of this study was to investigate whether susceptibility loci identified in genome-wide association studies (GWAS) of T1D were also associated with autoantibody positivity in individuals with diabetes. Fifty single nucleotide polymorphisms (SNPs) were genotyped in 6,556 multiethnic cases collected by the Type 1 Diabetes Genetics Consortium (T1DGC). These were tested for association with three islet autoantibodies—against autoantibodies to GAD (GADA), IA-2 (IA-2A), and zinc transporter 8 (ZnT8A)—and autoantibodies against thyroid peroxidase (TPOA) in autoimmune thyroid disease, gastric parietal cells (PCA) in autoimmune gastritis, transglutaminase (TGA) in celiac disease, and 21-hydroxylase (21-OHA) in autoimmune hypoadrenalism. In addition to the MHC region, we identify SNPs in five susceptibility loci (IFIH1, PTPN22, SH2B3, BACH2, and CTLA4) as significantly associated with more than one autoantibody at a false discovery rate less than 5%. IFIH1/2q24 demonstrated the most unrestricted association, as significant association was demonstrated for PCA, TPOA, GADA, 21-OHA, and IA-2A. In addition, 11 loci were significantly associated with a single autoantibody.
Shared genetic origins of allergy and autoimmune diseases

Parallel increases in allergy and autoimmune disease prevalence in recent time suggest shared, but yet unknown, etiologies. Here, we investigated shared genetic loci and molecular pathways to identify possible shared disease mechanisms between allergy and autoimmune diseases.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Copenhagen, Helmholtz Zentrum München, Imperial College London, University of Queensland, University of Groningen, Boston Children’s Hospital, Busselton Population Medical Research Foundation, University of Manchester, 23andMe, University of Western Australia, University of Bristol, QIMR Berghofer Medical Research Institute, University of London
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Web of Science (2017): Indexed yes
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Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 3.13 SNIP 2.127 CiteScore 5.73
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.464 SNIP 2.121 CiteScore 5.51
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 2.195 SNIP 1.902 CiteScore 4.91
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 2.008 SNIP 1.818 CiteScore 4.81
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 2.328 SNIP 1.781 CiteScore 4.89
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.826 SNIP 1.845
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.681 SNIP 0.958
SNPsnap: a Web-based tool for identification and annotation of matched SNPs

Summary: An important computational step following genome-wide association studies (GWAS) is to assess whether disease or trait-associated single-nucleotide polymorphisms (SNPs) enrich for particular biological annotations. SNP-based enrichment analysis needs to account for biases such as co-localization of GWAS signals to gene-dense and high linkage disequilibrium (LD) regions, and correlations of gene size, location and function. The SNPsnap Web server enables SNP-based enrichment analysis by providing matched sets of SNPs that can be used to calibrate background expectations. Specifically, SNPsnap efficiently identifies sets of randomly drawn SNPs that are matched to a set of query SNPs based on allele frequency, number of SNPs in LD, distance to nearest gene and gene density.

Availability and implementation: SNPsnap server is available at http://www.broadinstitute.org/mpg/snpsnap/. Contact: joelh@broadinstitute.org

Supplementary information: Supplementary data are available at Bioinformatics online.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Behavioral Phenomics, Boston Children's Hospital
Authors: Pers, T. H. (Intern), Timshel, P. (Ekstern), Hirschhorn, J. N. (Ekstern)
Number of pages: 3
Pages: 418-420
Publication date: 2015
Main Research Area: Technical/natural sciences

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ISSN (Print): 1367-4803
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BFI (2017): BFI-level 2
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 6.42
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Software-Supported USER Cloning Strategies for Site-Directed Mutagenesis and DNA Assembly
USER cloning is a fast and versatile method for engineering of plasmid DNA. We have developed a user friendly Web server tool that automates the design of optimal PCR primers for several distinct USER cloning-based applications. Our Web server, named AMUSER (Automated DNA Modifications with USER cloning), facilitates DNA assembly and introduction of virtually any type of site-directed mutagenesis by designing optimal PCR primers for the desired genetic changes. To demonstrate the utility, we designed primers for a simultaneous two-position site-directed mutagenesis of green fluorescent protein (GFP) to yellow fluorescent protein (YFP), which in a single step reaction resulted in a 94% cloning efficiency. AMUSER also supports degenerate nucleotide primers, single insert combinatorial assembly, and flexible parameters for PCR amplification. AMUSER is freely available online at .

General information
State: Published
Organisations: Novo Nordisk Foundation Center for Biosustainability, Bacterial Cell Factories, Center for Biological Sequence Analysis, Department of Systems Biology, Department of Chemistry, Drug Resistance and Community Dynamics, University of Copenhagen
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Somatic Cell Fusions Reveal Extensive Heterogeneity in Basal-like Breast Cancer

Basal-like and luminal breast tumors have distinct clinical behavior and molecular profiles, yet the underlying mechanisms are poorly defined. To interrogate processes that determine these distinct phenotypes and their inheritance pattern, we generated somatic cell fusions and performed integrated genetic and epigenetic (DNA methylation and chromatin) profiling. We found that the basal-like trait is generally dominant and is largely defined by epigenetic repression of luminal transcription factors. Definition of super-enhancers highlighted a core program common in luminal cells but a high degree of heterogeneity in basal-like breast cancers that correlates with clinical outcome. We also found that protein extracts of basal-like cells are sufficient to induce a luminal-to-basal phenotypic switch, implying a trigger of basal-like autoregulatory circuits. We determined that KDM6A might be required for luminal-basal fusions, and we identified EN1, TBX18, and TCF4 as candidate transcriptional regulators of the luminal-to-basal switch. Our findings highlight the remarkable epigenetic plasticity of breast cancer cells.
Structural Characterization of Peptide Antibodies

The role of proteins as very effective immunogens for the generation of antibodies is indisputable. Nevertheless, cases in which protein usage for antibody production is not feasible or convenient compelled the creation of a powerful alternative consisting of synthetic peptides. Synthetic peptides can be modified to obtain desired properties or conformation, tagged for purification, isotopically labeled for protein quantitation or conjugated to immunogens for antibody production. The antibodies that bind to these peptides represent an invaluable tool for biological research and discovery. To better understand the underlying mechanisms of antibody-antigen interaction here we present a pipeline developed by us to structurally classify immunoglobulin antigen binding sites and to infer key sequence residues and other variables that have a prominent role in each structural class.

General Information
State: Published
Organisations: Immunological Bioinformatics, Department of Systems Biology, Center for Biological Sequence Analysis, University of Southern Denmark
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Series: Methods in Molecular Biology
ISSN: 1064-3745
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Clustering, Linear epitope, Peptide antibody, Structure
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Source: FindIt
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Structural Conservation Despite Huge Sequence Diversity Allows EPCR Binding by the PfEMP1 Family Implicated in Severe Childhood Malaria

The PfEMP1 family of surface proteins is central for Plasmodium falciparum virulence and must retain the ability to bind to host receptors while also diversifying to aid immune evasion. The interaction between CIDRa1 domains of PfEMP1 and endothelial protein C receptor (EPCR) is associated with severe
childhood malaria. We combine crystal structures of CIDRa1:EPCR complexes with analysis of 885 CIDRa1 sequences, showing that the EPCR-binding surfaces of CIDRa1 domains are conserved in shape and bonding potential, despite dramatic sequence diversity. Additionally, these domains mimic features of the natural EPCR ligand and can block this ligand interaction. Using peptides corresponding to the EPCR-binding region, antibodies can be purified from individuals in malaria-endemic regions that block EPCR binding of diverse CIDRa1 variants. This highlights the extent to which such a surface protein family can diversify while maintaining ligand-binding capacity and identifies features that should be mimicked in immunogens to prevent EPCR binding.

**General information**

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Metagenomics, University of Oxford, University of Copenhagen, National Institute for Medical Research
Authors: Lau, C. K. (Ekstern), Turner, L. (Ekstern), Jespersen, J. S. (Ekstern), Lowe, E. D. (Ekstern), Petersen, B. (Intern), Wang, C. W. (Ekstern), Petersen, J. E. (Ekstern), Lusingu, J. (Ekstern), Theander, T. G. (Ekstern), Lavstsen, T. (Ekstern), Higgins, M. K. (Ekstern)
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BFI (2014): BFI-level 2
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BFI (2013): BFI-level 2
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Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 7.606 SNIP 2.223 CiteScore 9.52
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 7.812 SNIP 2.454 CiteScore 9.61
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 6.737 SNIP 2.398
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 6.646 SNIP 2.445
BFI (2008): BFI-level 1
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**Bibliographical note**

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Tabhu: tools for antibody humanization.
Antibodies are rapidly becoming essential tools in the clinical practice, given their ability to recognize their cognate antigens with high specificity and affinity, and a high yield at reasonable costs in model animals. Unfortunately, when administered to human patients, xenogeneic antibodies can elicit unwanted and dangerous immunogenic responses. Antibody humanization methods are designed to produce molecules with a better safety profile still maintaining their ability to bind the antigen. This can be accomplished by grafting the non-human regions determining the antigen specificity into a suitable human template. Unfortunately, this procedure may result in a partial or complete loss of affinity of the grafted molecule that can be restored by back-mutating some of the residues of human origin to the corresponding murine ones. This trial-and-error procedure is hard and involves expensive and time-consuming experiments. Here we present tools for antibody humanization (Tabhu) a web server for antibody humanization. Tabhu includes tools for human template selection, grafting, back-mutation evaluation, antibody modelling and structural analysis, helping the user in all the critical steps of the humanization experiment protocol.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Immunological Bioinformatics, Sapienza University of Rome
Authors: Olimpieri, P. P. (Ekstern), Marcatili, P. (Intern), Tramontano, A. (Ekstern)
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BFI (2017): BFI-level 2
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Scopus rating (2016): CiteScore 6.42
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): CiteScore 6.06
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): CiteScore 5.5
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): CiteScore 5.78
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): CiteScore 6.73
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): CiteScore 5.61
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Web of Science (2010): Indexed yes
Targeting Human Cancer by a Glycosaminoglycan Binding Malaria Protein

Plasmodium falciparum engineer infected erythrocytes to present the malarial protein, VAR2CSA, which binds a distinct type chondroitin sulfate (CS) exclusively expressed in the placenta. Here, we show that the same CS modification is present on a high proportion of malignant cells and that it can be specifically targeted by recombinant VAR2CSA (rVAR2). In tumors, placental-like CS chains are linked to a limited repertoire of cancer-associated proteoglycans including CD44 and CSPG4. The rVAR2 protein localizes to tumors in vivo and rVAR2 fused to diphtheria toxin or conjugated to hemiasterlin compounds strongly inhibits in vivo tumor cell growth and metastasis. Our data demonstrate how an evolutionarily refined parasite-derived protein can be exploited to target a common, but complex, malignancy-associated glycosaminoglycan modification.

General information

State: Published
Organisations: Center for Biological Sequence Analysis, Cancer Systems Biology, Department of Systems Biology, University of Copenhagen, Vancouver Prostate Centre, Kairos Therapeutics Inc., Boston University School of Medicine, Translational Genomics Research Institute, University of British Columbia, Retrogenix Ltd., British Columbia Cancer Agency
Authors: Salanti, A. (Ekstern), Clausen, T. M. (Ekstern), Agerbæk, M. Ø. (Ekstern), Al Nakouzi, N. (Ekstern), Dahlbäck, M. (Ekstern), Oo, H. Z. (Ekstern), Lee, S. (Ekstern), Gustavsson, T. (Ekstern), Rich, J. R. (Ekstern), Hedberg, B. J. (Ekstern), Mao, Y. (Ekstern), Barington, L. (Ekstern), Pereira, M. A. (Ekstern), LoBello, J. (Ekstern), Endo, M. (Ekstern), Fazli, L. (Ekstern), Sørensen, P. H. (Ekstern), Daugaard, M. (Ekstern), Salanti, A. (Ekstern), Clausen, T. M. (Ekstern), Agerbæk, M. Ø. (Ekstern), Al Nakouzi, N. (Ekstern), Dahlbäck, M. (Ekstern), Oo, H. Z. (Ekstern), Lee, S. (Ekstern), Gustavsson, T. (Ekstern), Rich, J. R. (Ekstern), Hedberg, B. J. (Ekstern), Mao, Y. (Ekstern), Barington, L. (Ekstern), Pereira, M. A. (Ekstern), LoBello, J. (Ekstern), Endo, M. (Ekstern), Fazli, L. (Ekstern), Sørensen, P. H. (Ekstern), Daugaard, M. (Ekstern)
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Taxonomic and metagenomic profiling of rapid sand filter microbiome reveals a high Nitrospira incidence

General information
State: Published
Organisations: Department of Systems Biology, Department of Environmental Engineering, Urban Water Engineering, Center for Biological Sequence Analysis, Metagenomics
Authors: Palomo, A. (Intern), Gülay, A. (Intern), Rasmussen, S. (Intern), Sicheritz-Pontén, T. (Intern), Smets, B. F. (Intern)
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Source: PublicationPreSubmission
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Testing the Utility of a Data-Driven Approach for Assessing BMI from Face Images

Several lines of evidence suggest that facial cues of adiposity may be important for human social interaction. However, tests for quantifiable cues of body mass index (BMI) in the face have examined only a small number of facial proportions and these proportions were found to have relatively low predictive power. Here we employed a data-driven approach in which statistical models were built using principal components (PCs) derived from objectively defined shape and color characteristics in face images. The predictive power of these models was then compared with models based on previously studied facial proportions (perimeter-to-area ratio, width-to-height ratio, and cheek-to-jaw width). Models based on 2D shape-only PCs, color-only PCs, and 2D shape and color PCs combined each performed significantly and substantially better than models based on one or more of the previously studied facial proportions. A non-linear PC model considering both 2D shape and color PCs was the best predictor of BMI. These results highlight the utility of a "bottom-up", data-driven approach for assessing BMI from face images.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Behavioral Phenomics, University of Glasgow
Authors: Wolffhechel, K. M. B. (Intern), Hahn, A. C. (Ekstern), Jarmer, H. Ø. (Intern), Fisher, C. I. (Ekstern), Jones, B. C. (Ekstern), DeBruine, L. M. (Ekstern)
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Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.414 SNIP 1.131 CiteScore 3.32
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.545 SNIP 1.141 CiteScore 3.54
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.74 SNIP 1.147 CiteScore 3.94
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.945 SNIP 1.142 CiteScore 4.15
ISI indexed (2012): ISI indexed yes
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BFI (2011): BFI-level 1
Scopus rating (2011): SJR 2.369 SNIP 1.23 CiteScore 4.58
ISI indexed (2011): ISI indexed no
Web of Science (2011): Indexed yes
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Scopus rating (2010): SJR 2.631 SNIP 1.161
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General information
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Organisations: Department of Systems Biology, Integrative Systems Biology, Center for Biological Sequence Analysis
Authors: Brunak, S. (Intern), Løngreen, P. (Intern), Rapacki, K. (Intern), Sperotto, M. M. (Intern)
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The effect of maternal Inflammation on foetal programming of metabolic disease
Maternal obesity during pregnancy increases the child's risk of developing obesity and obesity-related diseases later in life. Key components in foetal programming of metabolic risk remain to be identified; however, chronic low-grade inflammation associated with obesity might be responsible for metabolic imprinting in the offspring. We have therefore surveyed the literature to evaluate the role of maternal obesity-induced inflammation in foetal programming of obesity and related diseases. The literature on this topic is limited, so this review also includes animal models where maternal inflammation is mimicked by single injections with lipopolysaccharide (LPS). An LPS challenge results in an immunological response that resembles the obesity-induced immune profile, although LPS injections provoke a stronger response than the subclinical obesity-associated response. Maternal LPS or cytokine exposures result in increased adiposity and impaired metabolic homeostasis in the offspring, similar to the phenotype observed after exposure to maternal obesity. The cytokine levels might be specifically important for the metabolic imprinting, as cytokines are both transferable from maternal to foetal circulation and have the capability to modulate placental nutrient transfer. However, the immune response associated with obesity is moderate and therefore potentially weakened by the pregnancy-driven immune modulation, dominated by anti-inflammatory Treg and Th2 cells. We know from other low-grade inflammatory diseases, such as rheumatoid arthritis, that pregnancy can improve disease state. If pregnancy is also capable of suppressing the obesity-associated inflammation, the immunological markers might be less likely to affect metabolic programming in the
developing foetus than otherwise implied.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Cambridge
Authors: Ingvorsen, C. (Intern), Pedersen, S. B. (Intern), Ozanne, S. E. (Ekstern), Hellgren, L. (Intern)
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BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.99 SJR 1.547 SNIP 1.063
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.611 SNIP 1.049 CiteScore 2.78
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.793 SNIP 1.241 CiteScore 3.5
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.613 SNIP 1.066 CiteScore 3.66
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.507 SNIP 1.19 CiteScore 4.05
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.427 SNIP 1.055 CiteScore 2.64
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
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BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.261 SNIP 1.058
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 1.125 SNIP 1.04
Scopus rating (2007): SJR 1.038 SNIP 0.915
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 1.203 SNIP 1.117
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 1.051 SNIP 0.939
Scopus rating (2004): SJR 1.004 SNIP 0.942
Scopus rating (2003): SJR 0.812 SNIP 0.867
Scopus rating (2002): SJR 0.769 SNIP 0.796
Scopus rating (2001): SJR 0.882 SNIP 0.984
Scopus rating (2000): SJR 0.758 SNIP 0.875
The potential role of Alu Y in the development of resistance to SN38 (Irinotecan) or oxaliplatin in colorectal cancer

Background: Irinotecan (SN38) and oxaliplatin are chemotherapeutic agents used in the treatment of colorectal cancer. However, the frequent development of resistance to these drugs represents a considerable challenge in the clinic. Alus as retrotransposons comprise 11% of the human genome. Genomic toxicity induced by carcinogens or drugs can reactivate Alus by altering DNA methylation. Whether or not reactivation of Alus occurs in SN38 and oxaliplatin resistance remains unknown. Results: We applied reduced representation bisulfite sequencing (RRBS) to investigate the DNA methylome in SN38 or oxaliplatin resistant colorectal cancer cell line models. Moreover, we extended the RRBS analysis to tumor tissue from 14 patients with colorectal cancer who either did or did not benefit from capecitabine + oxaliplatin treatment. For the clinical samples, we applied a concept of 'DNA methylation entropy' to estimate the diversity of DNA methylation states of the identified resistance phenotype-associated methylation loci observed in the cell line models. We identified different loci being characteristic for the different resistant cell lines. Interestingly, 53% of the identified loci were Alu sequences—especially the Alu Y subfamily. Furthermore, we identified an enrichment of Alu Y sequences that likely results from increased integration of new copies of Alu Y sequence in the drug-resistant cell lines. In the clinical samples, SOX1 and other SOX gene family members were shown to display variable DNA methylation states in their gene regions. The Alu Y sequences showed remarkable variation in DNA methylation states across the clinical samples.

Conclusion: Our findings imply a crucial role of Alu Y in colorectal cancer drug resistance. Our study underscores the complexity of colorectal cancer aggravated by mobility of Alu elements and stresses the importance of personalized strategies, using a systematic and dynamic view, for effective cancer therapy.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Integrative Systems Biology, Aarhus University, University of Copenhagen, Aarhus University Hospital, BGI-Shenzhen, Odense University Hospital
Authors: Lin, X. (Ekstern), Stenvang, J. (Ekstern), Rasmussen, M. H. (Ekstern), Zhu, S. (Ekstern), Jensen, N. F. (Ekstern), Tarpgaard, L. S. (Ekstern), Yang, G. (Ekstern), Belling, K. C. (Intern), Andersen, C. L. (Ekstern), Li, J. (Ekstern), Bolund, L. (Ekstern), Brunner, N. (Ekstern)
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Scopus rating (2016): CiteScore 4.05 SJR 2.065 SNIP 1.122
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.287 SNIP 1.172 CiteScore 4.3
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.297 SNIP 1.205 CiteScore 4.18
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 2.141 SNIP 1.174 CiteScore 4.39
ISI indexed (2013): ISI indexed yes
The vaginal microbiome is stable in prepubertal and sexually mature Ellegaard Göttinngen Minipigs throughout an estrous cycle

Although the pig has been introduced as an advanced animal model of genital tract infections in women, almost no knowledge exists on the porcine vaginal microbiota, especially in barrier-raised Göttinngen Minipigs. In women, the vaginal microbiota plays a crucial role for a healthy vaginal environment and the fate of sexually transmitted infections such as Chlamydia trachomatis infections. Therefore, knowledge on the vaginal microbiota is urgently needed for the minipig model. The aim of this study was to characterize the microbiota of the anterior vagina by 16s rRNA gene sequencing in prepubertal and sexually mature Göttinngen Minipigs during an estrous cycle. The dominating phyla in the vaginal microbiota consisted of Firmicutes, Proteobacteria, Actinobacteria, Bacteroidetes and Tenericutes. The most abundant bacterial families were Enterobacteriaceae, unclassified families from Gammaproteobacteria, Clostridiales Family XI Incertae Sedis, Paenibacillaceae, Lactobacillaceae, Ruminococcaceae and Syntrophaceae. We found a higher abundance of Lactobacillaceae in the prepubertal Göttinngen Minipigs compared to sexually mature non-pregnant Göttinngen Minipigs. However, correlation tests and diversity parameters revealed a very stable vaginal microbiota in the
Göttingen Minipigs, both before and after sexual maturity and on different days throughout an estrous cycle. The vaginal microbiota in Göttingen Minipigs was not dominated by lactobacilli, as it is in women and according to our results the minipig vaginal microbiota is very stable, in opposite to women. These differences should be considered when using the minipig as a model of the genital tract in women.

**General information**

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, DTU Multi Assay Core, University of Copenhagen, Ellegaard Göttingen Minipigs A/S, CToxLab Scantox
Authors: Lorenzen, E. (Ekstern), Kudirkienė, E. (Ekstern), Gutman, N. (Ekstern), Grossi, A. B. (Ekstern), Agerholm, J. S. (Ekstern), Erneholm, K. (Ekstern), Skytte, C. (Ekstern), Dalgaard, M. D. (Intern), Bojesen, A. M. (Ekstern)
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Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): SJR 1.281 SNIP 1.142
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 1.342 SNIP 1.006 CiteScore 2.66
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 1.189 SNIP 1.197 CiteScore 2.46
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 1.353 SNIP 1.457 CiteScore 3.13
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 1.254 SNIP 1.279 CiteScore 2.97
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 1.593 SNIP 1.645 CiteScore 3.85
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 1.506 SNIP 1.602
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 1.472 SNIP 1.702
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 1.557 SNIP 2.009
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 1.745 SNIP 2.184
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 1.348 SNIP 1.946
Scopus rating (2005): SJR 0.879 SNIP 1.593
Web of Science (2005): Indexed yes
There is increasing evidence that thrombocytosis is associated with tumor invasion and metastasis formation. It was shown in several solid tumor types that thrombocytosis prognosticates cancer progression. The aim of this study was to evaluate preoperative thrombocytosis as a potential prognostic biomarker in isolated metastases, in patients with liver metastasis of colorectal cancer (mCRC). Clinicopathological data of 166 patients with mCRC who had surgical resection between 2001 and 2011 were collected retrospectively. All primary tumors have been already resected. The platelet count was evaluated based on the standard preoperative blood profile. The patients were followed-up on average for 28 months. Overall survival (OS) of patients with thrombocytosis was significantly worse both in univariate (HR = 3.00, p = 0.03) and in multivariate analysis (HR = 4.68, p = 0.056) when adjusted for gender, age, tumor size and surgical margin. Thrombocytosis was also a good prognosticator of disease-free survival (DFS) with HR = 2.7, p = 0.018 and nearly significant in multivariate setting (HR = 2.26, p = 0.073). The platelet count is a valuable prognostic marker for the survival in patients with mCRC.
Towards High-throughput Immunomics for Infectious Diseases: Use of Next-generation Peptide Microarrays for Rapid Discovery and Mapping of Antigenic Determinants

Complete characterization of antibody specificities associated to natural infections is expected to provide a rich source of serologic biomarkers with potential applications in molecular diagnosis, follow-up of chemotherapeutic treatments, and prioritization of targets for vaccine development. Here, we developed a highly-multiplexed platform based on next-generation high-density peptide microarrays to map these specificities in Chagas Disease, an exemplar of a human infectious disease caused by the protozoan Trypanosoma cruzi. We designed a high-density peptide microarray containing more than 175,000 overlapping 15mer peptides derived from T. cruzi proteins. Peptides were synthesized in situ on microarray slides spanning the complete length of 457 parasite proteins with fully overlapped 15mers (1 residue shift). Screening of these slides with antibodies purified from infected patients and healthy donors demonstrated both a high technical reproducibility as well as epitope mapping consistency when compared with earlier low-throughput technologies. Using a conservative signal threshold to classify positive (reactive) peptides we identified 2,031 disease-specific peptides and 97 novel parasite antigens, effectively doubling the number of known antigens and providing a tenfold increase in the number of fine mapped antigenic determinants for this disease. Finally, further analysis of the chip data showed that optimizing the amount of sequence overlap of displayed peptides can increase the protein space covered in a single chip by at least ~3 fold without sacrificing sensitivity. In conclusion, we show the power of high-density peptide chips for the discovery of pathogen-specific linear B-cell epitopes from clinical samples, thus setting the stage for high-throughput biomarker discovery screenings and proteome-wide studies of immune responses against pathogens.

General information
State: Published
Organisations: Immunological Bioinformatics, Department of Systems Biology, Center for Biological Sequence Analysis, Universidad Nacional de San Martin, Hospital de Niños Dr. Ricardo Gutiérrez, Schafer-N
Traces of ATCV-1 associated with laboratory component contamination

Yolken et al. (1) claim detection of *Acanthocystis turfacea* chlorella virus 1 (ATCV-1, gi|119953744) in the normal human oropharyngeal viral flora and associate it with altered cognitive function. However, the reported presence of a freshwater algae virus, previously not known to infect other species, was based on a few sequence reads homologous to ATCV-1 identified with BLASTn. These reads span relatively few bases (97–698 bp) per sample, dispersed over a minor fraction (0.03–0.24%) of the 288 kb ATCV-1 genome.

General information

State: Published

Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Integrative Systems Biology, Metagenomics, University of Copenhagen, Statens Serum Institut

Tracking the origins of Yakutian horses and the genetic basis for their fast adaptation to subarctic environments

Yakutia, Sakha Republic, in the Siberian Far East, represents one of the coldest places on Earth, with winter record temperatures dropping below −70 °C. Nevertheless, Yakutian horses survive all year round in the open air due to striking phenotypic adaptations, including compact body conformations, extremely hairy winter coats, and acute seasonal differences in metabolic activities. The evolutionary origins of Yakutian horses and the genetic basis of their adaptations remain, however, contentious. Here, we present the complete genomes of nine present-day Yakutian horses and two ancient specimens dating from the early 19th century and ~5,200 y ago. By comparing these genomes with the genomes of two Late Pleistocene, 27 domesticated, and three wild Przewalski’s horses, we find that contemporary Yakutian horses do not descend from the native horses that populated the region until the mid-Holocene, but were most likely introduced following the migration of the Yakut people a few centuries ago. Thus, they represent one of the fastest cases of adaptation to the extreme temperatures of the Arctic. We find cis-regulatory mutations to have contributed more than nonsynonymous changes to their adaptation, likely due to the comparatively limited standing variation within gene bodies at the time the population was founded. Genes involved in hair development, body size, and metabolic and hormone signaling pathways represent an essential part of the Yakutian horse adaptive genetic toolkit. Finally, we find evidence for convergent evolution with native human populations and woolly mammoths, suggesting that only a few evolutionary strategies are compatible with survival in extremely cold environments.

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Metagenomics, University of Copenhagen, University College London, University of California, Joint Genome Institute, Universitat Pompeu Fabra, Russian National Research Centre Kurchatov Institute, Agroscope, University of Bern, Paul Sabatier University, King Saud University, North-Eastern Federal University, University of Minnesota, Russian Academy of Sciences, MTT Agrifood Research, Yakutian Research Institute of Agriculture
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Tracking the origins of Yakutian horses and the genetic basis for their fast adaptation to subarctic environments.
The insectivorous Venus flytrap (Dionaea muscipula) is renowned from Darwin's studies of plant carnivory and the origins of species. To provide tools to analyze the evolution and functional genomics of D. muscipula, we sequenced a normalized cDNA library synthesized from mRNA isolated from D. muscipula flowers and traps. Using the Oases transcriptome assembler, 79,165,657 quality trimmed reads were assembled into 80,806 cDNA contigs, with an average length of 679 bp and an N50 length of 1,051 bp. A total of 17,047 unique proteins were identified, and assigned to Gene Ontology (GO) and classified into functional categories. A total of 15,547 full-length cDNA sequences were identified, from which open reading frames were detected in 10,941. Comparative GO analyses revealed that D. muscipula is highly represented in molecular functions related to catalytic, antioxidant, and electron carrier activities. Also, using a single copy sequence PCR-based method, we estimated that the genome size of D. muscipula is approx. 3 Gb. Our genome size estimate and transcriptome analyses will contribute to future research on this fascinating, monotypic species and its heterotrophic adaptations.
Transcriptome profiling of brown adipose tissue during cold exposure reveals extensive regulation of glucose metabolism

We applied digital gene expression profiling to determine the transcriptome of brown and white adipose tissues (BAT and WAT, respectively) during cold exposure. Male C57BL/6J mice were exposed to cold for 2 or 4 days. A notable induction of genes related to glucose uptake, glycolysis, glycogen metabolism, and the pentose phosphate pathway was observed in BAT from cold-exposed animals. In addition, glycerol-3-phosphate dehydrogenase 1 expression was induced in BAT from cold-challenged mice, suggesting increased synthesis of glycerol from glucose. Similarly, expression of lactate dehydrogenases was induced by cold in BAT. Pyruvate dehydrogenase kinase 2 (Pdk2) and Pdk4 were expressed at significantly higher levels in BAT than in WAT, and Pdk2 was induced in BAT by cold. Of notice, only a subset of the changes detected in BAT was observed in WAT. Based on changes in gene expression during cold exposure, we propose a model for the intermediary glucose metabolism in activated BAT: 1) fluxes through glycolysis and the pentose phosphate pathway are induced, the latter providing reducing equivalents for de novo fatty acid synthesis; 2) glycerol synthesis from glucose is increased, facilitating triacylglycerol synthesis/fatty acid re-esterification; 3) glycogen turnover and lactate production are increased; and 4) entry of glucose carbon into the tricarboxylic acid cycle is restricted by PDK2 and PDK4.

In summary, our results demonstrate extensive and diverse gene expression changes related to glucose handling in activated BAT.

General information
State: Published
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Scopus rating (2015): SJR 2.385 SNIP 1.12 CiteScore 3.95
TumorTracer: a method to identify the tissue of origin from the somatic mutations of a tumor specimen

A substantial proportion of cancer cases present with a metastatic tumor and require further testing to determine the primary site; many of these are never fully diagnosed and remain cancer of unknown primary origin (CUP). It has been previously demonstrated that the somatic point mutations detected in a tumor can be used to identify its site of origin with limited accuracy. We hypothesized that higher accuracy could be achieved by a classification algorithm based on the following feature sets: 1) the number of nonsynonymous point mutations in a set of 232 specific cancer-associated genes, 2) frequencies of the 96 classes of single-nucleotide substitution determined by the flanking bases, and 3) copy number profiles, if available. We used publicly available somatic mutation data from the COSMIC database to train random forest classifiers to distinguish among those tissues of origin for which sufficient data was available. We selected feature sets using cross-validation and then derived two final classifiers (with or without copy number profiles) using 80% of the available tumors. We evaluated the accuracy using the remaining 20%. For further validation, we assessed accuracy of the without-copy-number classifier on three independent data sets: 1669 newly available public tumors of various types, a cohort of 91 breast metastases, and a set of 24 specimens from 9 lung cancer patients subjected to multiregion sequencing. The cross-validation accuracy was highest when all three types of information were used. On the left-out COSMIC data not used for training, we achieved a classification accuracy of 85% across 6 primary sites (with copy numbers), and 69% across 10 primary sites (without copy numbers). Importantly, a derived confidence score could distinguish tumors that could be identified with 96% accuracy (32%/75% of tumors with/without copy numbers) from those that were less certain. Accuracy in the independent data sets was 46%, 53% and 89% respectively, similar to the accuracy expected from the training data. Identification of primary site from point mutation and/or copy number data may be accurate enough to aid clinical diagnosis of cancers of unknown primary origin.
Two Lactococcus lactis thioredoxin paralogues play different roles in responses to arsenaate and oxidative stress

Thioredoxin (Trx) maintains intracellular thiol groups in a reduced state and is involved in a wide range of cellular processes, including ribonucleotide reduction, sulphur assimilation, oxidative stress responses and arsenaate detoxification. The industrially important lactic acid bacterium Lactococcus lactis contains two Trxs. TrxA is similar to the well-characterized Trx homologue from Escherichia coli and contains the common WCGPC active site motif, while TrxD is atypical and contains an aspartate residue in the active site (WCGDC). To elucidate the physiological roles of the two Trx paralogues, deletion mutants ΔtrxA, ΔtrxD and ΔtrxAΔtrxD were constructed. In general, the ΔtrxAΔtrxD strain was significantly more sensitive than either of the ΔtrxA and ΔtrxD mutants. Upon exposure to oxidative stress, growth of the ΔtrxA strain was diminished while that of the ΔtrxD mutant was similar to the wild-type. The lack of TrxA also appears to impair methionine sulfoxide reduction. Both ΔtrxA and ΔtrxD strains displayed growth inhibition after treatment with sodium arsenaate and tellurite as compared with the wild-type, suggesting partially overlapping functions of TrxA and TrxD. Overall the phenotype of the ΔtrxA mutant matches established functions of WCGPC-type Trx while TrxD appears to play a more restricted role in stress resistance of Lact. lactis.
Ultra-high density peptide arrays demonstrate unique patient-specific IgE and IgG4 epitope patterns for peanut allergens that persist over multiple years

Clinicians are seeing a growing number of cashew nut allergic patients. One of the peculiarities of this allergy is that a minimal amount of cashew nut allergen may cause severe allergic reactions, suggesting high potency of the allergen comparable to other tree nuts and peanuts. The double blind placebo controlled food challenge (DBPCFC) test is currently the gold standard to establish cashew nut allergy. The development of predictive tools in diagnosing cashew nut allergy is needed and research should be done on cross-sensitization between cashew nut and other botanically related allergens.
Unique and conserved genome regions in Vibrio harveyi and related species in comparison with the shrimp pathogen Vibrio harveyi CAIM 1792

Vibrio harveyi CAIM 1792 is a marine bacterial strain that causes mortality in farmed shrimp in north-west Mexico, and the identification of virulence genes in this strain is important for understanding its pathogenicity. The aim of this work was to compare the V. harveyi CAIM 1792 genome with related genome sequences to determine their phylogenetic relationship and explore unique regions in silico that differentiate this strain from other V. harveyi strains. Twenty-one newly sequenced genomes were compared in silico against the CAIM 1792 genome at nucleotide and predicted proteome levels. The proteome of CAIM 1792 had higher similarity to those of other V. harveyi strains (78%) than to those of the other closely related species Vibrio owensii (67%), Vibrio rotiferianus (63%) and Vibrio campbellii (59%). Pan-genome ORFans trees showed the best fit with the accepted phylogeny based on DNA-DNA hybridization and multi-locus sequence analysis of 11 concatenated housekeeping genes. SNP analysis clustered 34/38 genomes within their accepted species. The pan-genomic and SNP trees showed that V. harveyi is the most conserved of the four species studied and V. campbellii may be divided into at least three subspecies, supported by intergenomic distance analysis. blastp atlases were created to identify unique regions among the genomes most related to V. harveyi CAIM 1792; these regions included genes encoding glycosyltransferases, specific type restriction modification systems and a transcriptional regulator, LysR, reported to be involved in virulence, metabolism, quorum sensing and motility.

General information
State: Published
Organisations: National Food Institute, Research Group for Genomic Epidemiology, Department of Systems Biology, Center for Biological Sequence Analysis, CIAD A.C., Naval Research Laboratory, Australian Institute of Marine Science
Unmasking Determinants of Specificity in the Human Kinome

Protein kinases control cellular responses to environmental cues by swift and accurate signal processing. Breakdowns in this high-fidelity capability are a driving force in cancer and other diseases. Thus, our limited understanding of which amino acids in the kinase domain encode substrate specificity, the so-called determinants of specificity (DoS), constitutes a major obstacle in cancer signaling. Here, we systematically discover several DoS and experimentally validate three of them, named the αC1, αC3, and APE-7 residues. We demonstrate that DoS form sparse networks of non-conserved residues spanning distant regions. Our results reveal a likely role for inter-residue allostery in specificity and an evolutionary decoupling of kinase activity and specificity, which appear loaded on independent groups of residues. Finally, we uncover similar properties driving SH2 domain specificity and demonstrate how the identification of DoS can be utilized to elucidate a greater understanding of the role of signaling networks in cancer (Creixell et al., 2015 [this issue of Cell]).

General information
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BFI (2014): BFI-level 2
Scopus rating (2014): SJR 28.41 SNIP 5.687 CiteScore 24.91
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 27.895 SNIP 5.887 CiteScore 24.88
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
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What Can We Learn from a Metagenomic Analysis of a Georgian Bacteriophage Cocktail?

Phage therapy, a practice widespread in Eastern Europe, has untapped potential in the combat against antibiotic-resistant bacterial infections. However, technology transfer to Western medicine is proving challenging. Bioinformatics analysis could help to facilitate this endeavor. In the present study, the Intesti phage cocktail, a key commercial product of the Eliava Institute, Georgia, has been tested on a selection of bacterial strains, sequenced as a metagenomic sample, de novo assembled and analyzed by bioinformatics methods. Furthermore, eight bacterial host strains were infected with the cocktail and the resulting lysates sequenced and compared to the unamplified cocktail. The analysis identified 23 major phage clusters in different abundances in the cocktail, among those clusters related to the ICTV genera T4likevirus, T5likevirus, T7likevirus, Chilikevirus and Twortlikevirus, as well as a cluster that was quite distant to the database sequences and a novel Proteus phage cluster. Examination of the depth of coverage showed the clusters to have different abundances within the cocktail. The cocktail was found to be composed primarily of Myoviridae (35%) and Siphoviridae (32%), with Podoviridae being a minority (15%). No undesirable genes were found.
Whey-reduced weight gain is associated with a temporary growth reduction in young mice fed a high-fat diet

Whey protein consumption reportedly alleviates parameters of the metabolic syndrome. Here, we investigated the effects of whey protein isolate (whey) in young mice fed a high-fat diet. We hypothesized that whey as the sole protein source reduced early weight gain associated with retarded growth and decreased concentration of insulin-like growth factor-1. Moreover, we hypothesized that these changes were explained by increased nitrogen loss via elevated urea production and/or increased energy expenditure. Male 5-week-old C57BL/6 mice were fed high-fat diets with the protein source being either whey, casein or a combination of both for 5 weeks. After 1, 3 or 5 weeks, respectively, the mice were subjected to a meal challenge with measurements of blood and urinary urea before and 1 and 3 h after eating a weighed meal of their respective diets. In a subset of mice, energy expenditure was measured by indirect calorimetry during the first week of dietary intervention. Observed exclusively during the first week of intervention, whey significantly reduced body length (P < 0.01) and weight gain correlating positively with plasma concentrations of insulin-like growth factor-1. The combination diet displayed intermediate results indicating an interactive effect. Urea production, urea cycle activity, food intake and energy expenditure were unaffected by protein source. In conclusion, whey decreased growth-related parameters exclusively during the first week of dietary intervention. The early effect of whey could not be explained by food intake, energy expenditure, urea production or urea cycle activity but was correlated with plasma levels of insulin-like growth factor-1.
Why Big Data is relevant in Health care

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Functional Human Variation, Integrative Systems Biology
Authors: Gupta, R. (Intern), Pedersen, H. K. (Intern), Yadav, R. (Intern)
Number of pages: 1
Within-host microevolution of *Pseudomonas aeruginosa* in Italian cystic fibrosis patients

Chronic infection with *Pseudomonas aeruginosa* is a major cause of morbidity and mortality in cystic fibrosis (CF) patients, and a more complete understanding of *P. aeruginosa* within-host genomic evolution, transmission, and population genomics may provide a basis for improving intervention strategies. Here, we report the first genomic analysis of *P. aeruginosa* isolates sampled from Italian CF patients. By genome sequencing of 26 isolates sampled over 19 years from four patients, we elucidated the within-host evolution of clonal lineages in each individual patient. Many of the identified mutations were located in pathoadaptive genes previously associated with host adaptation, and we correlated mutations with changes in CF-relevant phenotypes such as antibiotic resistance. In addition, the genomic analysis revealed that three patients shared the same clone. Furthermore, we compared the genomes of the Italian CF isolates to a panel of genome sequenced strains of *P. aeruginosa* from other countries. Isolates from two of the Italian lineages belonged to clonal complexes of *P. aeruginosa* that have previously been identified in Danish CF patients, and our genomic comparison showed that clonal isolates from the same country may be more distantly related than clonal isolates from different countries. This is the first whole-genome analysis of *P. aeruginosa* isolated from Italian CF patients, and together with both phenotypic and clinical information this dataset facilitates a more detailed understanding of *P. aeruginosa* within-host genomic evolution, transmission, and population genomics. We conclude that the evolution of the Italian lineages resembles what has been found in other countries.
A computational approach to mechanistic and predictive toxicology of pesticides

Emerging challenges of managing and interpreting large amounts of complex biological data have given rise to the growing field of computational biology. We investigated the applicability of an integrated systems toxicology approach on five selected pesticides to get an overview of their modes of action in humans, to group them according to their modes of action, and to hypothesize on their potential effects on human health. We extracted human proteins associated to prochloraz, tebuconazole, epoxiconazole, procymidone, and mancozeb and enriched each protein set by using a high confidence human protein interactome. Then, we explored modes of action of the chemicals, by integrating protein-disease information to the resulting protein networks. The dominating human adverse effects affected were reproductive disorders followed by adrenal diseases. Our results indicated that prochloraz, tebuconazole, and procymidone exerted their effects mainly via interference with steroidogenesis and nuclear receptors. Prochloraz was associated to a large number of human diseases, and together with tebuconazole showed several significant associations to Testicular Dysgenesis Syndrome. Mancozeb showed a differential mode of action, involving inflammatory processes. This method provides an efficient way of overviewing data and grouping chemicals according to their mode of action and potential human adverse effects. Such information is valuable when dealing with predictions of mixture effects of chemicals and
may contribute to the development of adverse outcome pathways.

**General information**

State: Published
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**Acute and perinatal-programming effects of a fat-rich diet on rat muscle mitochondrial function and hepatic lipid accumulation.**

Objective. Maternal high-fat intake during pregnancy may have long-term consequences in the offspring. Since this might relate to the capacity of mitochondrial metabolic adaptation and hepatic lipid metabolism, we investigated how maternal high-fat intake affected mitochondrial function and hepatic steatosis in the offspring. Design. Sprague–Dawley rats were fed a high-fat (20% w/w) or a control diet (chow, C) from 10 days before pregnancy and throughout lactation. At weaning the litters were split into two groups; one was continued on the maternal diet and the other was fed low-fat chow. Sample. Skeletal muscle mitochondria and liver lipids. Methods. Mitochondrial respiration and hepatic lipid content were determined during and after weaning, on days 20 and 70 postpartum. Main outcome measures. Mitochondrial function and hepatic lipid content were determined during and after weaning, on days 20 and 70 postpartum. Main outcome measures. Mitochondrial function and hepatic lipids. Results. At 20 days, maternal high-fat diet caused increased VO2max with pyruvate as substrate (p = 0.047), at 70 days, pups born by C-dams, but not those born by high-fat-dams, showed increased oxidation of palmitoylcarnitine in the absence of ADP (p = 0.018). Rates of ADP-stimulated oxygen consumption, maximal respiratory capacity and mitochondrial respiratory control ratio with pyruvate, increased post weaning (p < 0.001), whereas respiratory control ratio with palmitoylcarnitine decreased (p = 0.013). The increase in respiratory control ratio was most pronounced in pups from C-dams (p = 0.05). The high-fat-diet caused pronounced hepatic steatosis in pups at weaning (p < 0.001), without concomitant ceramide accumulation, while high-fat-feeding after weaning induced triacylglycerol and ceramide accumulation (p < 0.01), regardless of maternal diet. Conclusion. Intake of a fat-rich diet during pregnancy and lactation reduced the age-induced increases in un-coupled fat oxidation.
Adipose tissue trans fatty acids and changes in body weight and waist circumference

Previous studies have suggested that the intake of trans-fatty acids (TFA) plays a role in the development of obesity. The proportions of adipose tissue fatty acids not synthesised endogenously in humans, such as TFA, usually correlate well with the dietary intake. Hence, the use of these biomarkers may provide a more accurate measure of habitual TFA intake than that obtained with dietary questionnaires. The objective of the present study was to investigate the associations between the proportions of specific TFA in adipose tissue and subsequent changes in weight and waist circumference (WC). The relative content of fatty acids in adipose tissue biopsies from a random sample of 996 men and women aged 50–64 years drawn from a Danish cohort study was determined by GC. Baseline data on weight, WC and potential confounders were available together with information on weight and WC 5 years after enrolment. The exposure measures were total trans-octadecenoic acids (18 : 1t), 18 : 1 D6-10t, vaccenic acid (18 : 1 D11t) and rumenic acid (18 : 2 D9c, 11t). Data were analysed using multiple regression with cubic spline modelling. The median proportion of total adipose tissue 18 : 1t was 1.52% (90% central range 0.98, 2.19) in men and 1.47% (1.01, 2.19) in women. No significant associations were observed between the proportions of total 18 : 1t, 18:1 D6-10t, vaccenic acid or rumenic acid and changes in weight or WC. The present study suggests that the proportions of specific TFA in adipose tissue are not associated with subsequent changes in weight or WC within the exposure range observed in this population.

General information
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A DNA-binding-site landscape and regulatory network analysis for NAC transcription factors in Arabidopsis thaliana.

Target gene identification for transcription factors is a prerequisite for the systems wide understanding of organismal behaviour. NAM-ATAF1/2-CUC2 (NAC) transcription factors are amongst the largest transcription factor families in plants, yet limited data exist from unbiased approaches to resolve the DNA-binding preferences of individual members. Here, we present a TF-target gene identification workflow based on the integration of novel protein binding microarray data with gene expression and multi-species promoter sequence conservation to identify the DNA-binding specificities and the gene regulatory networks of 12 NAC transcription factors. Our data offer specific single-base resolution fingerprints for most TFs studied and indicate that NAC DNA-binding specificities might be predicted from their DNA-binding domain's sequence. The developed methodology, including the application of complementary functional genomics filters, makes it possible to translate, for each TF, protein binding microarray data into a set of high-quality target genes. With this approach, we confirm NAC target genes reported from independent in vivo analyses. We emphasize that candidate target gene sets together with the workflow associated with functional modules offer a strong resource to unravel the regulatory potential of NAC genes and that this workflow could be used to study other families of transcription factors.

General information
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Organisations: Novo Nordisk Foundation Center for Biosustainability, Synthetic Biology Tools for Yeast, Department of Systems Biology, Center for Biological Sequence Analysis, Ghent University, University of Copenhagen
Ageing of atrazine in manure amended soils assessed by bioavailability to Pseudomonas sp. strain ADP

Animal manure is applied to agricultural land in areas of high livestock production. In the present study, we evaluated ageing of atrazine in two topsoils with and without addition of manure and in one subsoil. Ageing was assessed as the bioavailability of atrazine to the atrazine mineralizing bacteria Pseudomonas sp. strain ADP. Throughout an ageing period of 90 days bioavailability was investigated at days 1, 10, 32, 60 and 90, where ~108 cells g−1 of the ADP strain was inoculated to the 14C-atrazine exposed soil and 14CO2 was collected over 7 days as a measure of mineralized atrazine. Even though the bioavailable residue decreased in all of the three soils as time proceeded, we found that ageing occurred faster in the topsoils rich in organic carbon than in subsoil. For one topsoil rich in organic carbon content, Simmelkær, we observed a higher degree of ageing when treated with manure. Contrarily, sorption experiments showed less sorption to Simmelkær treated with manure than the untreated soil indicating that sorption processes are not the only mechanisms of ageing. The other topsoil low in organic carbon content, Ringe, showed no significant difference in ageing between the manure-treated and untreated soil. The present study illustrates that not simply the organic carbon content influences adsorption and ageing of atrazine in soil but the origin and composition of organic matter plays an important role.

General information

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Organisations: Novo Nordisk Foundation Center for Biosustainability, Center for Biological Sequence Analysis, Metagenomics, Geological Survey of Denmark and Greenland, University of Copenhagen
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Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.103 SNIP 1.435 CiteScore 2.63
ISI indexed (2013): ISI indexed yes
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ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 1
A Generally Applicable Translational Strategy Identifies S100A4 as a Candidate Gene in Allergy

The identification of diagnostic markers and therapeutic candidate genes in common diseases is complicated by the involvement of thousands of genes. We hypothesized that genes co-regulated with a key gene in allergy, IL13, would form a module that could help to identify candidate genes. We identified a T helper 2 (TH2) cell module by small interfering RNA–mediated knockdown of 25 putative IL13-regulating transcription factors followed by expression profiling. The module contained candidate genes whose diagnostic potential was supported by clinical studies. Functional studies of human TH2 cells as well as mouse models of allergy showed that deletion of one of the genes, S100A4, resulted in decreased signs of allergy including TH2 cell activation, humoral immunity, and infiltration of effector cells. Specifically, dendritic cells required S100A4 for activating T cells. Treatment with an anti-S100A4 antibody resulted in decreased signs of allergy in the mouse model as well as in allergen-challenged T cells from allergic patients. This strategy, which may be generally applicable to complex diseases, identified and validated an important diagnostic and therapeutic candidate gene in allergy.

General information
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Functional Human Variation, Integrative Systems Biology, Linköping University, Cenix BioScience GmbH, Albert Einstein College of Medicine, Borås Hospital, University of Copenhagen
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Volume: 6
A genome-wide association study identifies CDHR3 as a susceptibility locus for early childhood asthma with severe exacerbations.

Asthma exacerbations are among the most frequent causes of hospitalization during childhood, but the underlying mechanisms are poorly understood. We performed a genome-wide association study of a specific asthma phenotype characterized by recurrent, severe exacerbations occurring between 2 and 6 years of age in a total of 1,173 cases and 2,522 controls. Cases were identified from national health registries of hospitalization, and DNA was obtained from the Danish Neonatal Screening Biobank. We identified five loci with genome-wide significant association. Four of these, GSDMB, IL33, RAD50 and IL1RL1, were previously reported as asthma susceptibility loci, but the effect sizes for these loci in our cohort were considerably larger than in the previous genome-wide association studies of asthma. We also obtained strong evidence for a new susceptibility gene, CDHR3 (encoding cadherin-related family member 3), which is highly expressed in airway epithelium. These results demonstrate the strength of applying specific phenotyping in the search for asthma susceptibility genes.

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Analysis of the contribution of bacteriophage ST64B to in vitro virulence traits of Salmonella enterica serovar Typhimurium

Comparison of the publicly available genomes of the virulent Salmonella enterica serovar Typhimurium (S. Typhimurium) strains SL1344, 14028s and D23580 to that of the virulence-attenuated isolate LT2 revealed the absence of a full sequence of bacteriophage ST64B in the latter. Four selected ST64B regions of unknown function (sb7–sb11, sb46, sb49–sb50 and sb54) were mapped by PCR in two strain collections: (i) 310 isolates of S. Typhimurium from human blood or stool samples, and from food, animal and environmental reservoirs; and (ii) 90 isolates belonging to other serovars. The region sb49–sb50 was found to be unique to S. Typhimurium and was strongly associated with strains isolated from blood samples (100 and 28.4 % of the blood and non-blood isolates, respectively). The region was cloned into LT2 and knocked out in SL1344, and these strains were compared to wild-type isogenic strains in in vitro assays used to predict virulence association. No difference in invasion of the Int407 human cell line was observed between the wild-type and mutated strains, but the isolate carrying the whole ST64B prophage was found to have a slightly better survival in blood. The study showed a high prevalence and a strong association between the prophage ST64B and isolates of S. Typhimurium collected from blood, and may indicate that such strains constitute a selected subpopulation within this serovar. Further studies are indicated to determine whether the slight increase in blood survival observed in the strain carrying ST64B genes is of paramount importance for systemic infections.

General information
State: Published
Organisations: National Food Institute, Comparative Microbial Genomics, Division of Epidemiology and Microbial Genomics, University of Copenhagen
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BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.123 SNIP 0.986 CiteScore 2.27
Web of Science (2015): Indexed yes
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Scopus rating (2014): SJR 1.038 SNIP 1.062 CiteScore 2.26
Web of Science (2014): Indexed yes
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Scopus rating (2013): SJR 1.021 SNIP 1.047 CiteScore 2.34
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Scopus rating (2012): SJR 1.05 SNIP 1.168 CiteScore 2.54
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An elevated pro-inflammatory cytokine profile in multiple chemical sensitivity

Background
Multiple chemical sensitivity (MCS) is a medically unexplained condition characterized by reports of recurrent unspecific symptoms attributed to exposure to low levels of common volatile chemicals. The etiology of MCS is poorly understood, but dysregulation of the immune system has been proposed as part of the pathophysiology. Objective
To compare plasma levels of cytokines in Danish MCS individuals with a healthy, sex- and age-matched control group.
Method
Blood samples were obtained from 150 un-exposed MCS individuals and from 148 age- and sex-matched healthy controls. Plasma concentrations of 14 cytokines, chemokines and growth and allergen-specific IgE were measured. All participants completed a questionnaire including questions on MCS, psychological distress, morbidities and medication use at the time of the study. Results
Plasma levels of interleukin-1β, -2, -4, and -6 were significantly (P
An integrated catalog of reference genes in the human gut microbiome

Many analyses of the human gut microbiome depend on a catalog of reference genes. Existing catalogs for the human gut microbiome are based on samples from single cohorts or on reference genomes or protein sequences, which limits coverage of global microbiome diversity. Here we combined 249 newly sequenced samples of the Metagenomics of the Human Intestinal Tract (MetaHit) project with 1,018 previously sequenced samples to create a cohort from three continents that is at least threefold larger than cohorts used for previous gene catalogs. From this we established the integrated gene catalog (IGC) comprising 9,879,896 genes. The catalog includes close-to-complete sets of genes for most gut microbes, which are also of considerably higher quality than in previous catalogs. Analyses of a group of samples from Chinese and Danish individuals using the catalog revealed country-specific gut microbial signatures. This expanded catalog should facilitate quantitative characterization of metagenomic, metatranscriptomic and metaproteomic data from the gut microbiome to understand its variation across populations in human health and disease.

General information
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Novo Nordisk Foundation Center for Biosustainability, Integrative Systems Biology, South China University of Technology, BGI-Shenzhen, BGI Hong Kong Research Institute, University of Copenhagen, European Molecular Biology Laboratory, INRA Institut National
An international effort towards developing standards for best practices in analysis, interpretation and reporting of clinical genome sequencing results in the CLARITY Challenge

Background: There is tremendous potential for genome sequencing to improve clinical diagnosis and care once it becomes routinely accessible, but this will require formalizing research methods into clinical best practices in the areas of sequence data generation, analysis, interpretation and reporting. The CLARITY Challenge was designed to spur convergence in methods for diagnosing genetic disease starting from clinical case history and genome sequencing data. DNA samples were obtained from three families with heritable genetic disorders and genomic sequence data were donated by sequencing platform vendors. The challenge was to analyze and interpret these data with the goals of identifying disease-causing variants and reporting the findings in a clinically useful format. Participating contestant groups were solicited broadly, and an independent panel of judges evaluated their performance.

Results: A total of 30 international groups were engaged. The entries reveal a general convergence of practices on most elements of the analysis and interpretation process. However, even given this commonality of approach, only two groups identified the consensus candidate variants in all disease cases, demonstrating a need for consistent fine-tuning of the generally accepted methods. There was greater diversity of the final clinical report content and in the patient consenting process, demonstrating that these areas require additional exploration and standardization.

Conclusions: The CLARITY Challenge provides a comprehensive assessment of current practices for using genome sequencing to diagnose and report genetic diseases. There is remarkable convergence in bioinformatic techniques, but medical interpretation and reporting are areas that require further development by many groups.

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Annotation of loci from genome-wide association studies using tissue-specific quantitative interaction proteomics

Genome-wide association studies (GWAS) have identified thousands of loci associated with complex traits, but it is challenging to pinpoint causal genes in these loci and to exploit subtle association signals. We used tissue-specific quantitative interaction proteomics to map a network of five genes involved in the Mendelian disorder long QT syndrome (LOTS). We integrated the LOTS network with GWAS loci from the corresponding common complex trait, QT-interval variation, to identify candidate genes that were subsequently confirmed in *Xenopus laevis* oocytes and zebrafish. We used the LOTS protein network to filter weak GWAS signals by identifying single-nucleotide polymorphisms (SNPs) in proximity to genes in the network supported by strong proteomic evidence. Three SNPs passing this filter reached genome-wide significance after replication genotyping. Overall, we present a general strategy to propose candidates in GWAS loci for functional studies and to systematically filter subtle association signals using tissue-specific quantitative interaction proteomics.

General information

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Copenhagen, Harvard Medical School, Technical University of Munich, Leiden University, University of Glasgow, Erasmus Medical Center, The Netherlands Consortium for Healthy Ageing, University College London, Massachusetts General Hospital, University of Groningen, Netherlands Heart Institute, University Medical Centre Utrecht

A novel approach for characterisation of conformational allergen epitopes combining phage display and high-throughput sequencing
Antibody informatics for drug discovery

More and more antibody therapeutics are being approved every year, mainly due to their high efficacy and antigen selectivity. However, it is still difficult to identify the antigen, and thereby the function, of an antibody if no other information is available. There are obstacles inherent to the antibody science in every project in antibody drug discovery. Recent experimental technologies allow for the rapid generation of large-scale data on antibody sequences, affinity, potency, structures, and biological functions; this should accelerate drug discovery research. Therefore, a robust bioinformatic infrastructure for these large data sets has become necessary. In this article, we first identify and discuss the typical obstacles faced during the antibody drug discovery process. We then summarize the current status of three sub-fields of antibody informatics as follows: (i) recent progress in technologies for antibody rational design using computational approaches to affinity and stability improvement, as well as ab-initio and homology-based antibody modeling; (ii) resources for antibody sequences, structures, and immune epitopes and open drug discovery resources for development of antibody drugs; and (iii) antibody numbering and IMGT. Here, we review “antibody informatics,” which may integrate the above three fields so that bridging the gaps between industrial needs and academic solutions can be accelerated. This article is part of a Special Issue entitled: Recent advances in molecular engineering of antibody.
Antibody structural modeling with prediction of immunoglobulin structure (PIGS).

Antibodies (or immunoglobulins) are crucial for defending organisms from pathogens, but they are also key players in many medical, diagnostic and biotechnological applications. The ability to predict their structure and the specific residues involved in antigen recognition has several useful applications in all of these areas. Over the years, we have developed or collaborated in developing a strategy that enables researchers to predict the 3D structure of antibodies with a very satisfactory accuracy. The strategy is completely automated and extremely fast, requiring only a few minutes (∼10 min on average) to build a structural model of an antibody. It is based on the concept of canonical structures of antibody loops and on our understanding of the way light and heavy chains pack together.
A pan-cancer analysis of inferred homologous recombination deficiency identifies potential platinum benefit in novel subtypes

Personalized medicine in cancer aims to improve treatment outcome, by exploiting the molecular alterations of the individual tumor to inform therapeutic decisions. Ovarian and triple-negative breast cancers with defects in homologous recombination (HR) DNA repair are highly sensitive to treatment with platinum-based DNA-damaging agents. Reliable biomarkers to identify HR-deficient cancers prior to the initial treatment may be used to stratify patients for platinum chemotherapy. Extensive genome damage caused by deficient HR is readily observed as high frequencies of allelic imbalance and loss of heterozygosity in cancers with loss of either of the tumor suppressor genes BRCA1 or BRCA2, but is also common in ovarian and triple-negative breast cancers with no BRCA1/2 mutations, indicating HR loss due to alternative mechanisms. Recently, three independent methods were published that each quantitate the state of HR deficiency in a given cancer, by summarizing different types of DNA aberrations that are likely to be caused by improper DNA repair. Here we compare the three scores, named NtAI (1), LST (2), and HRD (3), utilizing a panel of 4400 patients representing 13 cancer types from The Cancer Genome Atlas. We found that the three scores are highly correlated with each other, suggesting they measure the effect of similar types of DNA damage. We found a strong association with overall survival only in ovarian cancer, which is consistent with frequent BRCA-related HR deficiency reported for this type of cancer. Next, we compared the distribution of the scores across cancer types, and found that those types ordinarily receiving platinum as standard of care have the highest median scores. Importantly, in most types not generally given platinum chemotherapy we also found small sub-populations of high scoring tumors, which may represent subtypes with a previously overlooked potential to respond to platinum agents. Lastly, we used RNAseq to identify genes whose expression is associated with high DNA aberration scores. We compared the 100 genes most highly correlated with each score and found a shared set of 53 genes; these were enriched for genes involved in cell cycle progression, mitosis and chromosome segregation. This suggests that replication stress, perhaps combined with or induced by HR deficiency, could play a role in the generation of the measured DNA aberrations. Overall, our results demonstrate that the three methods measure correlated aberration patterns possibly generated through replication stress, and that they show prognostic potential in patients who receive platinum chemotherapy. In addition, we identify subsets of patients suffering from cancers not presently receiving platinum chemotherapy, who may benefit from it.
Applicability of Computational Systems Biology in Toxicology

Systems biology as a research field has emerged within the last few decades. Systems biology, often defined as the antithesis of the reductionist approach, integrates information about individual components of a biological system. In integrative systems biology, large data sets from various sources and databases are used to model and predict effects of chemicals on, for instance, human health. In toxicology, computational systems biology enables identification of important pathways and molecules from large data sets; tasks that can be extremely laborious when performed by a classical literature search. However, computational systems biology offers more advantages than providing a high-throughput literature search; it may form the basis for establishment of hypotheses on potential links between environmental...
chemicals and human diseases, which would be very difficult to establish experimentally. This is possible due to the existence of comprehensive databases containing information on networks of human protein–protein interactions and protein–disease associations. Experimentally determined targets of the specific chemical of interest can be fed into these networks to obtain additional information that can be used to establish hypotheses on links between the chemical and human diseases. Such information can also be applied for designing more intelligent animal/cell experiments that can test the established hypotheses. Here, we describe how and why to apply an integrative systems biology method in the hypothesis-generating phase of toxicological research.

**General information**

State: Published
Organisations: National Food Institute, Division of Toxicology and Risk Assessment, Center for Biological Sequence Analysis, Integrative Systems Biology, Department of Systems Biology
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**Applying the ResFinder and VirulenceFinder web-services for easy identification of acquired antibiotic resistance and E. coli virulence genes in bacteriophage and prophage nucleotide sequences.**
Extensive research is currently being conducted on the use of bacteriophages for applications in human medicine, agriculture and food manufacturing. However, phages are important vehicles of horizontal gene transfer and play a significant role in bacterial evolution. As a result, concern has been raised that this increased use and dissemination of phages could result in spread of deleterious genes, e.g., antibiotic resistance and virulence genes. Meanwhile, in the wake of the genomic era, several tools have been developed for characterization of bacterial genomes. Here we describe how two of these tools, ResFinder and VirulenceFinder, can be used to identify acquired antibiotic resistance and virulence genes in phage genomes of interest. The general applicability of the tools is demonstrated on data sets of 1,642 phage genomes and 1,442 predicted prophages.

General information
State: Published
Organisations: National Food Institute, Division of Epidemiology and Microbial Genomics, Department of Systems Biology, Center for Biological Sequence Analysis, Technical University of Denmark
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Background: Prioritizing genetic variants is a challenge because disease susceptibility loci are often located in genes of unknown function or the relationship with the corresponding phenotype is unclear. A global data-mining exercise on the biomedical literature can establish the phenotypic profile of genes with respect to their connection to disease phenotypes. The importance of protein-protein interaction networks in the genetic heterogeneity of common diseases or complex traits is becoming increasingly recognized. Thus, the development of a network-based approach combined with phenotypic profiling would be useful for disease gene prioritization.

Results: We developed a random-set scoring model and implemented it to quantify phenotype relevance in a network-based disease gene-prioritization approach. We validated our approach based on different gene phenotypic profiles, which were generated from PubMed abstracts, OMIM, and GeneRIF records. We also investigated the validity of several vocabulary filters and different likelihood thresholds for predicted protein-protein interactions in terms of their effect on the network-based gene-prioritization approach, which relies on text-mining of the phenotype data. Our method demonstrated good precision and sensitivity compared with those of two alternative complex-based prioritization approaches. We then conducted a global ranking of all human genes according to their relevance to a range of human diseases. The resulting accurate ranking of known causal genes supported the reliability of our approach. Moreover, these data suggest many promising novel candidate genes for human disorders that have a complex mode of inheritance.

Conclusion: We have implemented and validated a network-based approach to prioritize genes for human diseases based on their phenotypic profile. We have devised a powerful and transparent tool to identify and rank candidate genes. Our global gene prioritization provides a unique resource for the biological interpretation of data from genome-wide association studies, and will help in the understanding of how the associated genetic variants influence disease or quantitative phenotypes.

General information
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Aarhus University
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Main Research Area: Technical/natural sciences
A Selective Sweep on a Deleterious Mutation in CPT1A in Arctic Populations

Arctic populations live in an environment characterized by extreme cold and the absence of plant foods for much of the year and are likely to have undergone genetic adaptations to these environmental conditions in the time they have been living there. Genome-wide selection scans based on genotype data from native Siberians have previously highlighted a 3 Mb chromosome 11 region containing 79 protein-coding genes as the strongest candidates for positive selection in Northeast Siberians. However, it was not possible to determine which of the genes might be driving the selection signal. Here, using whole-genome high-coverage sequence data, we identified the most likely causative variant as a nonsynonymous G>A transition (rs80356779; c.1436C>T [p.Pro479Leu] on the reverse strand) in CPT1A, a key regulator of mitochondrial long-chain fatty-acid oxidation. Remarkably, the derived allele is associated with hypoketotic hypoglycemia and high infant mortality yet occurs at high frequency in Canadian and Greenland Inuits and was also found at 68% frequency in our Northeast Siberian sample. We provide evidence of one of the strongest selective sweeps reported in humans; this sweep has driven this variant to high frequency in circum-Arctic populations within the last 6–23 ka despite associated deleterious consequences, possibly as a result of the selective advantage it originally provided to either a high-fat diet or a cold environment.
A Versatile System for USER Cloning-Based Assembly of Expression Vectors for Mammalian Cell Engineering

A new versatile mammalian vector system for protein production, cell biology analyses, and cell factory engineering was developed. The vector system applies the ligation-free uracil-excision based technique – USER cloning – to rapidly construct mammalian expression vectors of multiple DNA fragments and with maximum flexibility, both for choice of vector backbone and cargo. The vector system includes a set of basic vectors and a toolbox containing a multitude of DNA building blocks including promoters, terminators, selectable marker- and reporter genes, and sequences encoding an internal ribosome entry site, cellular localization signals and epitope- and purification tags. USER cloning with Flexible Assembly Sequence Tags, FASTs, allows rapid swaps of gene, promoter or selection marker in existing plasmids and simple construction of vectors encoding proteins, which are fused to fluorescence-, purification-, localization-, or epitope tags. The mammalian expression vector assembly platform currently allows for the assembly of up to seven fragments in a single cloning step with correct directionality and with a cloning efficiency above 90%. The functionality of basic vectors for FAST assembly was tested and validated by transient expression of fluorescent model proteins in CHO, U-2-OS and HEK293 cell lines. In this test, we included many of the most common vector elements for heterologous gene expression in mammalian cells, in addition the system is fully extendable by other users. The vector system is designed to facilitate high-throughput genome-scale studies of mammalian cells, such as the newly sequenced CHO cell lines, through the ability to rapidly generate high-fidelity assembly of customizable gene expression vectors.

General information
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Organisations: Department of Systems Biology, Network Engineering of Eukaryotic Cell Factories, Novo Nordisk Foundation Center for Biosustainability, CHO Cell Line Engineering and Design, Center for Biological Sequence Analysis, Systems Biotechnology, Eucaryotic Molecular Cell Biology, Technical University of Denmark
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Main Research Area: Technical/natural sciences

Publication information
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Volume: 9
Bacterial diversity in snow on North Pole ice floes

The microbial abundance and diversity in snow on ice floes at three sites near the North Pole was assessed using quantitative PCR and 454 pyrosequencing. Abundance of 16S rRNA genes in the samples ranged between 43 and 248 gene copies per millilitre of melted snow. A total of 291,331 sequences were obtained through 454 pyrosequencing of 16S rRNA genes, resulting in 984 OTUs at 97% identity. Two sites were dominated by Cyanobacteria (72 and 61%, respectively), including chloroplasts. The third site differed by consisting of 95% Proteobacteria. Principal component analysis showed that the three sites clustered together when compared to the underlying environments of sea ice and ocean water. The Shannon indices ranged from 2.226 to 3.758, and the Chao1 indices showed species richness between 293 and 353 for the three samples. The relatively low abundances and diversity found in the samples indicate a lower rate...
of microbial input to this snow habitat compared to snow in the proximity of terrestrial and anthropogenic sources of microorganisms. The differences in species composition and diversity between the sites show that apparently similar snow habitats contain a large variation in biodiversity, although the differences were smaller than the differences to the underlying environment. The results support the idea that a globally distributed community exists in snow and that the global snow community can in part be attributed to microbial input from the atmosphere.

**General information**
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Novo Nordisk Foundation Center for Biosustainability, Geological Survey of Denmark and Greenland, Aarhus University, University of Washington
Authors: Hauptmann, A. Z. E. L. (Intern), Stibal, M. (Ekstern), Bælum, J. (Intern), Sicheritz-Pontén, T. (Intern), Brunak, S. (Intern), Bowman, J. S. (Ekstern), Hansen, L. H. (Ekstern), Jacobsen, C. S. (Ekstern), Blom, N. (Intern)
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Scopus rating (2013): SJR 0.978 SNIP 1.003 CiteScore 2.55
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BFI (2012): BFI-level 1
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Scopus rating (2010): SJR 1.036 SNIP 0.855
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.086 SNIP 1.036
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Scopus rating (2008): SJR 1.115 SNIP 0.931
Scopus rating (2007): SJR 1.233 SNIP 1.15
Scopus rating (2006): SJR 1.039 SNIP 0.874
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 1.017 SNIP 0.881
Scopus rating (2004): SJR 1.008 SNIP 0.947
Scopus rating (2003): SJR 1.252 SNIP 0.989
Web of Science (2003): Indexed yes
Scopus rating (2002): SJR 1.048 SNIP 0.753
Benchmarking of methods for genomic taxonomy

One of the first issues that emerges when a prokaryotic organism of interest is encountered is the question of what it is—that is, which species it is. The 16S rRNA gene formed the basis of the first method for sequence-based taxonomy and has had a tremendous impact on the field of microbiology. Nevertheless, the method has been found to have a number of shortcomings. In the current study, we trained and benchmarked five methods for whole-genome sequence-based prokaryotic species identification on a common data set of complete genomes: (i) SpeciesFinder, which is based on the complete 16S rRNA gene; (ii) Reads2Type that searches for species-specific 50-mers in either the 16S rRNA gene or the gyrB gene (for the Enterobacteriaceae family); (iii) the ribosomal multilocus sequence typing (rMLST) method that samples up to 53 ribosomal genes; (iv) TaxonomyFinder, which is based on species-specific functional protein domain profiles; and finally (v) KmerFinder, which examines the number of cooccurring k-mers (substrings of k nucleotides in DNA sequence data). The performances of the methods were subsequently evaluated on three data sets of short sequence reads or draft genomes from public databases. In total, the evaluation sets constituted sequence data from more than 11,000 isolates covering 159 genera and 243 species. Our results indicate that methods that sample only chromosomal, core genes have difficulties in distinguishing closely related species which only recently diverged. The KmerFinder method had the overall highest accuracy and correctly identified from 93% to 97% of the isolates in the evaluations sets.
Biological insights from 108 schizophrenia-associated genetic loci

Schizophrenia is a highly heritable disorder. Genetic risk is conferred by a large number of alleles, including common alleles of small effect that might be detected by genome-wide association studies. Here we report a multi-stage schizophrenia genome-wide association study of up to 36,989 cases and 113,075 controls. We identify 128 independent associations spanning 108 conservatively defined loci that meet genome-wide significance, 83 of which have not been previously reported. Associations were enriched among genes expressed in brain, providing biological plausibility for the findings. Many findings have the potential to provide entirely new insights into aetiology, but associations at DRD2 and several genes involved in glutamatergic neurotransmission highlight molecules of known and potential therapeutic relevance to schizophrenia, and are consistent with leading pathophysiological hypotheses. Independent of genes expressed in brain, associations were enriched among genes expressed in tissues that have important roles in immunity, providing support for the speculated link between the immune system and schizophrenia.
Targeted cancer treatment is becoming the goal of newly developed oncology medicines and has already shown promise in some spectacular cases such as the case of BRAF kinase inhibitors in BRAF-mutant (e.g. V600E) melanoma. These developments are driven by the advent of high-throughput sequencing, which continues to drop in cost, and that has enabled the sequencing of the genome, transcriptome, and epigenome of the tumors of a large number of cancer patients in order to discover the molecular aberrations that drive the oncogenesis of several types of cancer. Applying these technologies in the clinic promises to transform cancer treatment by identifying therapeutic vulnerabilities of each patient's tumor. These approaches will need to address the panomics of cancer—the integration of the complex combination of patient-specific characteristics that drive the development of each person's tumor and response to therapy. This in turn necessitates new computational methods to integrate large-scale "omics" data for each patient with their electronic medical records, and in the context of the results from large-scale pan-cancer research studies, to select the best therapy and/or clinical trial for the patient at hand.

Cesarean section imprints cord blood immune cell distributions
Immune programming in early life may affect the risk of developing immune-related diseases later in life. Children born by cesarean section seem to be at higher risk of asthma, allergic rhinitis, and type-1 diabetes. We hypothesized that delivery by cesarean section may affect immune maturation in newborns. The objective of the study was to profile innate and adaptive immune cell subsets in cord blood of children born by cesarean section or natural birth.
Characterisation of the Ara h 1-specific IgE repertoire in peanut allergic patients using phage display technology and next generation sequencing

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Organisations: Department of Micro- and Nanotechnology, Fluidic Array Systems and Technology, National Food Institute, Division of Toxicology and Risk Assessment, Department of Systems Biology, Center for Biological Sequence Analysis, Immunological Bioinformatics, Institute of Food Research, Medical University of Vienna
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Scopus rating (2015): SJR 3.13 SNIP 2.127 CiteScore 5.73
Web of Science (2015): Indexed yes
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Scopus rating (2014): SJR 2.464 SNIP 2.121 CiteScore 5.51
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 2.195 SNIP 1.902 CiteScore 4.91
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 2.008 SNIP 1.818 CiteScore 4.81
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Characterization of binding specificities of bovine leucocyte class I molecules: impacts for rational epitope discovery.

The binding of peptides to classical major histocompatibility complex (MHC) class I proteins is the single most selective step in antigen presentation. However, the peptide-binding specificity of cattle MHC (bovine leucocyte antigen, BoLA) class I (BoLA-I) molecules remains poorly characterized. Here, we demonstrate how a combination of high-throughput assays using positional scanning combinatorial peptide libraries, peptide dissociation, and peptide-binding affinity binding measurements can be combined with bioinformatics to effectively characterize the functionality of BoLA-I molecules. Using this strategy, we characterized eight BoLA-I molecules, and found the peptide specificity to resemble that of human MHC-I molecules with primary anchors most often at P2 and P9, and occasional auxiliary P1/P3/P5/P6 anchors. We analyzed nine reported CTL epitopes from *Theileria parva*, and in eight cases, stable and high affinity binding was confirmed. A set of peptides were tested for binding affinity to the eight BoLA proteins and used to refine the predictors of peptide-MHC binding NetMHC and NetMHCpan. The inclusion of BoLA-specific peptide-binding data led to a significant improvement in prediction accuracy for reported *T. parva* CTL epitopes. For reported CTL epitopes with weak or no predicted binding, these refined prediction methods suggested presence of nested minimal epitopes with high-predicted binding affinity. The enhanced affinity of the alternative peptides was in all cases confirmed experimentally. This study demonstrates how biochemical high-throughput assays combined with immunoinformatics can be used to characterize the peptide-binding motifs of BoLA-I molecules, boosting performance of MHC peptide-binding prediction methods, and empowering rational epitope discovery in cattle.
Children developing asthma by school-age display aberrant immune responses to pathogenic airway bacteria as infants

Asthma is a highly prevalent chronic lung disease that commonly originates in early childhood. Colonisation of neonatal airways with the pathogenic bacterial strains H. influenzae, M. catarrhalis and S. pneumoniae is associated with increased risk of later childhood asthma. We hypothesized that children developing asthma have an abnormal immune response to pathogenic bacteria in infancy. We aimed to assess the bacterial immune response in asymptomatic infants and the association with later development of asthma by age 7 years.

General information
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Web of Science (2016): Indexed yes
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Scopus rating (2015): SJR 3.13 SNIP 2.127 CiteScore 5.73
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.464 SNIP 2.121 CiteScore 5.51
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 2.195 SNIP 1.902 CiteScore 4.91
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 2.008 SNIP 1.818 CiteScore 4.81
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 2.328 SNIP 1.781 CiteScore 4.89
ISI indexed (2011): ISI indexed yes
Children with asthma by school age display aberrant immune responses to pathogenic airway bacteria as infants

Background
Asthma is a highly prevalent chronic lung disease that commonly originates in early childhood. Colonization of neonatal airways with the pathogenic bacterial strains Haemophilus influenzae, Moraxella catarrhalis, and Streptococcus pneumoniae is associated with increased risk of later childhood asthma. We hypothesized that children with asthma have an abnormal immune response to pathogenic bacteria in infancy.

Objective
We aimed to assess the bacterial immune response in asymptomatic infants and the association with later development of asthma by age 7 years.

Methods
The Copenhagen Prospective Studies on Asthma in Childhood birth cohort was followed prospectively, and asthma was diagnosed at age 7 years. The immune response to H influenzae, M catarrhalis, and S pneumoniae was analyzed in 292 infants using PBMCs isolated and stored since the age of 6 months. The immune response was assessed based on the pattern of cytokines produced and T-cell activation.

Results
The immune response to pathogenic bacteria was different in infants with asthma by 7 years of age (P = .0007). In particular, prospective asthmatic subjects had aberrant production of IL-5 (P = .008), IL-13 (P = .057), IL-17 (P = .001), and IL-10 (P = .028), whereas there were no differences in T-cell activation or peripheral T-cell composition. Conclusions
Children with asthma by school age exhibited an aberrant immune response to pathogenic bacteria colonizing the airways in early life might lead to chronic airway inflammation and childhood asthma.
Choice of bacterial DNA extraction method from fecal material influences community structure as evaluated by metagenomic analysis

General information
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Organisations: Center for Biological Sequence Analysis, Functional Human Variation, National Food Institute, Division of Food Microbiology, Behavioral Phenomics, Metagenomics, Department of Systems Biology, University of Copenhagen
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Source: dtu
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Publication: Research - peer-review › Journal article – Annual report year: 2014
Cofactory: Sequence-based prediction of cofactor specificity of Rossmann folds

Obtaining optimal cofactor balance to drive production is a challenge metabolically engineered microbial strains. To facilitate identification of heterologous enzymes with desirable altered cofactor requirements from native content, we have developed Cofactory, a method for prediction of enzyme cofactor specificity using only primary amino acid sequence information. The algorithm identifies potential cofactor binding Rossmann folds and predicts the specificity for the cofactors FAD(H2), NAD(H), and NADP(H). The Rossmann fold sequence search is carried out using hidden Markov models whereas artificial neural networks are used for specificity prediction. Training was carried out using experimental data from protein cofactor structure complexes. The overall performance was benchmarked against an independent evaluation set obtaining Matthews correlation coefficients of 0.94, 0.79, and 0.65 for FAD(H2), NAD(H), and NADP(H), respectively. The Cofactory method is made publicly available at http://www.cbs.dtu.dldservices/Cofactory.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Metagenomics, Novo Nordisk Foundation Center for Biosustainability, iLoop, Network Reconstruction in Silico Biology, Functional Human Variation, Integrative Systems Biology, Novozymes A/S
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Pages: 1819-1828
Publication date: 2014
Main Research Area: Technical/natural sciences
Colony morphology and transcriptome profiling of Pseudomonas putida KT2440 and its mutants deficient in alginate or all EPS synthesis under controlled matric potentials

Pseudomonas putida is a versatile bacterial species adapted to soil and its fluctuations. Like many other species living in soil, P. putida often faces water limitation. Alginate, an exopolysaccharide (EPS) produced by P. putida, is known to create hydrated environments and alleviate the effect of water limitation. In addition to alginate, P. putida is capable of producing cellulose (bcs), putida exopolysaccharide a (pea), and putida exopolysaccharide b (peb). However, unlike alginate, not much is known about their roles under water limitation. Hence, in this study we examined the role of different EPS components under mild water limitation. To create environmentally realistic water limited conditions as observed in soil, we used the Pressurized Porous Surface Model. Our main hypothesis was that under water limitation and in the absence of alginate
other exopolysaccharides would be more active to maintain homeostasis. To test our hypothesis, we investigated colony morphologies and whole genome transcriptomes of P. putida KT2440 wild type and its mutants deficient in synthesis of either alginate or all known EPS. Overall our results support that alginate is an important exopolysaccharide under water limitation and in the absence of alginate other tolerance mechanisms are activated.
BIBLIOCHEMICAL, MATHEMATICAL, MOLECULAR-DYNAMICS SIMULATIONS, INFERENTIAL STRUCTURE DETERMINATION, ENSEMBLE REFINEMENT, PROTEIN-STRUCTURE, ENERGY FUNCTION, MODELS, STATE, NMR, RECONSTRUCTION, POLYPEPTIDES

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Publication: Research - peer-review › Journal article – Annual report year: 2014
Comparative genomics of Lactobacillus and other LAB

The genomes of 66 LABs, belonging to five different genera, were compared for genome size and gene content. The analyzed genomes included 37 Lactobacillus genomes of 17 species, six Lactococcus lactis genomes, four Leuconostoc genomes of three species, six Streptococcus genomes of two species, twelve Enterococcus genomes of four species and a single Weissella genome. Genomes of pathogenic strains or species were not included. Since the gene density in these genomes is relatively constant, genome size is a measure of gene content. The genomes of Enterococcus were significantly larger than that of the others, with the two Streptococcus species having the shortest genomes. The widest distribution in genome content was observed for Lactobacillus. The number of tRNA and rRNA gene copies varied considerably, with exceptional high numbers observed for Lb. delbrueckii, while these numbers were relatively high for Lb. sanfransiscensis and Lb. salivarius, with respect to their moderate gene size. The phylogenetic relationship of the 16S ribosomal RNA genes of these genomes was established and pan- and core genomes were defined for each genus. In addition, core genome analysis was performed on all food isolates combined, as well as for all isolates that had been obtained from the gastro-intestinal tract of animals or humans. The Clusters of Orthologous Genes were deduced and compared for these core genomes. The presented data aim to illustrate how genome comparisons can complement experimental observations.

General information
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Comparative Microbial Genomics, Molecular Microbiology and Genomics Consultants
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Comparison of the Web Tools ARG-ANNOT and ResFinder for Detection of Resistance Genes in Bacteria

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Organisations: Immunological Bioinformatics, National Food Institute
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BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Compass: A hybrid method for clinical and biobank data mining
We describe a new method for identification of confident associations within large clinical data sets. The method is a hybrid of two existing methods; Self-Organizing Maps and Association Mining. We utilize Self-Organizing Maps as the initial step to reduce the search space, and then apply Association Mining in order to find association rules. We demonstrate that this procedure has a number of advantages compared to traditional Association Mining; it allows for handling numerical variables without a priori binning and is able to generate variable groups which act as “hotspots” for statistically significant associations. We showcase the method on infertility-related data from Danish military conscripts. The clinical data we analyzed contained both categorical type questionnaire data and continuous variables generated from biological measurements, including missing values. From this data set, we successfully generated a number of interesting association rules, which relate an observation with a specific consequence and the p-value for that finding. Additionally, we demonstrate that the method can be used on non-clinical data containing chemical–disease associations in order to find associations between different phenotypes, such as prostate cancer and breast cancer.

General information
State: Published
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BFI (2018): BFI-level 2
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BFI (2016): BFI-level 2
Scopus rating (2016): SJR 0.857 SNIP 1.521 CiteScore 3.23
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 1.281 SNIP 2.243 CiteScore 3.66
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 1.069 SNIP 2.372 CiteScore 3.48
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 1.057 SNIP 1.933 CiteScore 3.07
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 1.032 SNIP 2.1 CiteScore 3.08
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 0.851 SNIP 1.91 CiteScore 2.64
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 0.714 SNIP 1.639
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 1.004 SNIP 1.887
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 0.856 SNIP 1.542
Scopus rating (2007): SJR 0.958 SNIP 2.227
Scopus rating (2006): SJR 0.786 SNIP 2.114
Scopus rating (2005): SJR 1.162 SNIP 1.999
Scopus rating (2004): SJR 0.484 SNIP 1.299
Scopus rating (2003): SJR 0.283 SNIP 0.692
Scopus rating (2002): SJR 0.3 SNIP 0.776
Complete Genome Sequence of Border Disease Virus Genotype 3 Strain Gifhorn
The complete genome sequence of the genotype 3 border disease virus strain Gifhorn has been determined; this strain was originally isolated from pigs. This represents the consensus sequence for the virus used to produce the bacterial artificial chromosome (BAC) cDNA clone pBeloGif3, which yields a virus that is severely attenuated in cell culture.

Complete Genome Sequence of Classical Swine Fever Virus Genotype 2.2 Strain Bergen
The complete genome sequence of the genotype 2.2 classical swine fever virus strain Bergen has been determined; this strain was originally isolated from persistently infected domestic pigs in the Netherlands and is characterized to be of low virulence.
Computational and Experimental Approaches to Cancer Biomarker Discovery

Effective cancer treatment requires good biomarkers: measurable indicators of some biological state or condition that constitute the cornerstone of personalized medicine. Prognostic biomarkers provide information about the likely course of the disease, while predictive biomarkers enable prediction of a patient’s response to a particular treatment, thus helping to avoid unnecessary treatment and unwanted side effects in non-responding individuals. Currently, biomarker discovery is facilitated by recent advances in high-throughput technologies when association between a given biological phenotype and the state or level of a large number of molecular entities is investigated. Such associative analysis could be confounded by several factors, leading to false discoveries. For example, it is assumed that with the exception of the true biomarkers most molecular entities such as gene expression levels show random distribution in a given cohort. However, gene expression levels may also be affected by technical bias when the actual measurement technology or sample handling may introduce a systematic error. If the distribution of systematic errors correlates with the biological phenotype then the risk of producing false positive biomarkers increases. Therefore, understanding the sources of bias and removing it is essential for effective biomarker discovery. The first part of this thesis describes a tool for visualization of technical bias in the microarray data. The researcher can readily see whether a dataset of interest is biased, and whether the bias correction method used is effective to correct it. Thus the potential value of the various microarray data sets can be evaluated. Mutational signatures constitute a particularly attractive and robust class of biomarkers. They characterize and quantify at least two fundamental mechanisms responsible for DNA aberrations present in a given tumor: 1) active mutational processes caused either by endogenous or exogenous factors, for example chemical agents such as tobacco smoke or cancer cytotoxics, or by active enzymatic processes such as APOBEC related mutagenesis; and 2) the integrity of endogenous DNA repair processes as exemplified by BRCA1/2 dysfunction or MMR deficiency. Since lack of a given DNA repair process may make tumors particularly sensitive to certain types of therapy, identification of such defects will allow for potential enhancements of the therapy efficacy. State of the art mutational signatures are derived mathematically using nonnegative matrix factorization to solve a blind source separation problem arising from a multitude of mutational processes that form the observable mutational catalogs. In my ongoing projects I address this issue with a purely biological, experimental approach where the effects of treatment with cytotoxic agents or defects in DNA repair mechanisms can be individually quantified and turned into mutational signatures. In the second part of the thesis I present work towards identification and improvement of the current mutational signatures through an experimental approach. For that purpose a unique chicken cell line, DT40, was chosen, that allows for a relatively easy, HR-mediated knockout of DNA repair genes. In order to effectively use the DT40 in the subsequent mutational signatures analysis the DT40 genome was sequenced, assembled and characterized, which is described in the thesis. We are currently using it as a model system in our framework for functional analysis study of DNA repair mechanisms and cytotoxic effects. We hope that the experimentally derived mutational signatures will be useful as a part of patient diagnostics in the future. It is here that we had to focus our attention to various sources of biological bias while trying to address a particular demand within
cancer therapy. This part of the thesis describes our ongoing efforts; thus by the time of the defense some updates to this part are expected. This work, together with manifold of efforts being done all over the world, is hopefully a step towards implementation of personalized medicine and better treatments for cancer patients.

**General information**
State: Published
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**Construction of a dairy microbial genome catalog opens new perspectives for the metagenomic analysis of dairy fermented products**

Background: Microbial communities of traditional cheeses are complex and insufficiently characterized. The origin, safety and functional role in cheese making of these microbial communities are still not well understood. Metagenomic analysis of these communities by high throughput shotgun sequencing is a promising approach to characterize their genomic and functional profiles. Such analyses, however, critically depend on the availability of appropriate reference genome databases against which the sequencing reads can be aligned. Results: We built a reference genome catalog suitable for short read metagenomic analysis using a low-cost sequencing strategy. We selected 142 bacteria isolated from dairy products belonging to 137 different species and 67 genera, and succeeded to reconstruct the draft genome of 117 of them at a standard or high quality level, including isolates from the genera Kluyvera, Luteococcus and Marinilactibacillus, still missing from public database. To demonstrate the potential of this catalog, we analysed the microbial composition of the surface of two smear cheeses and one blue-veined cheese, and showed that a significant part of the microbiota of these traditional cheeses was composed of microorganisms newly sequenced in our study. Conclusions: Our study provides data, which combined with publicly available genome references, represents the most expansive catalog to date of cheese-associated bacteria. Using this extended dairy catalog, we revealed the presence in traditional cheese of dominant microorganisms not deliberately inoculated, mainly Gram-negative genera such as Pseudoalteromonas haloplanktis or Psychrobacter immobilis, that may contribute to the characteristics of cheese produced through traditional methods.

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Metagenomics, INRA Institut National de La Recherche Agronomique, AgroParisTech, University of Maryland
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Web of Science (2017): Indexed yes
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Scopus rating (2016): CiteScore 4.05 SJR 2.065 SNIP 1.122
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.287 SNIP 1.172 CiteScore 4.3
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.293 SNIP 1.205 CiteScore 4.18
CoreFlow: A computational platform for integration, analysis and modeling of complex biological data

A major challenge in mass spectrometry and other large-scale applications is how to handle, integrate, and model the data that is produced. Given the speed at which technology advances and the need to keep pace with biological experiments, we designed a computational platform, CoreFlow, which provides programmers with a framework to manage data in real-time. It allows users to upload data into a relational database (MySQL), and to create custom scripts in high-level languages such as R, Python, or Perl for processing, correcting and modeling this data. CoreFlow organizes these scripts into project-specific pipelines, tracks interdependencies between related tasks, and enables the generation of summary reports as well as publication-quality images. As a result, the gap between experimental and computational components of a typical large-scale biology project is reduced, decreasing the time between data generation, analysis and manuscript writing. CoreFlow is being released to the scientific community as an open-sourced software package complete with proteomics-specific examples, which include corrections for incomplete isotopic labeling of peptides (SILAC) or arginine-to-proline conversion, and modeling of multiple/selected reaction monitoring (MRM/SRM) results. Biological significanceCoreFlow was purposely designed as an environment for programmers to rapidly perform data analysis.
These analyses are assembled into project-specific workflows that are readily shared with biologists to guide the next stages of experimentation. Its simple yet powerful interface provides a structure where scripts can be written and tested virtually simultaneously to shorten the life cycle of code development for a particular task. The scripts are exposed at every step so that a user can quickly see the relationships between the data, the assumptions that have been made, and the manipulations that have been performed. Since the scripts use commonly available programming languages, they can easily be transferred to and from other computational environments for debugging or faster processing. This focus on ‘on the fly’ analysis sets CoreFlow apart from other workflow applications that require wrapping of scripts into particular formats and development of specific user interfaces. Importantly, current and future releases of data analysis scripts in CoreFlow format will be of widespread benefit to the proteomics community, not only for uptake and use in individual labs, but to enable full scrutiny of all analysis steps, thus increasing experimental reproducibility and decreasing errors. This article is part of a Special Issue entitled: Can Proteomics Fill the Gap Between Genomics and Phenotypes?
Database-driven primary analysis of raw sequencing data
The present invention relates to methods for identifying the source of a biological sequence containing sample from raw sequencing reads. The method may be used to identify the source of unknown DNA and can be used for diagnostic, biodefense, food safety and quality, and hygiene applications. In another aspect the invention relates to a database of reference sequences which can be used in the method of the invention.

Dataset size and composition impact the reliability of performance benchmarks for peptide-MHC binding predictions
Background: It is important to accurately determine the performance of peptide-MHC binding predictions, as this enables users to compare and choose between different prediction methods and provides estimates of the expected error rate. Two common approaches to determine prediction performance are cross-validation, in which all available data are iteratively split into training and testing data, and the use of blind sets generated separately from the data used to construct the predictive method. In the present study, we have compared cross-validated prediction performances generated on our last benchmark dataset from 2009 with prediction performances generated on data subsequently added to the Immune Epitope Database (IEDB) which served as a blind set. Results: We found that cross-validated performances systematically overestimated performance on the blind set. This was found not to be due to the presence of similar peptides in the cross-validation dataset. Rather, we found that small size and low sequence/affinity diversity of either training or blind datasets were associated with large differences in cross-validated vs. blind prediction performances. We use these findings to derive quantitative rules of how large and diverse datasets need to be to provide generalizable performance estimates. Conclusion: It has long been known that cross-validated prediction performance estimates often overestimate performance on independently generated blind set data. We here identify and quantify the specific factors contributing to this effect for MHC-I binding predictions. An increasing number of peptides for which MHC binding affinities are measured experimentally have been selected based on binding predictions and thus are less diverse than historic datasets sampling the entire sequence and affinity space, making them more difficult benchmark data sets. This has to be taken into account when comparing performance metrics between different benchmarks, and when deriving error estimates for predictions based on benchmark performance.
Decoding network dynamics in cancer

Biological systems are composed of highly dynamic and interconnected molecular networks that drive biological decision processes. The goal of network biology is to describe, quantify and predict the information flow and functional behaviour of living systems in a formal language and with an accuracy that parallels our characterisation of other physical systems such as Jumbo-jets. Decades of targeted molecular and biological studies have led to numerous pathway models of developmental and disease related processes. However, so far no global models have been derived from pathways, capable of predicting cellular trajectories in time, space or disease. The development of high-throughput methodologies has further enhanced our ability to obtain quantitative genomic, proteomic and phenotypic readouts for many genes/proteins simultaneously. Here, I will discuss how it is now possible to derive network models through computational integration of systematic, large-scale, high-dimensional quantitative data sets. I will review our latest advances in methods for exploring phosphorylation networks. In particular I will discuss how the combination of quantitative mass-spectrometry, systems-genetics and computational algorithms (NetworKIN [Linding et al. Cell 2007] and NetPhorest [Miller et al. Science Signaling 2008]) made it possible for us to derive systems-level models of JNK and EphR signalling networks [Bakal et al. Science 2008, Jørgensen et al. Science 2009]. I shall discuss work we have done in comparative phospho-proteomics and network evolution [Tan et al. Science Signaling 2009, Tan et al. Science 2009, Tan et al. Science 2011]. Finally, I will discuss our most recent work in analyzing genomic sequencing data from NGS studies and how we have developed new powerful algorithms to predict the impact of disease mutations on cellular signaling networks [Creixell et al. Nature Biotechnology 2012, Erler & Linding Cell 2012, Horn et al. Nature Methods 2014].

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis
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Publication information
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BFI (2017): BFI-level 1
Derived immune and ancestral pigmentation alleles in a 7,000-year-old Mesolithic European

Ancient genomic sequences have started to reveal the origin and the demographic impact of farmers from the Neolithic period spreading into Europe(1-3). The adoption of farming, stock breeding and sedentary societies during the Neolithic may have resulted in adaptive changes in genes associated with immunity and diet(4). However, the limited data available from earlier hunter-gatherers preclude an understanding of the selective processes associated with this crucial transition to agriculture in recent human evolution. Here we sequence an approximately 7,000-year-old Mesolithic skeleton discovered at the La Brana-Arintero site in Leon, Spain, to retrieve a complete pre-agricultural European human genome. Analysis of this genome in the context of other ancient samples suggests the existence of a common ancient genomic signature across western and central Eurasia from the Upper Paleolithic to the Mesolithic. The La Brana individual carries ancestral alleles in several skin pigmentation genes, suggesting that the light skin of modern Europeans was not yet ubiquitous in Mesolithic times. Moreover, we provide evidence that a significant number of derived, putatively adaptive variants associated with pathogen resistance in modern Europeans were already present in this hunter-gatherer.

General information
State: Published
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Detection of a caspase-3 cleaved tau fragment in the serum of Alzheimer's patients by using immunoprecipitation and lc-ms/ms

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Enzyme and Protein Chemistry, Nordic Bioscience A/S, Lillebaelt Hospital
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Web of Science (2016): Indexed yes
Scopus rating (2015): SJR 4.463 SNIP 2.794 CiteScore 9.27
Scopus rating (2014): SJR 6.26 SNIP 4.355 CiteScore 12.01
Scopus rating (2013): SJR 6.06 SNIP 4.41 CiteScore 11.97
ISI indexed (2013): ISI indexed yes
Scopus rating (2012): SJR 4.359 SNIP 3.137 CiteScore 9.34
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
Scopus rating (2011): SJR 2.136 SNIP 1.868 CiteScore 4.75
ISI indexed (2011): ISI indexed no
Scopus rating (2010): SJR 1.69 SNIP 1.359
Scopus rating (2009): SJR 0.972 SNIP 1.069
Scopus rating (2008): SJR 0.694 SNIP 0.62
Scopus rating (2007): SJR 0.663 SNIP 0.432
Scopus rating (2006): SJR 0.286 SNIP 0.183
Original language: English
DOIs:
10.1038/nature12960

Development of a Recombinant Antibody-Based Treatment of Snakebites
Antivenom for snakebites is produced by immunization of large mammals with snake venom using a traditional and expensive method developed in the 1890's. Due to the animal origin, the products are highly immunogenic and come with a high risk of adverse side effects such as serum sickness and anaphylaxis, possibly leading to death.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Network Engineering of Eukaryotic Cell Factories, Integrative Systems Biology, University of Copenhagen
Number of pages: 1
Development of synchronous VHL syndrome tumors reveals contingencies and constraints to tumor evolution

Background: Genomic analysis of multi-focal renal cell carcinomas from an individual with a germline VHL mutation offers a unique opportunity to study tumor evolution. Results: We perform whole exome sequencing on four clear cell renal cell carcinomas removed from both kidneys of a patient with a germline VHL mutation. We report that tumors arising in this context are clonally independent and harbour distinct secondary events exemplified by loss of chromosome 3p, despite an identical genetic background and tissue microenvironment. We propose that divergent mutational and copy number anomalies are contingent upon the nature of 3p loss of heterozygosity occurring early in tumorigenesis. However, despite distinct 3p events, genomic, proteomic and immunohistochemical analyses reveal evidence for convergence upon the PI3K-AKT-mTOR signaling pathway. Four germline tumors in this young patient, and in a second, older patient with VHL syndrome demonstrate minimal intra-tumor heterogeneity and mutational burden, and evaluable tumors appear to follow a linear evolutionary route, compared to tumors from patients with sporadic clear cell renal cell carcinoma. Conclusions: In tumors developing from a germline VHL mutation, the evolutionary principles of contingency and convergence in tumor development are complementary. In this small set of patients with early stage VHL-associated tumors, there is reduced mutation burden and limited evidence of intra-tumor heterogeneity.
Different binding motifs of the celiac disease-associated HLA molecules DQ2.5, DQ2.2, and DQ7.5 revealed by relative quantitative proteomics of endogenous peptide repertoires

Celiac disease is caused by intolerance to cereal gluten proteins, and HLA-DQ molecules are involved in the disease pathogenesis by presentation of gluten peptides to CD4+ T cells. The α- or β-chain sharing HLA molecules DQ2.5, DQ2.2, and DQ7.5 display different risks for the disease. It was recently demonstrated that T cells of DQ2.5 and DQ2.2 patients recognize distinct sets of gluten epitopes, suggesting that these two DQ2 variants select different peptides for display. To explore whether this is the case, we performed a comprehensive comparison of the endogenous self-peptides bound to HLA-DQ molecules of B-lymphoblastoid cell lines. Peptides were eluted from affinity-purified HLA molecules of nine cell lines and subjected to quadrupole orbitrap mass spectrometry and MaxQuant software analysis. Altogether, 12,712 endogenous peptides were identified at very different relative abundances. Hierarchical clustering of normalized quantitative data demonstrated significant differences in repertoires of peptides between the three DQ variant molecules. The neural network-based method, NNAlign, was used to identify peptide-binding motifs. The binding motifs of DQ2.5 and DQ7.5 concurred with previously established binding motifs. The binding motif of DQ2.2 was strikingly different from that of DQ2.5 with position P3 being a major anchor having a preference for threonine and serine. This is notable as three recently identified epitopes of gluten recognized by T cells of DQ2.2 celiac patients harbor serine at position P3. This study demonstrates that relative quantitative comparison of endogenous peptides sampled from our protein metabolism by HLA molecules provides clues to understand HLA association with disease.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Immunological Bioinformatics, University of Oslo, University of Copenhagen
Authors: Bergseng, E. (Ekstern), Dørum, S. (Ekstern), Arntzen, M. Ø. (Ekstern), Nielsen, M. (Intern), Nygård, S. (Ekstern), Buus, S. (Ekstern), de Souza, G. A. (Ekstern), Sollid, L. M. (Ekstern)
Number of pages: 12
Discovery of biomarkers for glycaemic deterioration before and after the onset of type 2 diabetes: rationale and design of the epidemiological studies within the IMI DIRECT Consortium

Aims/hypothesis The DIRECT (Diabetes Research on Patient Stratification) Study is part of a European Union Framework 7 Innovative Medicines Initiative project, a joint undertaking between four industry and 21 academic partners throughout Europe. The Consortium aims to discover and validate biomarkers that: (1) predict the rate of glycaemic deterioration before and after type 2 diabetes onset; (2) predict the response to diabetes therapies; and (3) help stratify type 2 diabetes into clearly definable disease subclasses that can be treated more effectively than without stratification. This paper describes two new prospective cohort studies conducted as part of DIRECT. Methods Prediabetic participants (target sample size 2,200-2,700) and patients with newly diagnosed type 2 diabetes (target sample size similar to 1,000) are undergoing detailed metabolic phenotyping at baseline and 18 months and 36 months later. Abdominal, pancreatic and liver fat is assessed using MRI. Insulin secretion and action are assessed using frequently sampled OGTTs in non-diabetic participants, and frequently sampled mixed-meal tolerance tests in patients with type 2 diabetes. Biosamples include venous blood, faeces, urine and nail clippings, which, among other biochemical analyses, will be characterised at genetic, transcriptomic, metabolomic, proteomic and metagenomic levels. Lifestyle is assessed using high-resolution triaxial accelerometer, 24 h diet record, and food habit questionnaires. Conclusions/interpretation DIRECT will yield an unprecedented array of biomaterials and data. This resource, available through managed access to scientists within and outside the Consortium, will facilitate the development of new treatments and therapeutic strategies for the prevention and management of type 2 diabetes.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Lund University, Newcastle University, University of Dundee, University of Eastern Finland, University of Amsterdam, Skåne University Hospital, University of Exeter, University of Oxford, German Center for Diabetes Research, Imperial College Hammersmith Campus, University of London, University of Copenhagen, Sanofi Aventis Deutschland GmbH, National Research Council of Italy, VUmc, University of Southern Denmark, Eli Lilly & Company
Number of pages: 11
Pages: 1132-1142
Publication date: 2014
Main Research Area: Technical/natural sciences

Publication information
Journal: DIABETOLOGIA
Volume: 57
Issue number: 6
ISSN (Print): 0012-186X
Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
More than 5.5 million people are bitten by venomous snakes per year on a global basis. This leads to approx. 125,000 deaths and 3 times as many amputations. Particularly Sub-Saharan Africa is affected by the problem. Current antivenoms are still being produced by a method developed in the 1890’s, in which large mammals (typically horses) are immunized with snake venom and antiserum is derived from the animals blood. The incompatibility with the human immune system of these animal derived antivenoms leads to a range of side effects, such as serum sickness, anaphylaxis, and sometimes even death. Despite the maturity of medicinal chemistry and advances in drug development, there remains a need for modern antivenoms with better safety profile and improved efficacy [4]. We have set out to tackle this challenge by
attempting to develop the World’s first antivenom based on recombinant, humanized antibodies. Such an antivenom will be cheaper to produce in large scale and is anticipated to have a much improved safety and efficacy profile.

**General information**

State: Published

Organisations: Department of Systems Biology, Network Engineering of Eukaryotic Cell Factories, Center for Biological Sequence Analysis, University of Copenhagen, Royal Danish Academy of Fine Arts, Schools of Architecture, Design and Conservation

Authors: Laustsen, A. H. (Intern), Engmark, M. (Intern), Redsted Rasmussen, A. (Ekstern), Lohse, B. (Ekstern)

Number of pages: 1

Publication date: 2014

Event: Poster session presented at PhD Day 2014, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark.

Main Research Area: Technical/natural sciences

Electronic versions:

Discovery_of_Human_IgGs_against_Cobratoxin_for_Development_of_Recombinant_Antibody_based_Antivenom.pdf

Publication: Research - peer-review › Poster – Annual report year: 2014

**Discovery of Peptide-Based Antitoxins against Neurotoxins from Green and Black Mamba (Dendroaspis Family)**

Globally, more than 5.5 million people are bitten by venomous snakes every year, leading to an estimated 125,000 deaths and 3 times as many amputations. The problem is most prevalent in Sub-Saharan Africa where affordability of antivenom is low, resulting in only 2% of snakebite victims receiving treatment. Since the introduction of antivenoms in the 1890’s, only modest advances in antivenom technology and production have been made. Current antivenoms are, therefore, still being produced by immunisation of large ruminants, typically horses, with snake venoms and subsequently bleeding them to collect blood comprising venom-specific antibodies [4]. The incompatibility of these antivenoms with the human immune system can lead to serious adverse effects. A novel approach is needed in order to introduce safer, cheaper and more efficacious antivenoms that are compatible with the human immune system to the market.

Figure 2: Phage display is a screening technique whereby peptides are displayed on the surface of bacteriophages, some of which bind with high affinity to snake toxins that are attached to plate wells. We attempt to discover cross-reactive, peptide-based antitoxins against the structurally similar dendrotoxins α-dendrotoxin (α-Dtx, UniProtKB00980), isolated from Dendroaspis angusticeps (Green mamba), and dendrotoxin I (Dtx I, UniProtKB00979) from Dendroaspis polylepis (Black mamba) by phage display [5,6]. Cross-reactive antitoxins with the ability to neutralise several toxins are of interest to antivenom development, since only a few cross-reactive antitoxins would be needed to neutralise a complete snake venom.

**General information**

State: Published

Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Network Engineering of Eukaryotic Cell Factories, Technical University of Denmark, University of Copenhagen

Authors: Jappe, E. C. (Intern), Munk, A. (Forskerdatabase), Laustsen, A. H. (Intern), Engmark, M. (Intern)

Number of pages: 1

Publication date: 2014

Event: Poster session presented at GRØN DYST, Lyngby Campus, Denmark.

Main Research Area: Technical/natural sciences

Electronic versions:

Discovery_of_Peptide_Based_Antitoxins_against_Neurotoxins_from_Green_and_Black_Mamba_Dendroaspis_Family_.pdf

Publication: Research - peer-review › Poster – Annual report year: 2014

**Discrepancies in listed adverse drug reactions in pharmaceutical product information supplied by the regulatory authorities in Denmark and the USA**

Pharmaceutical product information (PI) supplied by the regulatory authorities serves as a source of information on safe and effective use of drugs. The objectives of this study were to qualitatively and quantitatively compare PIs for selected drugs marketed in both Denmark and the USA with respect to consistency and discrepancy of listed adverse drug reaction (ADR) information. We compared individual ADRs listed in PIs from Denmark and the USA with respect to type and frequency. Consistency was defined as match of ADRs and of ADR frequency or match could not be ruled out. Discrepancies were defined as ADRs listed only in one country or listed with different frequencies. We analyzed PIs for 40 separate drugs from ten therapeutic groups and assigned the 4003 identified ADRs to System Organ Classes (Medical Dictionary for Regulatory Activities [MedDRA] terminology). Less than half of listed ADRs (n = 1874; 47%) showed consistency. Discrepancies (n = 2129; 53%) were split into ADRs listed only in the USA (n = 1558; 39%), ADRs listed only in Denmark (n = 325; 8%) and ADRs listed with different frequencies (n = 246; 6%). The majority of listed ADRs were of the type “gastrointestinal disorders” and “nervous system disorders”. Our results show great differences in PIs for drugs approved in both Denmark and the USA illuminating concerns about the credibility of the publicly available PIs. The results also represent an argument for further harmonization across borders to improve consistency between authority-supplied information.
General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Integrative Systems Biology, University of Southern Denmark, University of Copenhagen
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Number of pages: 10
Publication date: 2014
Main Research Area: Technical/natural sciences

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Journal: Pharmacology Research & Perspectives
Volume: 2
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ISSN (Print): 2052-1707
Ratings:
ISI indexed (2013): ISI indexed no
Original language: English
Adverse drug reaction, Denmark, drug approval, drug labeling, drug legislation, European Medicines Agency, Food and Drug Administration, Product information, Regulatory affairs, Summary of Product Characteristics, United States
Electronic versions:
prp238.pdf
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Publication: Research - peer-review › Journal article – Annual report year: 2014

DNA secondary structures are associated with recombination in major Plasmodium falciparum variable surface antigen gene families

Many bacterial, viral and parasitic pathogens undergo antigenic variation to counter host immune defense mechanisms. In Plasmodium falciparum, the most lethal of human malaria parasites, switching of var gene expression results in alternating expression of the adhesion proteins of the Plasmodium falciparum-erythrocyte membrane protein 1 class on the infected erythrocyte surface. Recombination clearly generates var diversity, but the nature and control of the genetic exchanges involved remain unclear. By experimental and bioinformatic identification of recombination events and genome-wide recombination hotspots in var genes, we show that during the parasite’s sexual stages, ectopic recombination between isogenous var paralogs occurs near low folding free energy DNA 50-mers and that these sequences are heavily concentrated at the boundaries of regions encoding individual Plasmodium falciparum-erythrocyte membrane protein 1 structural domains. The recombinogenic potential of these 50-mers is not parasite-specific because these sequences also induce recombination when transferred to the yeast Saccharomyces cerevisiae. Genetic cross data suggest that DNA secondary structures (DSS) act as inducers of recombination during DNA replication in P. falciparum sexual stages, and that these DSS-regulated genetic exchanges generate functional and diverse P. falciparum adhesion antigens. DSS-induced recombination may represent a common mechanism for optimizing the evolvability of virulence gene families in pathogens.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Edinburgh, Weill Cornell Medical College, University of Copenhagen
Pages: 2270-2281
Publication date: 2014
Main Research Area: Technical/natural sciences

Publication information
Journal: Nucleic Acids Research
Volume: 42
Issue number: 4
Dose-Specific Adverse Drug Reaction Identification in Electronic Patient Records: Temporal Data Mining in an Inpatient Psychiatric Population

Data collected for medical, filing and administrative purposes in electronic patient records (EPRs) represent a rich source of individualised clinical data, which has great potential for improved detection of patients experiencing adverse drug reactions (ADRs), across all approved drugs and across all indication areas. The aim of this study was to take advantage of techniques for temporal data mining of EPRs in order to detect ADRs in a patient- and dose-specific manner. We used a psychiatric hospital’s EPR system to investigate undesired drug effects. Within one workflow the method identified patient-specific adverse events (AEs) and links these to specific drugs and dosages in a temporal manner, based on integration of text mining results and structured data. The structured data contained precise information on drug identity, dosage and strength. When applying the method to the 3,394 patients in the cohort, we identified AEs linked with a drug in 2,402 patients (70.8%). Of the 43,528 patient-specific drug substances prescribed, 14,736 (33.9%) were linked with AEs. From these links we identified multiple ADRs (p <0.05) and found them to occur at similar frequencies, as stated by the manufacturer and in the literature. We showed that drugs displaying similar ADR profiles share targets, and we compared submitted spontaneous AE reports with our findings. For nine of the ten most prescribed antipsychotics in the patient population, larger doses were prescribed to sedated patients than non-sedated patients; five patients exhibited a significant difference (p <0.05). Finally, we present two cases (p <0.05) identified by the workflow. The method identified the potentially fatal AE QT prolongation caused by methadone, and a non-described likely ADR between levomepromazine and nightmares found among the hundreds of identified novel links between drugs and AEs (p <0.05). The developed method can be used to extract dose-dependent ADR information from already collected EPR data. Large-scale AE extraction from EPRs may complement or even replace current drug safety monitoring methods in the future, reducing or eliminating manual reporting and enabling much faster ADR detection.
Early immune response patterns to pathogenic bacteria are associated to increased risk of lower respiratory infections in children

Neonatal colonisation of the airways with respiratory pathogens is associated with increased risk of lower respiratory infections (LRI) in early childhood (1). Therefore, we hypothesized that children developing LRI have an abnormal immune response to pathogenic bacteria in infancy. We aimed to characterise the systemic immune response to pathogenic bacteria at the age of 6 months and study the association with incidence of LRI during the first 3 years of life.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Copenhagen
Authors: Vissing, N. H. (Ekstern), Larsen, J. M. (Intern), Rasmussen, M. A. (Ekstern), Thysen, A. H. (Intern), Chawes, B. L. (Ekstern), Bønnelykke, K. (Ekstern), Pedersen, S. B. (Intern), Bisgaard, H. F. (Ekstern)
Number of pages: 1
Pages: 37-37
Publication date: 2014
Conference: European Academy of Allergy and Clinical Immunology Congress 2014, Copenhagen, Denmark, 07/06/2014 - 07/06/2014
Main Research Area: Technical/natural sciences

Publication information
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Volume: 69
Issue number: Supplement s99
Article number: 84
ISSN (Print): 0105-4538
Ratings:
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BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Scopus rating (2016): CiteScore 6.23 SJR 2.724 SNIP 2.475
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 3.13 SNIP 2.127 CiteScore 5.73
Objectives Large amounts of biocides are used to reduce and control bacterial growth in the healthcare sector, food production and agriculture. This work explores the effect of subinhibitory concentrations of four commonly used biocides (ethanol, hydrogen peroxide, chlorhexidine digluconate and sodium hypochlorite) on the conjugative transposition of the mobile genetic element Tn916.

Methods Conjugation assays were carried out between Bacillus subtilis strains. The donor containing Tn916 was pre-exposed to subinhibitory concentrations of each biocide for a defined length of time, which was determined by an analysis of the transcriptional response of the promoter upstream of tet(M) using β-glucuronidase reporter assays.

Results Ethanol significantly (P = 0.01) increased the transfer of Tn916 by 5-fold, whereas hydrogen peroxide, chlorhexidine digluconate and sodium hypochlorite did not significantly affect the transfer frequency.

Conclusions These results suggest that exposure to subinhibitory concentrations of ethanol may induce the transfer of Tn916-like
elements and any resistance genes they contain.

**General information**
State: Published
Organisations: Comparative Microbial Genomics, National Food Institute, Division of Epidemiology and Microbial Genomics, National Veterinary Institute, University College London
Authors: Seier-Petersen, M. A. (Intern), Jasni, A. (Ekstern), Aarestrup, F. M. (Intern), Vigre, H. (Intern), Mullany, P. (Ekstern), Roberts, A. P. (Ekstern), Agersø, Y. (Intern)
Pages: 343-348
Publication date: 2014
Main Research Area: Technical/natural sciences

**Publication information**
Journal: Journal of Antimicrobial Chemotherapy
Volume: 69
Issue number: 2
ISSN (Print): 0305-7453
Ratings:
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BFI (2017): BFI-level 1
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 4.21 SJR 2.24 SNIP 1.527
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.203 SNIP 1.513 CiteScore 4.06
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.303 SNIP 1.772 CiteScore 4.61
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 2.416 SNIP 1.782 CiteScore 4.7
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 2.157 SNIP 1.654 CiteScore 4.35
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 2.235 SNIP 1.745 CiteScore 4.24
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 2.09 SNIP 1.642
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.873 SNIP 1.616
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 2.005 SNIP 1.522
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 1.73 SNIP 1.515
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 1.756 SNIP 1.438
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 1.744 SNIP 1.506
Web of Science (2005): Indexed yes
Effects of pregnancy on obesity-induced inflammation in a mouse model of fetal programming

Objective
Maternal obesity is associated with increased risk of metabolic dysfunction in the offspring. It is not clear whether it is the metabolic changes or chronic low-grade inflammation in the obese state that causes this metabolic programming. We therefore investigated whether low-grade inflammation was present in obese dams compared to controls dams at gestation day 18.

Methods
Female mice were fed either a standard chow diet or a highly palatable obesogenic diet for 6 weeks prior to conception. Mice were either euthanized before mating (n=12 in each group), or euthanized on gestation day 18 (n=8 in each group). Blood and tissues were collected for analysis.

Results
The obesogenic diet increased body weight and decreased insulin sensitivity prior to conception, while there was no difference between the groups at gestation day 18. Local inflammation was assayed by macrophage count in adipose tissue and liver. Macrophage count in the adipose tissue was increased significantly by the obesogenic diet, and the hepatic count also showed a tendency to increased macrophage infiltration prior to gestation. This was further supported by a decreased population of monocytes in the blood of the obese animals, which suggested that monocytes are being recruited from the blood to the liver and adipose tissue in the obese animals. Gestation reversed macrophage infiltration, such that obese dams showed a lower adipose tissue macrophage count at the end of gestation compared to pre-pregnancy obese mice, and there were no longer a tendency towards increased hepatic macrophage count. Placental macrophage count was also similar in the two groups.

Conclusion
At gestation day 18, obese dams were found to have similar macrophage infiltration in placenta, adipose tissue and liver as lean dams, despite an incipient infiltration before gestation. Thus, the obesity-induced inflammation was reversed during gestation.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Center for Microbial Biotechnology, Metabolic Signaling and Regulation, Technical University of Denmark, University of Cambridge
Pages: 1282-1289
Publication date: 2014
Main Research Area: Technical/natural sciences

Publication information
Journal: International Journal of Obesity
Volume: 38
Issue number: 10
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Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Effects on metabolic markers are modified by PPARG2 and COX2 polymorphisms in infants randomized to fish oil.

Long-chain n-3 fatty acids (n-3 LCPUFA) improve blood pressure (BP) and lipid profile in adults and improve insulin sensitivity in rodents. We have previously shown that n-3 LCPUFA reduces BP and plasma triacylglycerol (TAG) in infants. Few studies have found effects on glucose homeostasis in humans. We explored possible effect modification by FADS, PPARG2, and COX2 genotypes to support potential effects of n-3 LCPUFA on metabolic markers in infants. Danish infants (133) were randomly allocated to daily supplementation with a teaspoon (~5 mL/day) of fish oil (FO) or sunflower oil (SO) from 9 to 18 months of age. Before and after the intervention, we assessed BP, erythrocyte n-3 LCPUFA, plasma lipid profile, insulin, and glucose in addition to functional single nucleotide polymorphisms in FADS, PPARG2, and COX2. At 18 months, plasma TAG was lower in the FO compared with SO group (p = 0.014). This effect was modified by PPARG2-Pro12Ala, as TAG only decreased among heterozygotes. FO supplemented PPARG2 Pro12Ala heterozygotes also had decreased plasma glucose compared with the SO group (p = 0.043). The effect of FO on mean arterial BP at 18 months was gender dependent (p = 0.020) and reduced in boys only (p = 0.028). Diastolic BP was, however, lower among all FO supplemented homozygous COX2-T8473C variant allele carriers compared with the SO group (p = 0.001). In conclusion, our results confirm that FO supplementation in late infancy reduces TAG and BP and indicates that the effects are mediated via peroxisome proliferator-activated receptor-γ and cyclooxygenase-2. Furthermore, FO reduced plasma glucose only in PPARG2 heterozygotes.
Enhancing Reproducibility in Cancer Drug Screening: How Do We Move Forward?

Large-scale pharmacogenomic high-throughput screening (HTS) studies hold great potential for generating robust genomic predictors of drug response. Two recent large-scale HTS studies have reported results of such screens, revealing several known and novel drug sensitivities and biomarkers. Subsequent evaluation, however, found only moderate interlaboratory concordance in the drug response phenotypes, possibly due to differences in the experimental protocols used in the two studies. This highlights the need for community-wide implementation of standardized assays for measuring drug response phenotypes so that the full potential of HTS is realized. We suggest that the path forward is to
establish best practices and standardization of the critical steps in these assays through a collective effort to ensure that
the data produced from large-scale screens would not only be of high intrastudy consistency, so that they could be
replicated and compared successfully across multiple laboratories.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Cancer Systems Biology,
Zhanjiang Center for Translational Medicine, University of Toronto, Yale University, Harvard University, Georgetown
University
Authors: Shi, L. (Ekstern), Haibe-Kains, B. (Ekstern), Birkbak, N. J. (Intern), Bedard, P. L. (Ekstern), Hatzis, C. (Ekstern),
Stern, D. F. (Ekstern), Clarke, R. (Ekstern), Quackenbush, J. (Ekstern), Beck, A. H. (Ekstern), Aerts, H. J. W. L. (Ekstern)
Number of pages: 8
Pages: 4016-4023
Publication date: 2014
Main Research Area: Technical/natural sciences

Publication information
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Volume: 74
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BFI (2017): BFI-level 2
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 8.55 SJR 4.753 SNIP 1.986
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 5.324 SNIP 2.017 CiteScore 8.57
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 5.655 SNIP 2.092 CiteScore 8.69
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 5.624 SNIP 2.098 CiteScore 8.75
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 5.028 SNIP 2.033 CiteScore 8.38
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 5.288 SNIP 1.838 CiteScore 7.88
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 5.345 SNIP 1.805
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 5.205 SNIP 1.795
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 5.175 SNIP 1.773
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 5.019 SNIP 1.76
Web of Science (2007): Indexed yes
Web of Science (2006): Indexed yes
Environmental factors influencing neonatal immunity and development of diseases later in life

The prevalence of chronic inflammatory diseases in children, including childhood asthma, has increased during the past decades resulting in reduced quality of life for the implicated child and family, and an increased socioeconomic burden. Complex interactions between genetic factors (genetic predisposition) and the exposed environment, beginning as early as in perinatal life, are recognized causes of chronic inflammatory diseases.

This PhD thesis focuses on two potential environmental risk exposures for development of childhood asthma, namely maternal parity, and postpartum bacterial colonisation of the upper respiratory tract. The aim with this thesis was to investigate how maternal parity history affected neonatal immunity; and whether hereditary and environmental risk factors affected bacterial diversity in the upper respiratory tract of asymptomatic neonates. The study is based on clinical material from the birth cohorts of Copenhagen Prospective Studies on Asthma in Childhood (COPSAC).

The first study in the PhD thesis assessed how purified cord blood T cells from newborns of primiparous versus multiparous mothers react upon polyclonal activation in vitro. These data showed a reduced anti-inflammatory T cell function in first-born children as the IL-10 secretion and CD25 expression on CD4+ helper T cells were diminished as opposed to second- or later-born children. The result suggested that in utero T cell programing is responsible for this finding, which could be one of the explanations for the well-known epidemiological observations of enhanced risk for development of immune-mediated diseases in first-born children.

The second study assessed the associations between bacterial diversity and genetic predisposition for atopy and environmental risk factors relevant to establishment of a microbiota in the upper airways of newborns. The study showed a high diversity of nasopharyngeal bacterial in asymptomatic 1-month old infants. Moreover, season of birth was found to associate to nasopharyngeal bacterial diversity, with a higher bacterial diversity as well as specific bacteria profiles representing Gram-negative alphaproteobacteria and Gram-positive Bacilli in the nasopharynx of summer-born children. The result suggested that early postnatal colonization of the upper airways may reflect surrounding air at birth. A focus on the aspect of seasonality in modelling the impact of early dynamic changes in airway communities in relation to later disease development should be included in future studies.

Overall, these findings contribute to our understanding of how common environmental factors, such as maternal parity and season of birth are associated to the development of the newborn’s immune system and nasal microbiota. These environmental factors tend to be overlooked both in the study design, statistical analysis and reporting of scientific studies. This may result in misinterpretations and errors in our search for causes of childhood asthma and other chronic inflammatory diseases.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis
Authors: Kragh, M. (Intern), Pedersen, S. B. (Intern), Hellgren, L. (Intern)
Number of pages: 103
Publication date: 2014
Equilibrium simulations of proteins using molecular fragment replacement and NMR chemical shifts

Significance: Chemical shifts are the most fundamental parameters measured in nuclear magnetic resonance spectroscopy. Since these parameters are exquisitely sensitive to the local atomic environment, they can provide detailed information about the three-dimensional structures of proteins. It has recently been shown that using such information directly as input in molecular simulations based on the molecular fragment replacement strategy can help the process of protein structure determination. Here, we show how to implement this strategy to determine not only the structures of proteins but also their thermal fluctuations, thereby broadening the scope of chemical shifts in structural biology.
Erratum to: Dose-Specific Adverse Drug Reaction Identification in Electronic Patient Records: Temporal Data Mining in an Inpatient Psychiatric Population

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Functional Human Variation, Integrative Systems Biology, Copenhagen University Hospital, University of Copenhagen
Authors: Eriksson, R. (Intern), Werge, T. (Ekstern), Jensen, L. J. (Ekstern), Brunak, S. (Intern)
Number of pages: 1
Pages: 379
Publication date: 2014
Main Research Area: Technical/natural sciences

Publication information
Journal: Drug Safety
Volume: 37
ISSN (Print): 0114-5916
Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 2
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): SJR 1.445 SNIP 1.609 CiteScore 3.34
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 1.387 SNIP 1.623 CiteScore 3.03
BFI (2014): BFI-level 2
Salmonella enterica is a common cause of minor and large food borne outbreaks. To achieve successful and nearly 'real-time' monitoring and identification of outbreaks, reliable sub-typing is essential. Whole genome sequencing (WGS) shows great promises for using as a routine epidemiological typing tool. Here we evaluate WGS for typing of S. Typhimurium including different approaches for analyzing and comparing the data. A collection of 34 S. Typhimurium isolates was sequenced. This consisted of 18 isolates from six outbreaks and 16 epidemiologically unrelated background strains. In addition, 8 S. Enteritidis and 5 S. Derby were also sequenced and used for comparison. A number of different bioinformatics approaches were applied on the data; including pan-genome tree, k-mer tree, nucleotide difference tree and SNP tree. The outcome of each approach was evaluated in relation to the association of the isolates to specific outbreaks. The pan-genome tree clustered 65% of the S. Typhimurium isolates according to the pre-defined epidemiology, the k-mer tree 88%, the nucleotide difference tree 100% and the SNP tree 100% of the strains within S. Typhimurium. The resulting outcome of the four phylogenetic analyses were also compared to PFGE reveling that WGS typing achieved the greater performance than the traditional method. In conclusion, for S. Typhimurium, SNP analysis and nucleotide difference approach of WGS data seem to be the superior methods for epidemiological typing compared to other phylogenetic analytic approaches that may be used on WGS. These approaches were also superior to the more classical typing method, PFGE. Our study also indicates that WGS alone is insufficient to determine whether strains are related or un-related to outbreaks. This still requires the combination of epidemiological data and whole genome sequencing results.

Evaluation of whole genome sequencing for outbreak detection of Salmonella enterica

Salmonella enterica is a common cause of minor and large food borne outbreaks. To achieve successful and nearly 'real-time' monitoring and identification of outbreaks, reliable sub-typing is essential. Whole genome sequencing (WGS) shows great promises for using as a routine epidemiological typing tool. Here we evaluate WGS for typing of S. Typhimurium including different approaches for analyzing and comparing the data. A collection of 34 S. Typhimurium isolates was sequenced. This consisted of 18 isolates from six outbreaks and 16 epidemiologically unrelated background strains. In addition, 8 S. Enteritidis and 5 S. Derby were also sequenced and used for comparison. A number of different bioinformatics approaches were applied on the data; including pan-genome tree, k-mer tree, nucleotide difference tree and SNP tree. The outcome of each approach was evaluated in relation to the association of the isolates to specific outbreaks. The pan-genome tree clustered 65% of the S. Typhimurium isolates according to the pre-defined epidemiology, the k-mer tree 88%, the nucleotide difference tree 100% and the SNP tree 100% of the strains within S. Typhimurium. The resulting outcome of the four phylogenetic analyses were also compared to PFGE reveling that WGS typing achieved the greater performance than the traditional method. In conclusion, for S. Typhimurium, SNP analysis and nucleotide difference approach of WGS data seem to be the superior methods for epidemiological typing compared to other phylogenetic analytic approaches that may be used on WGS. These approaches were also superior to the more classical typing method, PFGE. Our study also indicates that WGS alone is insufficient to determine whether strains are related or un-related to outbreaks. This still requires the combination of epidemiological data and whole genome sequencing results.

General information
State: Published
Organisations: Comparative Microbial Genomics, National Food Institute, Division of Epidemiology and Microbial Genomics, Department of Systems Biology, Center for Systems Microbiology, Center for Biological Sequence Analysis, Immunological Bioinformatics, Statens Serum Institut
Authors: Leekitcharoenphon, P. (Intern), Nielsen, E. M. (Ekstern), Kaas, R. S. (Intern), Lund, O. (Intern), Aarestrup, F. M. (Intern)
Number of pages: 11
Publication date: 2014
Evolution Reveals A Glutathione-dependent Mechanism Of 3-hydroxypropionic Acid Detoxification

Biologically produced 3-hydroxypropionic acid (3HP) is a potential source for sustainable acrylates and can also find direct use as monomer in the production of biodegradable polymers. For industrial-scale production, high titer, rate and yield are essential; thus there is a need for robust cell factories tolerant to high concentration of 3HP, preferably at low pH. Through
adaptive laboratory evolution we selected *S. cerevisiae* strains with improved tolerance to 3HP at pH 3.5. Genome sequencing of three independent clones identified single-nucleotide changes in the SFA1 gene encoding S-(hydroxymethyl)glutathione dehydrogenase. Introduction of the mutated SFA1 alleles or overexpression of any of the SFA1 alleles in a sfa16 strain enabled growth in the presence of above 40 g/L 3HP. We further found that aldehyde dehydrogenase (ALD6), S-formylglutathione hydrolase (YJL068C) and glutathione play a role in 3HP detoxification. Addition of glutathione relieved growth inhibition by 3HP for several yeast species and for *E. coli*; but glutathione could not enable growth of a *S. cerevisiae* sfa16 strain. Based on our findings we propose a 3-hydroxypropionic aldehyde-mediated mechanism underlying 3HP toxicity as well as a glutathione-dependent route for detoxification of 3-hydroxypropionic aldehyde (reuterin). The identified molecular response to 3HP and reuterin may well be a general mechanism for handling resistance to organic acids and aldehydes by living cells.

**General information**

State: Published
Organisations: Novo Nordisk Foundation Center for Biosustainability, Research Groups, iLoop, CFB - Core Flow, Bacterial Cell Factories, Metagenomics, Fungal Cell Factories, KTH - Royal Institute of Technology, University of Copenhagen
Number of pages: 1
Publication date: 2014
Event: Abstract from Metabolic Engineering X, Vancouver, Canada.
Main Research Area: Technical/natural sciences
Publication: Research - peer-review › Conference abstract for conference – Annual report year: 2015

**Evolution reveals a glutathione-dependent mechanism of 3-hydroxypropionic acid tolerance**

Biologically produced 3-hydroxypropionic acid (3HP) is a potential source for sustainable acrylates and can also find direct use as monomer in the production of biodegradable polymers. For industrial-scale production there is a need for robust cell factories tolerant to high concentration of 3HP, preferably at low pH. Through adaptive laboratory evolution we selected *S. cerevisiae* strains with improved tolerance to 3HP at pH 3.5. Genome sequencing followed by functional analysis identified the causal mutation in SFA1 gene encoding S-(hydroxymethyl)glutathione dehydrogenase. Based on our findings, we propose that 3HP toxicity is mediated by 3-hydroxypropionic aldehyde (reuterin) and that glutathione-dependent reactions are used for reuterin detoxification. The identified molecular response to 3HP and reuterin may well be a general mechanism for handling resistance to organic acid and aldehydes by living cells.

**General information**

State: Published
Organisations: Novo Nordisk Foundation Center for Biosustainability, Research Groups, iLoop, CFB - Core Flow, Bacterial Cell Factories, Metagenomics, Fungal Cell Factories, KTH - Royal Institute of Technology, University of Copenhagen
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Publication date: 2014
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**Publication information**

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BFI (2018): BFI-level 2
BFI (2017): BFI-level 2
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BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 8.33 SJR 3.54 SNIP 1.864
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 3.611 SNIP 1.822 CiteScore 8.2
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Expanding user’s query with tag-neighbors for effective medical information retrieval

Medical information is a natural human demand. Existing search engines on the Web often are unable to handle medical search well because they do not consider its special requirements. Often a medical information searcher is uncertain about his exact questions and unfamiliar with medical terminology. Under-specified queries often lead to undesirable search results that do not contain the information needed. To overcome the limitations of under-specified queries, we utilize tags to enhance information retrieval capabilities by expanding users’ original queries with context-relevant information. We compute a set of significant tag neighbor candidates based on the neighbor frequency and weight, and utilize the qualified tag neighbors to expand an entry query. The proposed approach is evaluated by using MedWorm medical article collection and results show considerable precision improvements over state-of-the-art approaches.
Experimental and computational tools for analysis of signaling networks in primary cells

Cellular information processing in signaling networks forms the basis of responses to environmental stimuli. At any given time, cells receive multiple simultaneous input cues, which are processed and integrated to determine cellular responses such as migration, proliferation, apoptosis, or differentiation. Protein phosphorylation events play a major role in this process and are often involved in fundamental biological and cellular processes such as protein-protein interactions, enzyme activity, and immune responses. Determining which kinases phosphorylate specific phospho sites poses a challenge; this information is critical when trying to elucidate key proteins involved in specific cellular responses. Here, methods to generate high-quality quantitative phosphorylation data from cell lysates originating from primary cells, and how to analyze the generated data to construct quantitative signaling network models, are presented. These models can subsequently be used to guide follow-up in vitro/in vivo validation studies.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Cellular Signal Integration, University of Copenhagen
Authors: Schoof, E. M. (Ekstern), Linding, R. (Intern)
Number of pages: 11
Publication date: 2014
Main Research Area: Technical/natural sciences

Publication information
Journal: Current Protocols in Immunology
Volume: 104
ISSN (Print): 1934-3671
Ratings:
Scopus rating (2016): SJR 0.949 SNIP 0.415 CiteScore 1.72
Scopus rating (2015): SJR 1.003 SNIP 0.405 CiteScore 1.59
Scopus rating (2014): SJR 0.674 SNIP 0.478 CiteScore 0.88
Scopus rating (2013): SJR 0.926 SNIP 0.469 CiteScore 1.05
ISI indexed (2013): ISI indexed no
Scopus rating (2012): SJR 1.011 SNIP 0.502 CiteScore 1.26
ISI indexed (2012): ISI indexed no
Scopus rating (2011): SJR 0.968 SNIP 0.688 CiteScore 1.32
ISI indexed (2011): ISI indexed no
Scopus rating (2010): SJR 0.907 SNIP 0.657
Scopus rating (2009): SJR 0.499 SNIP 0.396
Scopus rating (2008): SJR 0.12
Scopus rating (2007): SJR 0.1
Scopus rating (2006): SJR 0.109
Scopus rating (2005): SJR 0.127
Scopus rating (2004): SJR 0.101
Scopus rating (2003): SJR 0.1
Scopus rating (2002): SJR 0.1
Original language: English
Animals, Cell line, Computational biology, Computer simulation, Humans, Mass spectrometry, Metabolic networks and pathways, Phosphorylation, Primary cell culture, Protein binding, Signal transduction, Software
DOIs:
10.1002/0471142735.im1111s104
Source: Findit
Source-ID: 2194706673
Publication: Research - peer-review › Journal article – Annual report year: 2014

Exploring mechanisms of diet-colon cancer associations through candidate molecular interaction networks

Background: Epidemiological studies in the recent years have investigated the relationship between dietary habits and disease risk demonstrating that diet has a direct effect on public health. Especially plant-based diets—fruits, vegetables, and herbs—are known as a source of molecules with pharmacological properties for treatment of several malignancies. Unquestionably, for developing specific intervention strategies to reduce cancer risk there is a need for a more extensive and holistic examination of the dietary components for exploring the mechanisms of action and understanding the nutrient-nutrient interactions. Here, we used colon cancer as a proof-of-concept for understanding key regulatory sites of diet on the disease pathway. Results: We started from a unique vantage point by having a database of 158 plants positively
associated to colon cancer reduction and their molecular composition (similar to 3,500 unique compounds). We generated
a comprehensive picture of the interaction profile of these edible and non-edible plants with a predefined candidate colon
cancer target space consisting of similar to 1,900 proteins. This knowledge allowed us to study systematically the key
components in colon cancer that are targeted synergistically by phytochemicals and identify statistically significant and
highly correlated protein networks that could be perturbed by dietary habits. Conclusion: We propose here a framework for
interrogating the critical targets in colon cancer processes and identifying plant-based dietary interventions as important
modifiers using a systems chemical biology approach. Our methodology for better delineating prevention of colon cancer
by nutritional interventions relies heavily on the availability of information about the small molecule constituents of our diet
and it can be expanded to any other disease class that previous evidence has linked to lifestyle.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Hong Kong
Authors: Westergaard, D. (Ekstern), Li, J. (Ekstern), Jensen, K. (Intern), Kouskoumvekaki, I. (Intern), Panagiotou, G.
(Intern)
Publication date: 2014
Main Research Area: Technical/natural sciences

Publication information
Journal: B M C Genomics
Volume: 15
Issue number: 1
ISSN (Print): 1471-2164
Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 4.05 SJR 2.065 SNIP 1.122
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.287 SNIP 1.172 CiteScore 4.3
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.297 SNIP 1.205 CiteScore 4.18
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 2.141 SNIP 1.174 CiteScore 4.39
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 2.181 SNIP 1.225 CiteScore 4.61
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 2.271 SNIP 1.197 CiteScore 4.38
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 2.109 SNIP 1.038
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 2.181 SNIP 1.015
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 2.067 SNIP 1.005
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 1.846 SNIP 1.04
Expression of regulators of mitotic fidelity are associated with intercellular heterogeneity and chromosomal instability in primary breast cancer.

Regulators of transition through mitosis such as SURVIVIN and Aurora kinase A (AURKA) have been previously implicated in the initiation of chromosomal instability (CIN), a driver of intratumour heterogeneity. We investigate the relationship between protein expression of these genes and directly quantified CIN, and their prognostic utility in breast cancer. The expression of SURVIVIN and AURKA was determined by immunohistochemistry in a cohort of 426 patients with primary breast cancer. The association between protein expression and histopathological characteristics, clinical outcome and CIN status, as determined by centromeric FISH and defined by modal centromere deviation, was analysed. Significantly poorer clinical outcome was observed in patients with high AURKA expression levels. Expression of SURVIVIN was elevated in ER-negative relative to ER-positive breast cancer. Both AURKA and SURVIVIN increased expression were significantly associated with breast cancer grade. There was a significant association between increased CIN and both increased AURKA and SURVIVIN expression. AURKA gene amplification was also associated with increased CIN. To our knowledge this is the largest study assessing CIN status in parallel with the expression of the mitotic regulators AURKA and SURVIVIN. These data suggest that elevated expression of AURKA and SURVIVIN, together with AURKA gene amplification, are associated with increased CIN in breast cancer, and may be used as a proxy for CIN in breast cancer samples in the absence of more advanced molecular measurements.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Cancer Research UK, London Research Institute, University of Applied Sciences., The Institute of Cancer Research, St James's University Hospital
Pages: 221-229
Publication date: 2014
Main Research Area: Technical/natural sciences

Publication information
Facilitating the use of large-scale biological data and tools in the era of translational bioinformatics

As both the amount of generated biological data and the processing compute power increase, computational experimentation is no longer the exclusivity of bioinformaticians, but it is moving across all biomedical domains. For bioinformatics to realize its translational potential, domain experts need access to user-friendly solutions to navigate, integrate and extract information out of biological databases, as well as to combine tools and data resources in bioinformatics workflows. In this review, we present services that assist biomedical scientists in incorporating bioinformatics tools into their research. We review recent applications of Cytoscape, BioGPS and DAVID for data
visualization, integration and functional enrichment. Moreover, we illustrate the use of Taverna, Kepler, GenePattern, and Galaxy as open-access workbenches for bioinformatics workflows. Finally, we mention services that facilitate the integration of biomedical ontologies and bioinformatics tools in computational workflows.

**General information**

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Novo Nordisk Foundation Center for Biosustainability, CFB - Metagenomic Systems Biology, University College London
Authors: Kouskoumvekaki, I. (Intern), Shublaq, N. (Ekstern), Brunak, S. (Intern)
Number of pages: 11
Pages: 942-952
Publication date: 2014
Main Research Area: Technical/natural sciences

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Journal: Briefings in Bioinformatics
Volume: 15
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ISSN (Print): 1467-5463
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- BFI (2018): BFI-level 2
- BFI (2017): BFI-level 2
- Web of Science (2017): Indexed Yes
- BFI (2016): BFI-level 2
- Scopus rating (2016): CiteScore 6.72 SJR 4.16 SNIP 2.22
- BFI (2015): BFI-level 2
- Scopus rating (2015): SJR 3.989 SNIP 2.067 CiteScore 6.37
- Web of Science (2015): Indexed yes
- BFI (2014): BFI-level 2
- Scopus rating (2014): SJR 3.687 SNIP 2.098 CiteScore 5.58
- Web of Science (2014): Indexed yes
- BFI (2013): BFI-level 2
- Scopus rating (2013): SJR 2.844 SNIP 1.983 CiteScore 4.96
- ISI indexed (2013): ISI indexed yes
- BFI (2012): BFI-level 2
- Scopus rating (2012): SJR 3.131 SNIP 1.922 CiteScore 5.71
- ISI indexed (2012): ISI indexed yes
- Web of Science (2012): Indexed yes
- BFI (2011): BFI-level 2
- Scopus rating (2011): SJR 4.176 SNIP 4.102 CiteScore 9.53
- ISI indexed (2011): ISI indexed yes
- BFI (2010): BFI-level 2
- Scopus rating (2010): SJR 3.443 SNIP 2.922
- Web of Science (2010): Indexed yes
- BFI (2009): BFI-level 1
- Scopus rating (2009): SJR 3.084 SNIP 2.543
- Web of Science (2009): Indexed yes
- BFI (2008): BFI-level 2
- Scopus rating (2008): SJR 2.066 SNIP 1.62
- Scopus rating (2006): SJR 5.927 SNIP 1.381
- Web of Science (2006): Indexed yes
- Scopus rating (2005): SJR 2.232
- Scopus rating (2004): SJR 1.597
- Scopus rating (2003): SJR 1.095
- Scopus rating (2002): SJR 0.736
- Scopus rating (2001): SJR 0.462
Genetic association study of QT interval highlights role for calcium signaling pathways in myocardial repolarization

The QT interval, an electrocardiographic measure reflecting myocardial repolarization, is a heritable trait. QT prolongation is a risk factor for ventricular arrhythmias and sudden cardiac death (SCD) and could indicate the presence of the potentially lethal mendelian long-QT syndrome (LQTS). Using a genome-wide association and replication study in up to 100,000 individuals, we identified 35 common variant loci associated with QT interval that collectively explain ~8-10% of QT-interval variation and highlight the importance of calcium regulation in myocardial repolarization. Rare variant analysis of 6 new QT interval-associated loci in 296 unrelated probands with LQTS identified coding variants not found in controls but of uncertain causality and therefore requiring validation. Several newly identified loci encode proteins that physically interact with other recognized repolarization proteins. Our integration of common variant association, expression and orthogonal protein-protein interaction screens provides new insights into cardiac electrophysiology and identifies new candidate genes for ventricular arrhythmias, LQTS and SCD. © 2014 Nature America, Inc.

General information

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis
Genome-wide Ancestry Patterns in Rapanui Suggest Pre-European Admixture with Native Americans

Background: Rapa Nui (Easter Island), located in the easternmost corner of the Polynesian Triangle, is one of the most isolated locations on the planet inhabited by humans. Archaeological and genetic evidence suggests that the island was first colonized by Polynesians around AD 1200, during their eastward expansion. Although it remains contentious whether Polynesians reached South America, suggestive evidence has been brought forward supporting the possibility of Native American contact prior to the European “discovery” of the island in AD 1722. Results: We generated genome-wide data for 27 Rapanui. We found a mostly Polynesian ancestry among Rapanui and detected genome-wide patterns consistent with Native American and European admixture. By considering the distribution of local ancestry tracts of eight unrelated Rapanui, we found statistical support for Native American admixture dating to AD 1280–1495 and European admixture dating to AD 1850–1895. Conclusions: These genetic results can be explained by one or more pre-European trans-Pacific contacts.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Metagenomics, University of Copenhagen, University of California at Berkeley, University of Oslo
Authors: Moreno-Mayar, J. V. (Ekstern), Rasmussen, S. (Intern), Seguin-Orlando, A. (Ekstern), Rasmussen, M. (Ekstern), Liang, M. (Ekstern), Flåm, S. T. (Ekstern), Lie, B. A. (Ekstern), Gilfillan, G. D. (Ekstern), Nielsen, R. (Ekstern), Thorsby, E. (Ekstern), Willerslev, E. (Ekstern), Malaspinas, A. (Ekstern)
Number of pages: 8
Pages: 2518-2525
Publication date: 2014
Main Research Area: Technical/natural sciences

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Journal: Current Biology
Volume: 24
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ISSN (Print): 0960-9822
Ratings:
BFI (2018): BFI-level 2
BFI (2017): BFI-level 2
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): SJR 4.143 SNIP 1.552 CiteScore 4.99
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 4.669 SNIP 1.596 CiteScore 5.21
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 4.479 SNIP 1.602 CiteScore 5.02
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Genome-wide association analyses identify variants in developmental genes associated with hypospadias

Hypospadias is a common congenital condition in boys in which the urethra opens on the underside of the penis. We performed a genome-wide association study on 1,006 surgery-confirmed hypospadias cases and 5,486 controls from Denmark. After replication genotyping of an additional 1,972 cases and 1,812 controls from Denmark, the Netherlands and Sweden, 18 genomic regions showed independent association with P < 5 x 10^-8. Together, these loci explain 9% of the liability to developing this condition. Several of the identified regions harbor genes with key roles in embryonic development (including HOXA4, IRX5, IRX6 and EYA1). Subsequent pathway analysis with GRAIL and DEPICT provided additional insight into possible genetic mechanisms causing hypospadias.
Livestock-associated methicillin-resistant Staphylococcus aureus (LA-MRSA) Sequence Type 398 (ST398) is an opportunistic pathogen that is able to colonize and cause disease in several animal species including humans. To better understand the adaptation, evolution, transmission and pathogenic capacity, further investigations into the importance of the different genes harboured by LA-MRSA ST398 are required. In this study we generated a genome-wide transposon mutant library in an LA-MRSA ST398 isolate to evaluate genes important for bacterial survival in laboratory and host-specific environments. The transposon mutant library consisted of approximately 1 million mutants with around 140,000 unique insertion sites and an average number of unique inserts per gene of 44.8. We identified LA-MRSA ST398 essential genes comparable to other high-throughput S. aureus essential gene studies. As ST398 is the most common MRSA isolated from pigs, the transposon mutant library was screened in whole porcine blood. Twenty-four genes were specifically identified as important for bacterial survival in porcine blood. Mutations in 23 of these genes resulted in attenuated bacterial fitness. Seven of the 23 genes were of unknown function, whereas 16 genes were annotated with functions predominantly related to carbon metabolism, pH shock and a variety of regulations and only indirectly to virulence factors. Mutations in one gene of unknown function resulted in a hypercompetitive mutant. Further evaluation of these genes is required to determine their specific relevance in blood survival.
Gliadin affects glucose homeostasis and intestinal metagenome in C57BL/6 mice fed and high-fat diet

Dietary gluten and its component gliadin are well-known environmental triggers of celiac disease and important actors in type-1 diabetes, and are reported to induce alterations in the intestinal microbiota. However, research on the impact of gluten on type-2 diabetes in non-celiac subjects is more limited. The aim of this study was to investigate the effect of gliadin on glucose homeostasis and intestinal ecology in the mouse. Forty male C57BL/6 mice were fed a high-fat diet containing either 4% gliadin or no gliadin for 22 weeks. Gliadin consumption significantly increased the HbA1c level over
time, with a borderline significance of higher HOMA-IR (homeostasis model assessment of insulin resistance) after 22 weeks. Sequencing of the V3 region of the bacterial 16S rRNA genes showed that gliadin changed the abundance of 81 bacterial taxa, separating the intestinal microbial profile of the gliadin consuming mice from the control mice in the principal coordinate analysis (PCoA) of weighted UniFrac distance. No difference was found in body weight gain, feed consumption or circulating cytokines (IL-1β, IL-6, IFN-γ, TNF-α and IL-10). Our study is the first to show that gliadin as part of a defined synthetic feed exacerbates the glycaemia and alters the intestinal microbiota composition. Comprehensive analyses of the profile of specific immune cells, metabolites and intestinal permeability are in progress to elucidate the mechanism behind the observed effects.

**General information**
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Organisations: National Food Institute, Division of Food Microbiology, Department of Systems Biology, Center for Biological Sequence Analysis, University of Copenhagen
Number of pages: 1
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Event: Abstract from The Danish Microbiological Society Annual Congress 2014, Copenhagen, Denmark.
Main Research Area: Technical/natural sciences
Electronic versions: Abstract_DMS_Li_1.pdf

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Activities: Gliadin Affects Glucose Homeostasis and Intestinal Metagenome in C57BL/6 Mice Fed a High-Fat Diet
Source: PublicationPreSubmission
Source-ID: 102165068
Publication: Research - peer-review › Conference abstract for conference – Annual report year: 2014

**Hearing loss in relation to sound exposure of professional symphony orchestra musicians**
OBJECTIVES: The objectives of this study were to: (1) estimate the hearing status of classical symphony orchestra musicians and (2) investigate the hypothesis that occupational sound exposure of symphony orchestra musicians leads to elevated hearing thresholds. DESIGN: The study population comprised all the musicians from five symphony orchestras. Questionnaires were filled in by 337 subjects, and 212 subjects performed an audiometric test. For a group of 182 musicians (363 ears) the results of the audiometry was analyzed in relation to the individual exposure, which was estimated on the basis of sound measurements and questionnaire data regarding the exposure time. The mean hearing threshold at the frequencies 3, 4, and 6 kHz, corrected for age and sex, was used as outcome. RESULTS: The musician ears with the highest exposure (29 of 363) had an additional threshold shift of 6.3 dB compared with the 238 ears with lowest exposure. The observed hearing loss of musicians was smaller compared with the noise-induced permanent threshold shift (NIPTS) predicted from ISO1999. A remaining confounding effect of age after ISO7029 age corrections could be observed to explain the difference in observed and predicted NIPTS. However, the observed hearing loss difference between the left and the right ear of musicians was 2.5 dB (95% confidence interval 1.5-3.6), which was similar to the NIPTS predicted from ISO1999. Most of the musicians had better hearing at 3, 4, and 6 kHz for age than expected, however, 29 ears with the highest exposure above 90.4 dBA with a mean exposure time of 41.7 years had significantly elevated hearing thresholds. Trumpet players and the left ear of first violinists had significantly elevated hearing thresholds compared with other musicians. CONCLUSION: Most of the symphony orchestra musicians had better hearing than expected but they had a work-related risk of developing additional noise-induced hearing loss. The additional NIPTS of the left ear compared with the right ear was at the expected level based on the cumulated sound exposure and ISO1999, indicating that performing music may induce hearing loss to the same extent as industrial noise.

**General information**
State: Published
Organisations: Department of Electrical Engineering, Department of Systems Biology, Center for Biological Sequence Analysis, Metagenomics, Urban Water Engineering, University of Southern Denmark
Authors: Schmidt, J. H. (Ekstern), Pedersen, E. R. (Ekstern), Paarup, H. M. (Ekstern), Christensen-Dalsgaard, J. (Intern), Andersen, T. (Ekstern), Poulsen, T. (Ekstern), Bælum, J. (Intern)
Pages: 448-460
Publication date: 2014
Main Research Area: Technical/natural sciences

**Publication information**
Journal: Ear and Hearing
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High-Resolution Melt Analysis for Rapid Comparison of Bacterial Community Compositions

In the study of bacterial community composition, 16S rRNA gene amplicon sequencing is today among the preferred methods of analysis. The cost of nucleotide sequence analysis, including requisite computational and bioinformatic steps, however, takes up a large part of many research budgets. High-resolution melt (HRM) analysis is the study of the melt behavior of specific PCR products. Here we describe a novel high-throughput approach in which we used HRM analysis targeting the 16S rRNA gene to rapidly screen multiple complex samples for differences in bacterial community composition. We hypothesized that HRM analysis of amplified 16S rRNA genes from a soil ecosystem could be used as a screening tool to identify changes in bacterial community structure. This hypothesis was tested using a soil microcosm setup exposed to a total of six treatments representing different combinations of pesticide and fertilization treatments. The HRM analysis identified a shift in the bacterial community composition in two of the treatments, both including the soil fumigant Basamid GR. These results were confirmed with both denaturing gradient gel electrophoresis (DGGE) analysis and 454-based 16S rRNA gene amplicon sequencing. HRM analysis was shown to be a fast, high-throughput technique.
that can serve as an effective alternative to gel-based screening methods to monitor microbial community composition.

**General information**

State: Published

Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Metagenomics, Geological Survey of Denmark and Greenland, University of Copenhagen

Authors: Hjelmsø, M. H. (Ekstern), Hansen, L. H. (Ekstern), Bælum, J. (Intern), Feld, L. (Intern), Holben, W. E. (Ekstern), Jacobsen, C. S. (Ekstern)

Pages: 3568-3575

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Main Research Area: Technical/natural sciences

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Web of Science (2017): Indexed yes

BFI (2016): BFI-level 2

Scopus rating (2016): CiteScore 4.08

Web of Science (2016): Indexed yes

BFI (2015): BFI-level 2

Scopus rating (2015): SJR 1.891 SNIP 1.308 CiteScore 4.14

Web of Science (2015): Indexed yes

BFI (2014): BFI-level 2

Scopus rating (2014): SJR 1.857 SNIP 1.384 CiteScore 4.02

Web of Science (2014): Indexed yes

BFI (2013): BFI-level 2

Scopus rating (2013): SJR 1.899 SNIP 1.414 CiteScore 4.25

ISI indexed (2013): ISI indexed yes

Web of Science (2013): Indexed yes

BFI (2012): BFI-level 2

Scopus rating (2012): SJR 1.975 SNIP 1.429 CiteScore 4.29

ISI indexed (2012): ISI indexed yes

Web of Science (2012): Indexed yes

BFI (2011): BFI-level 2

Scopus rating (2011): SJR 1.914 SNIP 1.455 CiteScore 4.12

ISI indexed (2011): ISI indexed yes

Web of Science (2011): Indexed yes

BFI (2010): BFI-level 2

Scopus rating (2010): SJR 1.887 SNIP 1.436

Web of Science (2010): Indexed yes

BFI (2009): BFI-level 2

Scopus rating (2009): SJR 1.972 SNIP 1.528

Web of Science (2009): Indexed yes

BFI (2008): BFI-level 2

Scopus rating (2008): SJR 2.156 SNIP 1.572

Web of Science (2008): Indexed yes

Scopus rating (2007): SJR 2.043 SNIP 1.647

Web of Science (2007): Indexed yes

Scopus rating (2006): SJR 2.054 SNIP 1.602

Web of Science (2006): Indexed yes

Scopus rating (2005): SJR 2.074 SNIP 1.653

Web of Science (2005): Indexed yes
Host genome variations and risk of infections during induction treatment for childhood acute lymphoblastic leukaemia

Objectives: To investigate association of host genomic variation and risk of infections during treatment for childhood acute lymphoblastic leukaemia (ALL). Methods: We explored association of 34 000 singlenucleotide polymorphisms (SNPs) related primarily to pharmacogenomics and immune function to risk of infections among 69 ALL patients on induction therapy.

Results: Forty-eight (70%) patients experienced infectious events including 23 with positive blood cultures. Infectious events and positive blood cultures were associated significantly with 24 and 21 SNPs, respectively (P < 0.01). Classification and regression tree analysis demonstrated rs11033797 (OR51F1), rs2835265 (CBR1), rs28627172 (POLDIP3) and rs1129844 (CCL11) to be predictive of outcome. Among 61 patients for whom read-outs were available for all four SNPs, 40 of 41 patients with the worst SNP profile experienced at least one infectious event compared with five of the remaining 20 patients (Hazard ratio 9.0, 95% CI 3.4–23.5, which was unchanged after adjustments for neutrophil counts). Pathway analysis identified variations in 'G-protein-coupled receptor (GPCR) downstream signalling', 'Bile acid and bile salt metabolism' and 'Class I MHC-mediated antigen processing and presentation' to be highly predictive of infections.

Conclusions: Our data indicate that host genomic profiling may predict the risk of infections during induction therapy. This may facilitate development of individualised supportive care.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Functional Human Variation, Department of Systems Biology, Behavioral Phenomics, Metagenomics, Norwegian University of Science and Technology, Copenhagen University Hospital
Authors: Lund, B. (Ekstern), Wesolowska-Andersen, A. (Intern), Lausen, B. (Ekstern), Borst, L. (Ekstern), Rasmussen, K. K. (Ekstern), Müller, K. (Ekstern), Klungland, H. (Ekstern), Gupta, R. (Intern), Schmiegelow, K. (Ekstern)
Pages: 321-330
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Web of Science (2017): Indexed Yes
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Scopus rating (2016): SJR 0.32 SNIP 0.968 CiteScore 2.14
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.198 SNIP 0.955 CiteScore 2.06
Hybridization Capture Using Short PCR Products Enriches Small Genomes by Capturing Flanking Sequences (CapFlank)

Solution hybridization capture methods utilize biotinylated oligonucleotides as baits to enrich homologous sequences from next generation sequencing (NGS) libraries. Coupled with NGS, the method generates kilo to gigabases of high confidence consensus targeted sequence. However, in many experiments, a non-negligible fraction of the resulting sequence reads are not homologous to the bait. We demonstrate that during capture, the bait-hybridized library molecules add additional flanking library sequences iteratively, such that baits limited to targeting relatively short regions (e.g. few hundred nucleotides) can result in enrichment across entire mitochondrial and bacterial genomes. Our findings suggest that some of the off-target sequences derived in capture experiments are non-randomly enriched, and that CapFlank will
facilitate targeted enrichment of large contiguous sequences with minimal prior target sequence information.
Identification and assembly of genomes and genetic elements in complex metagenomic samples without using reference genomes

Most current approaches for analyzing metagenomic data rely on comparisons to reference genomes, but the microbial diversity of many environments extends far beyond what is covered by reference databases. De novo segregation of complex metagenomic data into specific biological entities, such as particular bacterial strains or viruses, remains a largely unsolved problem. Here we present a method, based on binning co-abundant genes across a series of metagenomic samples, that enables comprehensive discovery of new microbial organisms, viruses and co-inherited genetic entities and aids assembly of microbial genomes without the need for reference sequences. We demonstrate the method on data from 396 human gut microbiome samples and identify 7,381 co-abundance gene groups (CAGs), including 741 metagenomic species (MGS). We use these to assemble 238 high-quality microbial genomes and identify affiliations between MGS and hundreds of viruses or genetic entities. Our method provides the means for comprehensive profiling of the diversity within complex metagenomic samples.

General information

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Novo Nordisk Foundation Center for Biosustainability, Center for Biological sequence analysis, Comparative Microbial Genomics, National Food Institute, Division of Epidemiology and Microbial Genomics, INRA Institut National de La Recherche Agronomique, South China University of Technology, European Molecular Biology Laboratory, Centre National de la Recherche Scientifique, University of Southern Denmark, University Hospital Vall d’Hebron, University of Copenhagen, Vrije Universiteit Brussel, Beijing Genomics Institute Hong Kong, Wageningen IMARES, Tokyo Institute of Technology
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BFI (2016): BFI-level 2
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Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 17.892 SNIP 5.505 CiteScore 11.88
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 16.443 SNIP 5.433 CiteScore 11.4
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 13.849 SNIP 5.416 CiteScore 10.45
Human cytomegalovirus (HCMV) is an important human pathogen. It is a leading cause of congenital infection and a leading infectious threat to recipients of solid organ transplants as well as of allogeneic hematopoietic cell transplants. Moreover, it has recently been suggested that HCMV may promote tumor development. Both CD4(+) and CD8(+) T cell responses are important for long-term control of the virus, and adoptive transfer of HCMV-specific T cells has led to protection from reactivation and HCMV disease. Identification of HCMV-specific T cell epitopes has primarily focused on CD8(+) T cell responses against the pp65 phosphoprotein. In this study, we have focused on CD4(+) and CD8(+) T cell responses against the immediate early 1 and 2 proteins (IE1 and IE2). Using overlapping peptides spanning the entire IE1 and IE2 sequences, peripheral blood mononuclear cells from 16 healthy, HLA-typed, donors were screened by ex vivo IFN-gamma ELISpot and in vitro intracellular cytokine secretion assays. The specificities of CD4(+) and CD8(+) T cell responses were identified and validated by HLA class II and I tetramers, respectively. Eighty-one CD4(+) and 44 CD8(+) T cell responses were identified representing at least seven different CD4 epitopes and 14 CD8 epitopes restricted by seven and 11 different HLA class II and I molecules, respectively, in total covering 91 and 98% of the Caucasian population, respectively. Presented in the context of several different HLA class II molecules, two epitope areas in IE1 and IE2 were recognized in about half of the analyzed donors. These data may be used to design a versatile anti-HCMV vaccine and/or immunotherapy strategy.
Identification of Hypoxia-Regulated Proteins Using MALDI-Mass Spectrometry Imaging Combined with Quantitative Proteomics

Hypoxia is present in most solid tumors and is clinically correlated with increased metastasis and poor patient survival. While studies have demonstrated the role of hypoxia and hypoxia-regulated proteins in cancer progression, no attempts have been made to identify hypoxia-regulated proteins using quantitative proteomics combined with MALDI-mass spectrometry imaging (MALDI-MSI). Here we present a comprehensive hypoxic proteome study and are the first to investigate changes in situ using tumor samples. In vitro quantitative mass spectrometry analysis of the hypoxic proteome was performed on breast cancer cells using stable isotope labeling with amino acids in cell culture (SILAC). MS analyses were performed on laser-capture microdissected samples isolated from normoxic and hypoxic regions from tumors derived from the same cells used in vitro. MALDI-MSI was used in combination to investigate hypoxia-regulated protein localization within tumor sections. Here we identified more than 100 proteins, both novel and previously reported, that were associated with hypoxia. Several proteins were localized in hypoxic regions, as identified by MALDI-MSI. Visualization and data extrapolation methods for the in vitro SILAC data were also developed, and computational mapping of MALDI-MSI data to IHC results was applied for data validation. The results and limitations of the methodologies described are discussed.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Cellular Signal Integration, The Institute of Cancer Research, University of Copenhagen
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Pages: 2297-2313
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Main Research Area: Technical/natural sciences

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Scopus rating (2016): CiteScore 4.34 SJR 1.705 SNIP 1.002
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 1.934 SNIP 1.092 CiteScore 4.45
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 1.945 SNIP 1.185 CiteScore 4.64
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 2.002 SNIP 1.256 CiteScore 5.16
ISI indexed (2013): ISI indexed yes
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BFI (2012): BFI-level 2
Scopus rating (2012): SJR 2.027 SNIP 1.328 CiteScore 5.12
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 2.119 SNIP 1.267 CiteScore 5.12
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 2
Identification of novel immune and barrier genes in atopic dermatitis by laser capture micro-dissection

BACKGROUND:
The molecular signature of atopic dermatitis (AD) lesions is associated with TH2 and TH22 activation and epidermal alterations. However, the epidermal and dermal AD transcriptomes and their respective contributions to abnormalities in respective immune and barrier phenotypes are unknown.

OBJECTIVE:
We sought to establish the genomic profile of the epidermal and dermal compartments of lesional and nonlesional AD skin compared with normal skin.

METHODS:
Laser capture microdissection was performed to separate the epidermis and dermis of lesional and nonlesional skin from patients with AD and normal skin from healthy volunteers, followed by gene expression (microarrays and real-time PCR) and immunostaining studies.

RESULTS:
Our study identified novel immune and barrier genes, including the IL-34 cytokine and claudins 4 and 8, and showed increased detection of key AD genes usually undetectable on arrays (ie, IL22, thymic stromal lymphopoietin [TSLP], CCL22, and CCL26). Overall, the combined epidermal and dermal transcriptomes enlarged the AD transcriptome, adding 674 upregulated and 405 downregulated differentially expressed genes between lesional and nonlesional skin to the AD transcriptome. We were also able to localize individual transcripts as primarily epidermal (defensin, beta 4A [DEFB4A]) or dermal (IL22, cytotoxic T-lymphocyte antigen 4 [CTLA4], and CCR7) and link their expressions to possible cellular sources.

CONCLUSIONS:
This is the first report that establishes robust epidermal and dermal genomic signatures of lesional and nonlesional AD skin compared with normal skin. These data establish the utility of laser capture microdissection to separate different compartments and cellular subsets in patients with AD, allowing localization of key barrier or immune molecules and enabling detection of gene products usually not detected on arrays.
Identification of Odorant-Receptor Interactions by Global Mapping of the Human Odorome

The human olfactory system recognizes a broad spectrum of odorants using approximately 400 different olfactory receptors (hORs). Although significant improvements of heterologous expression systems used to study interactions between ORs and odorant molecules have been made, screening the olfactory repertoire of hORs remains a tremendous challenge. We therefore developed a chemical systems level approach based on protein-protein association network to investigate novel hOR-odorant relationships. Using this new approach, we proposed and validated new bioactivities for odorant molecules and OR2W1, OR51E1 and OR5P3. As it remains largely unknown how human perception of odorants
influence or prevent diseases, we also developed an odorant-protein matrix to explore global relationships between chemicals, biological targets and disease susceptibilities. We successfully experimentally demonstrated interactions between odorants and the cannabinoid receptor 1 (CB1) and the peroxisome proliferator-activated receptor gamma (PPAR gamma). Overall, these results illustrate the potential of integrative systems chemical biology to explore the impact of odorant molecules on human health, i.e. human odorome.

**General information**

**State:** Published  
**Organisations:** Department of Systems Biology, Center for Biological Sequence Analysis, Universite de Bourgogne, University of Copenhagen  
**Authors:** Audouze, K. M. L. (Intern), Tromelin, A. (Ekstern), Le Bon, A. M. (Ekstern), Belloir, C. (Ekstern), Petersen, R. K. (Ekstern), Kristiansen, K. (Ekstern), Brunak, S. (Intern), Taboureau, O. (Intern)  
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- Web of Science (2014): Indexed yes  
- Scopus rating (2014): CiteScore 3.11 SJR 1.201 SNIP 1.092  
- Web of Science (2013): Indexed yes  
- Scopus rating (2013): SJR 1.414 SNIP 1.131 CiteScore 3.32  
- Web of Science (2012): Indexed yes  
- Scopus rating (2012): SJR 1.545 SNIP 1.141 CiteScore 3.54  
- Web of Science (2011): Indexed yes  
- Scopus rating (2011): SJR 2.369 SNIP 1.23 CiteScore 4.58  
- Web of Science (2010): Indexed yes  
- Scopus rating (2010): SJR 2.631 SNIP 1.161  
- Web of Science (2009): Indexed yes  
- Scopus rating (2009): SJR 2.473 SNIP 0.985  
- Web of Science (2008): Indexed yes  
- Scopus rating (2008): SJR 2.323 SNIP 0.96  
- Web of Science (2007): Indexed yes  
- Scopus rating (2007): SJR 1.289 SNIP 0.525  
- Web of Science (2006): Indexed yes  
- Scopus rating (2006): SJR 1.289 SNIP 0.525  
- Web of Science (2005): Indexed yes  
- Scopus rating (2005): SJR 1.289 SNIP 0.525
**Lactococcus lactis** TrxD represents a subgroup of thioredoxins prevalent in Gram-positive bacteria containing WCXDC active site motifs

Three protein disulfide reductases of the thioredoxin superfamily from the industrially important Gram-positive *Lactococcus lactis* (LitTrxA, LitTrxD and LinNrdH) are compared to the "classical" thioredoxin from *Escherichia coli* (EcTrx1). LitTrxA resembles EcTrx1 with a WCGPC active site motif and other key residues conserved. By contrast, LitTrxD is more distantly related and contains a WCGDC motif. Bioinformatics analysis suggests that LitTrxD represents a subgroup of thioredoxins from Gram-positive bacteria. LinNrdH is a glutaredoxin-like electron donor for ribonucleotide reductase class Ib. Based on protein-protein equilibria LitTrxA (E⁰ = -259 mV) and LitNrdH (E⁰ = -238 mV) show approximately 10 mV higher standard state redox potentials than the corresponding *E. coli* homologues, while E⁰ of LitTrxD is -243 mV, more similar to glutaredoxin than "classical" thioredoxin. EcTrx1 and LitTrxA have high capacity to reduce insulin disulfides and their exposed active site thiol is alkylated at a similar rate at pH 7.0. LitTrxD on the other hand, is alkylated by iodoacetamide at almost 100 fold higher rate and shows no activity towards insulin disulfides. LitTrxA, LitTrxD and LinNrdH are all efficiently reduced by NADPH dependent thioredoxin reductase (TrxR) from *L. lactis* and good cross-reactivity towards *E. coli* TrxR was observed with LitTrxD as the notable exception.
Immunoinformatics of Placental Malaria Vaccine Development

Malaria is an infectious disease caused by a protozoan parasite of the genus Plasmodium, which is transferred by female Anopheles mosquitoes. WHO estimates that in 2012 there were 207 million cases of malaria, of which 627,000 were fatal. People living in malaria-endemic areas, gradually acquire immunity with multiple infections. Placental malaria (PM) is caused by P. falciparum sequestering in the placenta of pregnant women due to the presence of novel receptors in the placenta. An estimated 200,000 infants die a year as a result of PM. In 2004 the specific protein responsible for the pathogenesis of PM was identified as the P. falciparum Erythrocyte Membrane Protein 1 (Pf EMP1) variant VAR2CSA. VAR2CSA is the leading candidate for a vaccine against PM.

The thesis is divided into 4 parts, where part I provide the reader with an introduction and background for the subjects covered in the thesis. Part II presents the first paper: “SigniSite: Identification of residue-level genotype-phenotype correlations in protein multiple sequence alignments”. SigniSite is based on a non-parametric statistical evaluation of the positional distribution of amino acid residues in a multiple sequence alignment (MSA), thereby quantifying residue association to MSA phenotype. SigniSite was found to outperform comparable state-of-the-art methods. Furthermore part II addresses the issue of controlling type I and type II error probabilities in multiple testing scenarios and lastly the
Dissertation advisor: Prof. Ole Lund Leon Eyrich Jessen. Analysis of the MHC-I:peptide binding interaction by application of the SigniSite method. Part III presents the second paper: "Insight into Antigenic Diversity of VAR2CSA-DBL5ε Domain from Multiple Plasmodium falciparum Placental Isolates". The data consisted of 70 VAR2CSA-DBL5ε sequences each with associated phenotypes. Immunity towards PM is gradually acquired, therefore if a given sequence motif can be phenotype-correlated then the motif may be involved in VAR2CSA immunogenicity. Motifs defining VAR2CSA immunogenicity are naturally interesting in vaccine development context. The motif 'TFKNI' was found to be correlated with the birth weight of the child. Part IV presents the development of two methods for analysis of high-throughput data from a novel High Density Peptide Microarray (HDPMa) chip technology. Subsequently the HDPMa chip is applied for the discovery of linear B-cell VAR2CSA epitopes. Peptides 'GMDDEFKNTFKNIKE' and 'SCGSARTMKRYKNDNYELCKYC' were identified as linear B-cell epitopes. The latter subsequently experimentally found to be highly immunogenic, but not capable of blocking VAR2CSA:receptor interaction.

In summary, the work described in this thesis centres around the development and application of bioinformatics tools for in silico analysis of VAR2CSA, with an emphasis on statistical methodology. It is the hope of the author that the tools, developed, presented and applied in this thesis, may serve as an offset for further research and development in the field of placental malaria vaccine development.

General information
State: Published
Organisations: Department of Systems Biology, Immunological Bioinformatics, Agricultural and Environmental Proteomics, Center for Biological Sequence Analysis, University of Copenhagen
Authors: Jessen, L. E. (Intern), Lund, O. (Intern), Hviid, L. (Ekstern), Nielsen, M. (Intern)
Number of pages: 239
Publication date: 2014

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Original language: English
Main Research Area: Technical/natural sciences
Electronic versions:
Leon_Eyrich_Jessen_phd_afhandling.pdf
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Improved pan-specific MHC class I peptide-binding predictions using a novel representation of the MHC-binding cleft environment

Major histocompatibility complex (MHC) molecules play a key role in cell-mediated immune responses presenting bounded peptides for recognition by the immune system cells. Several in silico methods have been developed to predict the binding affinity of a given peptide to a specific MHC molecule. One of the current state-of-the-art methods for MHC class I is NetMHCpan, which has a core ingredient for the representation of the MHC class I molecule using a pseudo-sequence representation of the binding cleft amino acid environment. New and large MHC-peptide-binding data sets are constantly being made available, and also new structures of MHC class I molecules with a bound peptide have been published. In order to test if the NetMHCpan method can be improved by integrating this novel information, we created new pseudo-sequence definitions for the MHC-binding cleft environment from sequence and structural analyses of different MHC data sets including human leukocyte antigen (HLA), non-human primates (chimpanzee, macaque and gorilla) and other animal alleles (cattle, mouse and swine). From these constructs, we showed that by focusing on MHC sequence positions found to be polymorphic across the MHC molecules used to train the method, the NetMHCpan method achieved a significant increase in the predictive performance, in particular, of non-human MHCs. This study hence showed that an improved performance of MHC-binding methods can be achieved not only by the accumulation of more MHC-peptide-binding data but also by a refined definition of the MHC-binding environment including information from non-human species.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Immunological Bioinformatics, Universidad Peruana Cayetano Heredia
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BFI (2014): BFI-level 1

Scopus rating (2014): SJR 0.667 SNIP 0.667 CiteScore 1.07

Web of Science (2014): Indexed yes

BFI (2013): BFI-level 1

Scopus rating (2013): SJR 0.994 SNIP 1.356 CiteScore 1.74

ISI indexed (2013): ISI indexed yes

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BFI (2012): BFI-level 1

Scopus rating (2012): SJR 0.661 SNIP 0.968 CiteScore 1.73

ISI indexed (2012): ISI indexed yes

BFI (2011): BFI-level 1

Scopus rating (2011): SJR 0.74 SNIP 0.834 CiteScore 1.75

ISI indexed (2011): ISI indexed yes

BFI (2010): BFI-level 1

Scopus rating (2010): SJR 0.593 SNIP 0.663

BFI (2009): BFI-level 1

Scopus rating (2009): SJR 0.616 SNIP 0.7

BFI (2008): BFI-level 1

Scopus rating (2008): SJR 0.677 SNIP 0.81

Scopus rating (2007): SJR 0.868 SNIP 1.138

Scopus rating (2006): SJR 1.182 SNIP 1.23

Scopus rating (2005): SJR 1.544 SNIP 0.801

Scopus rating (2004): SJR 0.842 SNIP 0.732

Web of Science (2004): Indexed yes

Scopus rating (2003): SJR 0.81 SNIP 0.791

Web of Science (2003): Indexed yes

Scopus rating (2002): SJR 1.011 SNIP 1.067

Scopus rating (2001): SJR 1.415 SNIP 1.118

Scopus rating (2000): SJR 1.22 SNIP 1.042

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Improving biotech education through gamified laboratory simulations

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State: Published
Organisations: Department of Systems Biology, Novo Nordisk Foundation Center for Biosustainability, Bacterial Cell Factories, Center for Biological Sequence Analysis, Immunological Bioinformatics, Behavioral Phenomics, Drug Resistance and Community Dynamics, Research Groups, University of Southern Denmark, NordicMetrics, University of Copenhagen
Authors: Bonde, M. (Intern), Makransky, G. (Ekstern), Wandall, J. (Ekstern), Larsen, M. V. (Intern), Morsing, M. (Ekstern), Jarmer, H. Ø. (Intern), Sommer, M. (Intern)
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BFI (2018): BFI-level 3
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Scopus rating (2016): CiteScore 13.16 SJR 20.253 SNIP 6.303
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 17.892 SNIP 5.505 CiteScore 11.88
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 16.443 SNIP 5.433 CiteScore 11.4
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 13.849 SNIP 5.416 CiteScore 10.45
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 10.76 SNIP 4.96 CiteScore 8.44
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 11.627 SNIP 6.248 CiteScore 8.21
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 7.763 SNIP 5.607
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 6.046 SNIP 5.07
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 5.039 SNIP 4.588
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 5.74 SNIP 4.596
Scopus rating (2005): SJR 5.151 SNIP 3.832
Scopus rating (2004): SJR 4.673 SNIP 3.635
Improving the accuracy of the structure prediction of the third hypervariable loop of the heavy chains of antibodies

Motivation: Antibodies are able to recognize a wide range of antigens through their complementary determining regions formed by six hypervariable loops. Predicting the 3D structure of these loops is essential for the analysis and reengineering of novel antibodies with enhanced affinity and specificity. The canonical structure model allows high accuracy prediction for five of the loops. The third loop of the heavy chain, H3, is the hardest to predict because of its diversity in structure, length and sequence composition. Results: We describe a method, based on the Random Forest automatic learning technique, to select structural templates for H3 loops among a dataset of candidates. These can be used to predict the structure of the loop with a higher accuracy than that achieved by any of the presently available methods. The method also has the advantage of being extremely fast and returning a reliable estimate of the model quality.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Sapienza University of Rome
Authors: Messih, M. A. (Ekstern), Lepore, R. (Ekstern), Marcatili, P. (Intern), Tramontano, A. (Ekstern)
Pages: 2733-2740
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Main Research Area: Technical/natural sciences

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BFI (2018): BFI-level 2
BFI (2017): BFI-level 2
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 6.42
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): CiteScore 6.06
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): CiteScore 5.5
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): CiteScore 5.78
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
In Silico Detection and Typing of Plasmids using PlasmidFinder and Plasmid Multilocus Sequence Typing

In the work presented here, we designed and developed two easy-to-use Web tools for in silico detection and characterization of whole-genome sequence (WGS) and whole-plasmid sequence data from members of the family Enterobacteriaceae. These tools will facilitate bacterial typing based on draft genomes of multidrug-resistant Enterobacteriaceae species by the rapid detection of known plasmid types. Replicon sequences from 559 fully sequenced plasmids associated with the family Enterobacteriaceae in the NCBI nucleotide database were collected to build a consensus database for integration into a Web tool called PlasmidFinder that can be used for replicon sequence analysis of raw, contig group, or completely assembled and closed plasmid sequencing data. The PlasmidFinder database currently consists of 116 replicon sequences that match with at least at 80% nucleotide identity all replicon sequences identified in the 559 fully sequenced plasmids. For plasmid multilocus sequence typing (pMLST) analysis, a database that is updated weekly was generated from www.pubmlst.org and integrated into a Web tool called pMLST. Both databases were evaluated using draft genomes from a collection of Salmonella enterica serovar Typhimurium isolates. PlasmidFinder identified a total of 103 replicons and between zero and five different plasmid replicons within each of 49 S. Typhimurium draft genomes tested. The pMLST Web tool was able to subtype genomic sequencing data of plasmids, revealing both known plasmid sequence types (STs) and new alleles and ST variants. In conclusion, testing of the two Web tools using both fully assembled plasmid sequences and WGS-generated draft genomes showed them to be able to detect a broad variety of plasmids that are often associated with antimicrobial resistance in clinically relevant bacterial pathogens.

General information

State: Published
Organisations: National Food Institute, Division of Epidemiology and Microbial Genomics, Center for Biological Sequence Analysis, Immunological Bioinformatics, Department of Systems Biology, Istituto Superiore di Sanita
Authors: Carattoli, A. (Ekstern), Zankari, E. (Intern), García-Fernández, A. (Ekstern), Larsen, M. V. (Intern), Lund, O. (Intern), Villa, L. (Ekstern), Aarestrup, F. M. (Intern), Hasman, H. (Intern)
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Pages: 3895-3903
Publication date: 2014
Main Research Area: Technical/natural sciences
In silico prediction of Gallibacterium anatis pan-immunogens

The Gram-negative bacterium Gallibacterium anatis is a major cause of salpingitis and peritonitis in commercial egg-layers, leading to reduced egg production and increased mortality. Unfortunately, widespread multidrug resistance and antigenic diversity makes it difficult to control infections and novel prevention strategies are urgently needed. In this study, a pan-genomic reverse vaccinology (RV) approach was used to identify potential vaccine candidates. Firstly, the genomes of 10 selected Gallibacterium strains were analyzed and proteins selected on the following criteria; predicted surface-exposure or secretion, none or one transmembrane helix (TMH), and presence in six or more of the 10 genomes. In total, 42 proteins were selected. The genes encoding 27 of these proteins were successfully cloned in Escherichia coli and the proteins expressed and purified. To reduce the number of vaccine candidates for in vivo testing, each of the purified recombinant proteins was screened by ELISA for their ability to elicit a significant serological response with serum from chickens that had been infected with G. anatis. Additionally, an in silico prediction of the protective potential was carried out based on a protein property prediction method. Of the 27 proteins, two novel putative immunogens were identified; Gab_1309 and Gab_2312. Moreover, three previously characterized virulence factors; GtxA, FlfA and Gab_2156, were identified. Thus, by combining the pan-genomic RV approach with subsequent in vitro and in silico screening, we have narrowed down the pan-roteome of G. anatis to five vaccine candidates. Importantly, preliminary immunization trials indicated an in vivo protective potential of GtxA-N, FlfA and Gab_1309.

General information

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Immunological Bioinformatics, University of Copenhagen, Monash University
Authors: Bager, R. J. (Ekstern), Kudirkiene, E. (Ekstern), da Piedade, I. (Ekstern), Seemann, T. (Ekstern), Nielsen, T. K. (Ekstern), Pors, S. E. (Ekstern), Mattsson, A. H. (Intern), Boyce, J. D. (Ekstern), Adler, B. (Ekstern), Bojesen, A. M. (Forskerdatabase)
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Web of Science (2016): Indexed yes
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Scopus rating (2013): SJR 1.353 SNIP 1.457 CiteScore 3.13
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Web of Science (2013): Indexed yes
Interaction of Lactobacillus acidophilus NCFM grown on different carbohydrates with human intestinal epithelial cells: Adhesion Properties and roles of S-layer Proteins

General information
State: Published
Organisations: Department of Systems Biology, Enzyme and Protein Chemistry, Center for Biological Sequence Analysis, DuPont Nutrition and Health
Authors: Celebioglu, H. U. (Intern), Lahtinen, S. J. (Ekstern), Pedersen, S. B. (Intern), Abou Hachem, M. (Intern), Svensson, B. (Intern)
Intercorrelations of lipoprotein subfractions and their covariation with lifestyle factors in healthy men

So far, little is known about the effect of nutrition and lifestyle on the composition of circulating lipoprotein subfractions. In the current study, we measured the correlations among physical activity, nutrient intake, smoking, body-mass index (BMI), and age with the concentration of triglycerides, cholesterol, phospholipids, and apolipoproteins (ApoA1, ApoA2 and ApoB) in subfractions of LDL and HDL in 265 healthy working men. Concentrations of cholesterol, phospholipids, and ApoB in small, dense atherogenic LDL particles (sdLDL) correlated negatively ($p<0.001$) with those of cholesterol, phospholipids, and ApoA1 in HDL2, respectively. Age correlated positively with sdLDL while increasing BMI correlated with an atherogenic shift of cholesterol, phospholipids, and ApoB from large, buoyant LDL (lbLDL) to sdLDL and decreasing concentrations of HDL2 constituents. Physical activity and alcohol intake correlated negatively with sdLDL constituents and positively with HDL2 components. Consumption of monounsaturated fatty acids (MUFA) correlated with a lower ratio of sdLDL to HDL2 cholesterol. A favorable lipoprotein subfraction profile linked to a reduced risk of cardiovascular disease in men was associated with physical activity, moderate alcohol consumption, and dietary intake of MUFA, which might be exploited in future interventions for prevention of age- and BMI-associated atherogenic shifts of lipoprotein subfractions.
Interpretation of appearance: the effect of facial features on first impressions and personality.
Appearance is known to influence social interactions, which in turn could potentially influence personality development. In this study we focus on discovering the relationship between self-reported personality traits, first impressions and facial characteristics. The results reveal that several personality traits can be read above chance from a face, and that facial features influence first impressions. Despite the former, our prediction model fails to reliably infer personality traits from either facial features or first impressions. First impressions, however, could be inferred more reliably from facial features. We have generated artificial, extreme faces visualising the characteristics having an effect on first impressions for several traits. Conclusively, we find a relationship between first impressions, some personality traits and facial features and consolidate that people on average assess a given face in a highly similar manner.

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Department of Applied Mathematics and Computer Science, Image Analysis & Computer Graphics, Technical University of Denmark
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BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.11 SJR 1.201 SNIP 1.092
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.414 SNIP 1.131 CiteScore 3.32
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.545 SNIP 1.141 CiteScore 3.54
Web of Science (2014): Indexed yes
KinomeXplorer: an integrated platform for kinome biology studies
A letter to the editor is presented related to the KinomeXplorer, an integrated platform providing workflows to efficiently analyze phosphorylation dependent interaction networks or kinase signaling networks.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Cellular Signal Integration, Systems Biotechnology, Memorial Sloan-Kettering Cancer Center, European Molecular Biology Laboratory, University of Roma 'Tor Vergata', University of Copenhagen
Authors: Horn, H. (Ekstern), Schoof, E. (Intern), Kim, J. (Intern), Robin, X. (Intern), Miller, M. L. (Ekstern), Diella, F. (Ekstern), Palma, A. (Ekstern), Cesareni, G. (Ekstern), Jensen, L. J. (Intern), Linding, R. (Intern)
Number of pages: 2
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Publication date: 2014
Main Research Area: Technical/natural sciences

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ISSN (Print): 1548-7091
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BFI (2017): BFI-level 2
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Lactate dehydrogenase as a selection criterion for ipilimumab treatment in metastatic melanoma

Ipilimumab, a cytotoxic T lymphocyte-associated antigen-4 blocking antibody, has improved overall survival (OS) in metastatic melanoma in phase III trials. However, about 80% of patients fail to respond, and no predictive markers for benefit from therapy have been identified. We analysed a 'real world' population of patients treated with ipilimumab to identify markers for treatment benefit.

Patients with advanced cutaneous melanoma were treated in the Netherlands (NL) and the United Kingdom (UK) with ipilimumab at 3 mg/kg. Baseline characteristics and peripheral blood parameters were assessed, and patients were monitored for the occurrence of adverse events and outcomes.

A total of 166 patients were treated in the Netherlands. Best overall response and disease control rates were 17 and 35%, respectively. Median follow-up was 17.9 months, with a median progression-free survival of 2.9 months. Median OS was 7.5 months, and OS at 1 year was 37.8% and at 2 years was 22.9%. In a multivariate model, baseline serum lactate dehydrogenase (LDH) was demonstrated to be the strongest predictive factor for OS. These findings were validated in an independent cohort of 64 patients from the UK.

In both the NL and UK cohorts, long-term benefit of ipilimumab treatment was unlikely for patients with baseline serum LDH greater than twice the upper limit of normal. In the absence of prospective data, clinicians treating melanoma may wish to consider the data presented here to guide patient selection for ipilimumab therapy.
Large-scale analysis of B-cell epitopes on influenza virus hemagglutinin - implications for cross-reactivity of neutralizing antibodies.

Influenza viruses continue to cause substantial morbidity and mortality worldwide. Fast gene mutation on surface proteins of influenza virus result in increasing resistance to current vaccines and available antiviral drugs. Broadly neutralizing antibodies (bnAbs) represent targets for prophylactic and therapeutic treatments of influenza. We performed a systematic bioinformatics study of cross-reactivity of neutralizing antibodies (nAbs) against influenza virus surface glycoprotein hemagglutinin (HA). This study utilized the available crystal structures of HA complexed with the antibodies for the analysis of tens of thousands of HA sequences. The detailed description of B-cell epitopes, measurement of epitope area similarity among different strains, and estimation of antibody neutralizing coverage provide insights into cross-reactivity status of existing nAbs against influenza virus. We have developed a method to assess the likely cross-reactivity potential of bnAbs for influenza strains, either newly emerged or existing. Our method catalogs influenza strains by a new concept named discontinuous peptide, and then provide assessment of cross-reactivity. Potentially cross-reactive strains are those that share 100% identity with experimentally verified neutralized strains. By cataloging influenza strains and their B-cell epitopes for known bnAbs, our method provides guidance for selection of representative strains for further experimental design. The knowledge of sequences, their B-cell epitopes, and differences between historical influenza strains, we enhance our preparedness and the ability to respond to the emerging pandemic threats.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Harvard Medical School, Technical University of Denmark, Tongji University
Authors: Sun, J. (Ekstern), Kudahl, U. J. (Ekstern), Simon, C. (Intern), Cao, Z. (Ekstern), Reinherz, E. L. (Ekstern), Brusic, V. (Ekstern)
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Main Research Area: Technical/natural sciences

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BFI (2017): BFI-level 1
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Web of Science (2016): Indexed yes
Scopus rating (2015): SJR 2.818 SNIP 1.29 CiteScore 5.09
Web of Science (2015): Indexed yes
Scopus rating (2014): SJR 2.382 SNIP 1.056 CiteScore 4.24
Web of Science (2014): Indexed yes
Scopus rating (2013): SJR 1.842 SNIP 0.837 CiteScore 3.55
ISI indexed (2013): ISI indexed no
Scopus rating (2012): SJR 0.785 SNIP 0.193 CiteScore 1.38
ISI indexed (2012): ISI indexed no
Scopus rating (2011): SJR 0.121
Web of Science (2011): Indexed yes
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Library sequencing strategies for comparative analysis of stress resistance mechanisms in Escherichia coli strains

Transposon insertion sequencing (Tn-Seq) has recently emerged as a powerful next-generation sequencing method that enables querying the contributions of all genes in a bacterial genome toward the fitness of a growing organism. In this method, transposon insertion mutant libraries are constructed and subjected to growth selections. Following selection, the locations of all insertions in the population are counted and can be compared between a control and a target condition, enabling the identification of genes that are both conditionally essential and conditionally detrimental. We have exploited Tn-Seq to probe the basis for the large variations in osmotic and acetate stress tolerance of different laboratory strains of Escherichia coli (K-12 MG1655, BL21(DE3), W, and Crooks). Little is currently known to explain the source of this variation and to enable rational engineering to impart stress tolerance. Tn-Seq revealed many differences and similarities in resistance mechanisms at the genetic level across strains, allowing correlations to be made with growth phenotypes. Cross-strain comparisons of conditionally essential genes and their relative essentiality also suggest a large degree of variation in metabolic flux distributions and regulation of gene expression between strains. A number of direct targets for metabolic engineering of stress resistance via loss-of-function mutations were also discovered, and we show that deletion of a selection of these genes results in improved growth under the original selection condition.
Lineage-specific interface proteins match up the cell cycle and differentiation in embryo stem cells.

The shortage of molecular information on cell cycle changes along embryonic stem cell (ESC) differentiation prompts an in silico approach, which may provide a novel way to identify candidate genes or mechanisms acting in coordinating the two programs. We analyzed germ layer specific gene expression changes during the cell cycle and ESC differentiation by combining four human cell cycle transcriptome profiles with thirteen in vitro human ESC differentiation studies. To detect cross-talk mechanisms we then integrated the transcriptome data that displayed differential regulation with protein interaction data. A new class of non-transcriptionally regulated genes was identified, encoding proteins which interact systematically with proteins corresponding to genes regulated during the cell cycle or cell differentiation, and which therefore can be seen as interface proteins coordinating the two programs. Functional analysis gathered insights in fate-specific candidates of interface functionalities. The non-transcriptionally regulated interface proteins were found to be highly regulated by post-translational ubiquitylation modification, which may synchronize the transition between cell proliferation and differentiation in ESCs.
LocTree3 prediction of localization

The prediction of protein sub-cellular localization is an important step toward elucidating protein function. For each query protein sequence, LocTree2 applies machine learning (profile kernel SVM) to predict the native sub-cellular localization in 18 classes for eukaryotes, in six for bacteria and in three for archaea. The method outputs a score that reflects the reliability of each prediction. LocTree2 has performed on par with or better than any other state-of-the-art method. Here, we report the availability of LocTree3 as a public web server. The server includes the machine learning-based LocTree2 and improves over it through the addition of homology-based inference. Assessed on sequence-unique data, LocTree3 reached an 18-state accuracy $Q_{18} = 80 \pm 3\%$ for eukaryotes and a six-state accuracy $Q_{6} = 89 \pm 4\%$ for bacteria. The server accepts submissions ranging from single protein sequences to entire proteomes. Response time of the unloaded server is about 90 s for a 300-residue eukaryotic protein and a few hours for an entire eukaryotic proteome not considering the generation of the alignments. For over 1000 entirely sequenced organisms, the predictions are directly available as downloads. The web server is available at http://www.rostlab.org/services/loctree3.
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 9.28 SJR 7.397 SNIP 2.657
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 7.239 SNIP 2.639 CiteScore 9.48
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 6.576 SNIP 2.568 CiteScore 8.74
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 6.582 SNIP 2.266 CiteScore 8.46
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 6.13 SNIP 2.392 CiteScore 8.62
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 5.758 SNIP 2.172 CiteScore 7.86
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 5.24 SNIP 2.034
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 5.571 SNIP 1.869
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 4.641 SNIP 1.557
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 4.86 SNIP 1.787
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 4.55 SNIP 2.04
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 4.992 SNIP 2.152
Web of Science (2005): Indexed yes
Scopus rating (2004): SJR 4.809 SNIP 1.971
Web of Science (2004): Indexed yes
Scopus rating (2003): SJR 0.108 SNIP 1.862
Web of Science (2003): Indexed yes
Scopus rating (2002): SJR 0.12 SNIP 1.535
Scopus rating (2001): SJR 0.131 SNIP 1.402
Scopus rating (2000): SJR 0.141 SNIP 1.672
Web of Science (2000): Indexed yes
Scopus rating (1999): SJR 0.149 SNIP 1.562

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Lysine deacetylase inhibition prevents diabetes by chromatin-independent immunoregulation and β-cell protection

Type 1 diabetes is due to destruction of pancreatic β-cells. Lysine deacetylase inhibitors (KDACi) protect β-cells from inflammatory destruction in vitro and are promising immunomodulators. Here we demonstrate that the clinically well-tolerated KDACi vorinostat and givinostat revert diabetes in the nonobese diabetic (NOD) mouse model of type 1 diabetes and counteract inflammatory target cell damage by a mechanism of action consistent with transcription factor-rather than global chromatin-hyperacetylation. Weaning NOD mice received low doses of vorinostat and givinostat in their drinking water until 100-120 d of age. Diabetes incidence was reduced by 38% and 45%, respectively, there was a 15% increase in the percentage of islets without infiltration, and pancreatic insulin content increased by 200%. Vorinostat treatment increased the frequency of functional regulatory T-cell subsets and their transcription factors Gata3 and FoxP3 in parallel to a decrease in inflammatory dendritic cell subsets and their cytokines IL-6, IL-12, and TNF-α. KDACi also inhibited LPS-induced Cox-2 expression in peritoneal macrophages from C57BL/6 and NOD mice. In insulin-producing β-cells, givinostat did not upregulate expression of the anti-inflammatory genes Socs1-3 or sirtuin-1 but reduced levels of IL-1β + IFN-γ-induced proinflammatory Il1α, Il1b, Tnfa, Fas, Cxcl2, and reduced cytokine-induced ERK phosphorylation. Further, NF-κB genomic iNos promoter binding was reduced by 50%, and NF-κB-dependent mRNA expression was blocked. These effects were associated with NF-κB subunit p65 hyperacetylation. Taken together, these data provide a rationale for clinical trials of safety and efficacy of KDACi in patients with autoimmune disease such as type 1 diabetes.

General information
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Regulatory Genomics, University of Copenhagen, Katholieke Universiteit, University of Southern Denmark, San Raffaele Scientific Institute, Hagedorn Research Institute, Italfarmaco SpA, McGill University, University of Colorado
Authors: Christensen, D. P. (Ekstern), Gysemans, C. (Ekstern), Lundh, M. (Ekstern), Dahllöf, M. S. (Ekstern), Noesgaard, D. (Ekstern), Schmidt, S. F. (Ekstern), Mandrup, S. (Ekstern), Birkbak, N. J. (Intern), Workman, C. (Intern), Piemonti, L. (Ekstern), Blaabjerg, L. (Ekstern), Monzani, V. (Ekstern), Fossati, G. (Ekstern), Mascagni, P. (Ekstern), Paraskevas, S. (Ekstern), Aikin, R. A. (Ekstern), Billestrup, N. (Ekstern), Grunnet, L. G. (Ekstern), Dinarello, C. A. (Ekstern), Mathieu, C. (Ekstern), Mandrup-Poulsen, T. (Ekstern)
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BFI (2017): BFI-level 2
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 8.56 SJR 6.321 SNIP 2.629
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 6.767 SNIP 2.682 CiteScore 8.84
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 6.853 SNIP 2.725 CiteScore 8.86
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 6.989 SNIP 2.73 CiteScore 9.5
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 6.792 SNIP 2.682 CiteScore 9.49
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 6.771 SNIP 2.636 CiteScore 9.31
Metagenomics reveals sediment microbial community response to Deepwater Horizon oil spill

The Deepwater Horizon (DWH) oil spill in the spring of 2010 resulted in an input of similar to 4.1 million barrels of oil to the Gulf of Mexico; >22% of this oil is unaccounted for, with unknown environmental consequences. Here we investigated the impact of oil deposition on microbial communities in surface sediments collected at 64 sites by targeted sequencing of 16S rRNA genes, shotgun metagenomic sequencing of 14 of these samples and mineralization experiments using C-14-labeled model substrates. The 16S rRNA gene data indicated that the most heavily oil-impacted sediments were enriched in an uncultured Gammaproteobacterium and a Colwellia species, both of which were highly similar to sequences in the DWH deep-sea hydrocarbon plume. The primary drivers in structuring the microbial community were nitrogen and hydrocarbons. Annotation of unassembled metagenomic data revealed the most abundant hydrocarbon degradation pathway encoded genes involved in degrading aliphatic and simple aromatics via butane monooxygenase. The activity of key hydrocarbon degradation pathways by sediment microbes was confirmed by determining the mineralization of C-14-labeled model substrates in the following order: propylene glycol, dodecane, toluene and phenanthrene. Further, analysis of metagenomic sequence data revealed an increase in abundance of genes involved in denitrification pathways in samples that exceeded the Environmental Protection Agency (EPA)'s benchmarks for polycyclic aromatic hydrocarbons (PAHs) compared with those that did not. Importantly, these data demonstrate that the indigenous sediment microbiota contributed an important ecosystem service for remediation of oil in the Gulf. However, PAHs were more recalcitrant to degradation, and their persistence could have deleterious impacts on the sediment ecosystem.
Metagenomic Systems Biology of the Human Microbiome

The human microbiome is an integrated part of the human body, outnumbering the human cells by approximately a factor 10. These microorganisms are very important for human health, hence knowledge about this, “our other genome”, has been growing rapidly in recent years. This is mainly due to the advances in next generation sequencing, which has allowed for large-scale metagenomics studies of different niches of the human microbiota. Especially the gut microbiota has been studied intensively. However, most studies have been purely descriptive, thus there is still a lot to learn regarding the interplay between species in the microbiota and also between the host and the inhabiting microorganisms. Additionally, the non-bacterial part of the microbiota, which includes bacteriophages, plasmids and micro-eukaryotes, is not very well described.

In this thesis, metagenomics data from the human gut, nose and oral cavity has been analyzed. The central method has been a co-abundance clustering method, which separates genes from metagenomics data under the assumption that genes originating from the same DNA (e.g. a bacterial genome, a phage or a plasmid) will co-vary across samples. Thus, co-abundance gene groups (CAGs) are obtained, which represent bacterial genomes, phages, plasmids or other genetic elements in the system. The ability to reassemble the metagenome in this way opens up new possibilities for analyzing the functional potential of species in the microbiota as well as the interactions in the system. Applying the CAG clustering method to data from the human gut microbiome, we identified dependency-associations between plasmids, phages and clone-specific gene sets to their bacterial host. Connections between CRISPR-elements and phages were also observed. Additionally, the persistence of some bacterial species in the human gut could be predicted based on absence or presence of specific genetic modules.

Based on the same CAG clustering of the human gut microbiome data, the link between bile acid degradation of bacteria in the gut and obesity was investigated. There seemed to be a slight correlation between the two. However, this remains to be a hypothesis for further studies. Furthermore, the prevalence of the parasite Blastocystis in the human gut microbiome data was analyzed. This is the first time a metagenomics approach has been applied to this problem and the results were similar to previous Blastocystis prevalence studies. Moreover, it was found that individuals with a Bacteroides-driven enterotype were less prone to harbor the Blastocystis parasite.

Finally, the CAG clustering method was applied to metagenomics data from the human nose- and oral-cavity. It was concluded that this method needs further improvement in order for it to be directly transferable to other datasets. In summary this thesis presents co-abundance gene groups (CAG) clustering as a valuable tool for analyzing human microbiome data. Furthermore, results based on this method regarding important topics in relation to the human gut microbiota are described, including the interplay between bacterial species and other genetic elements in the system, factors that might influence development of obesity and prevalence studies of eukaryotes. Studies of other areas of the human microbiome might also benefit from CAG based analyses once the tool has been optimized.
Modulation of the Chromatin Phosphoproteome by the Haspin Protein Kinase

Recent discoveries have highlighted the importance of Haspin kinase activity for the correct positioning of the kinase Aurora B at the centromere. Haspin phosphorylates Thr3 of the histone H3 (H3), which provides a signal for Aurora B to localize to the centromere of mitotic chromosomes. To date, histone H3 is the only confirmed Haspin substrate. We used a combination of biochemical, pharmacological, and mass spectrometric approaches to study the consequences of Haspin inhibition in mitotic cells. We quantified 3964 phosphorylation sites on chromatin-associated proteins and identified a Haspin protein-protein interaction network. We determined the Haspin consensus motif and the co-crystal structure of the kinase with the histone H3 tail. The structure revealed a unique bent substrate binding mode positioning the histone H3 residues Arg2 and Lys4 adjacent to the Haspin phosphorylated threonine into acidic binding pockets. This unique conformation of the kinase-substrate complex explains the reported modulation of Haspin activity by methylation of Lys4 of the histone H3. In addition, the identification of the structural basis of substrate recognition and the amino acid sequence preferences of Haspin aided the identification of novel candidate Haspin substrates. In particular, we validated the phosphorylation of Ser137 of the histone variant macroH2A as a target of Haspin kinase activity. MacroH2A Ser137 resides in a basic stretch of about 40 amino acids that is required to stabilize extranucleosomal DNA, suggesting that phosphorylation of Ser137 might regulate the interactions of macroH2A and DNA. Overall, our data suggest that Haspin activity affects the phosphorylation state of proteins involved in gene expression regulation and splicing.
Many common diseases, such as asthma, diabetes or obesity, involve altered interactions between thousands of genes. High-throughput techniques (omics) allow identification of such genes and their products, but functional understanding is a formidable challenge. Network-based analyses of omics data have identified modules of disease-associated genes that have been used to obtain both a systems level and a molecular understanding of disease mechanisms. For example, in allergy a module was used to find a novel candidate gene that was validated by functional and clinical studies. Such analyses play important roles in systems medicine. This is an emerging discipline that aims to gain a translational understanding of the complex mechanisms underlying common diseases. In this review, we will explain and provide examples of how network-based analyses of omics data, in combination with functional and clinical studies, are aiding our understanding of disease, as well as helping to prioritize diagnostic markers or therapeutic candidate genes. Such analyses involve significant problems and limitations, which will be discussed. We also highlight the steps needed for clinical implementation.
MR1-restricted MAIT cells display ligand discrimination and pathogen selectivity through distinct T cell receptor usage. Mucosal-associated invariant T (MAIT) cells express a semi-invariant T cell receptor (TCR) that detects microbial metabolites presented by the nonpolymorphic major histocompatibility complex (MHC)-like molecule MR1. The highly conserved nature of MR1 in conjunction with biased MAIT TCRα chain usage is widely thought to indicate limited ligand presentation and discrimination within a pattern-like recognition system. Here, we evaluated the TCR repertoire of MAIT cells responsive to three classes of microbes. Substantial diversity and heterogeneity were apparent across the functional MAIT cell repertoire as a whole, especially for TCRβ chain sequences. Moreover, different pathogen-specific responses were characterized by distinct TCR usage, both between and within individuals, suggesting that MAIT cell adaptation was a direct consequence of exposure to various exogenous MR1-restricted epitopes. In line with this interpretation, MAIT cell clones with distinct TCRs responded differentially to a riboflavin metabolite. These results suggest that MAIT cells can discriminate between pathogen-derived ligands in a clonotype-dependent manner, providing a basis for adaptive memory via recruitment of specific repertoires shaped by microbial exposure.

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Multiparametric Bioinformatics Distinguish the CD4/CD8 Ratio as a Suitable Laboratory Predictor of Combined T Cell Pathogenesis in HIV Infection

HIV disease progression is characterized by numerous pathological changes of the cellular immune system. Still, the CD4 cell count and viral load represent the laboratory parameters that are most commonly used in the clinic to determine the disease progression. In this study, we conducted an interdisciplinary investigation to determine which laboratory parameters (viral load, CD4 count, CD68 count, CD4 %, CD68 %, CD4/CD8) are most strongly associated with pathological changes of the immune system. Multiparametric flow cytometry was used to assess markers of CD4+ and CD8+ T cell activation (CD38, HLA-DR), exhaustion (PD-1, Tim-3), senescence (CD28, CD57), and memory differentiation (CD45RO, CD27) in a cohort of 47 untreated HIV-infected individuals. Using bioinformatical methods, we identified 139 unique populations, representing the "combined T cell pathogenesis," which significantly differed between the HIV-infected individuals and healthy control subjects. CD38, HLA-DR, and PD-1 were particularly expressed within these unique T cell populations. The CD4/CD8 ratio was correlated with more pathological T cell populations (n = 10) and had a significantly higher average correlation coefficient than any other laboratory parameters. We also reduced the dimensionalities of the 139-unique populations by Z-transformations and principal component analysis, which still identified the CD4/CD8 ratio as the preeminent surrogate of combined T cell pathogenesis. Importantly, the CD4/CD8 ratio at baseline was shown to be significantly associated with CD4 recovery 2 y after therapy initiation. These results indicate that the CD4/CD8 ratio would be a suitable laboratory predictor in future clinical and therapeutic settings to monitor pathological T cell events in HIV infection.
Mycobacterium tuberculosis promotes Th17 expansion via regulation of human dendritic cells toward a high CD14 and low IL-12p70 phenotype that reprograms upon exogenous IFN-γ.

The capacity to develop protective immunity against mycobacteria is heterogeneously distributed among human beings, and it is currently unknown why the initial immune response induced against Mycobacterium tuberculosis (MtB) does not provide proper clearance of this pathogen. Dendritic cells (DCs) are some of the first cells to interact with MtB and they play an essential role in development of protective immunity against MtB. Given that MtB-infected macrophages have difficulties in degrading MtB, they need help from IFN-γ-producing CD4+ T cells propagated via IL-12p70-producing DCs. Here we report that MtB modifies human DC plasticity by expanding a CD14+ DC subset with weak IL-12p70-producing capacity. The CD14+ MtB-promoted subset was furthermore poor inducers of IFN-γ by naive CD4+ T cells, but instead prompted IL-17A-producing RORγT+ CD4+ T cells. MtB-derived peptidoglycan and mannosylated lipoarabinomannan partly recapitulated the subset partition induced by MtB. Addition of IFN-γ, but neither IL-17A nor IL-22, which are potentially produced by MtB-exposed γ/δ-T cells in mucosal linings, inhibited the differentiation toward CD14+ DCs and promoted high-level IL-12p70 in MtB-challenged DCs. We conclude that MtB exploits DC plasticity to reduce production of IL-12p70, and that this process is entirely divertible by exogenous IFN-γ. These data suggest that strategies to increase local IFN-γ production in the lungs of tuberculosis patients may boost host immunity toward MtB.
Natural genetic variation impacts expression levels of coding, non-coding, and antisense transcripts in fission yeast.

Our current understanding of how natural genetic variation affects gene expression beyond well-annotated coding genes is still limited. The use of deep sequencing technologies for the study of expression quantitative trait loci (eQTLs) has the potential to close this gap. Here, we generated the first recombinant strain library for fission yeast and conducted an RNA-seq-based QTL study of the coding, non-coding, and antisense transcriptomes. We show that the frequency of distal effects (trans-eQTLs) greatly exceeds the number of local effects (cis-eQTLs) and that non-coding RNAs are as likely to be affected by eQTLs as protein-coding RNAs. We identified a genetic variation of swc5 that modifies the levels of 871 RNAs, with effects on both sense and antisense transcription, and show that this effect most likely goes through a compromised deposition of the histone variant H2A.Z. The strains, methods, and datasets generated here provide a rich resource for future studies.
Natural mannosylation of HIV-1 gp120 imposes no immunoregulatory effects in primary human plasmacytoid dendritic cells

Plasmacytoid dendritic cells (pDCs) play a vital role in activation of anti-HIV-1 immunity, and suppression of pDCs might mitigate immune responses against HIV-1. HIV-1 gp120 high-mannose has been attributed immunosuppressive roles in human myeloid DCs, but no receptors for high-mannose have so far been reported on human pDCs. Here we show that upon activation with HIV-1 or by a synthetic compound triggering the same receptor in human pDCs as single-stranded RNA, human pDCs upregulate the mannose receptor (MR, CD206). To examine the functional outcome of this upregulation, inactivated intact or viable HIV-1 particles with various degrees of mannosylation were cultured with pDCs. Activation of pDCs was determined by assaying secretion of IFN-alpha, viability, and upregulation of several pDC-activation markers: CD40, CD86, HLA-DR, CCR7, and PD-L1. The level of activation negatively correlated with degree of mannosylation, however, subsequent reduction in the original mannosylation level had no effect on the pDC phenotype. Furthermore, two of the infectious HIV-1 strains induced profound necrosis in pDCs, also in a mannose-independent
manner. We therefore conclude that natural mannosylation of HIV-1 is not involved in HIV-1-mediated immune suppression of pDCs.
Negation scope and spelling variation for text-mining of Danish electronic patient records

Electronic patient records are a potentially rich data source for knowledge extraction in biomedical research. Here we present a method based on the ICD10 system for text-mining of Danish health records. We have evaluated how adding functionalities to a baseline text-mining tool affected the overall performance. The purpose of the tool was to create enriched phenotypic profiles for each patient in a corpus consisting of records from 5,543 patients at a Danish psychiatric hospital, by assigning each patient additional ICD10 codes based on freetext parts of these records. The tool was benchmarked by manually curating a test set consisting of all records from 50 patients. The tool evaluated was designed to handle spelling and ending variations, shuffling of tokens within a term, and introduction of gaps in terms. In particular we investigated the importance of negation identification and negation scope. The most important functionality of the tool was handling of spelling variation, which greatly increased the number of phenotypes that could be identified in the records, without noticeably decreasing the precision. Further, our results show that different negations have different optimal scopes, some spanning only a few words, while others span up to whole sentences.
NetTepi: an integrated method for the prediction of T cell epitopes

Multiple factors determine the ability of a peptide to elicit a cytotoxic T cell lymphocyte response. Binding to a major histocompatibility complex class I (MHC-I) molecule is one of the most essential factors, as no peptide can become a T cell epitope unless presented on the cell surface in complex with an MHC-I molecule. As such, peptide-MHC (pMHC) binding affinity predictors are currently the premier methods for T cell epitope prediction, and these prediction methods have been shown to have high predictive performances in multiple studies. However, not all MHC-I binders are T cell epitopes, and multiple studies have investigated what additional factors are important for determining the immunogenicity of a peptide. A recent study suggested that pMHC stability plays an important role in determining if a peptide can become a T cell epitope. Likewise, a T cell propensity model has been proposed for identifying MHC binding peptides with amino acid compositions favoring T cell receptor interactions. In this study, we investigate if improved accuracy for T cell epitope discovery can be achieved by integrating predictions for pMHC binding affinity, pMHC stability, and T cell propensity. We show that a weighted sum approach allows pMHC stability and T cell propensity predictions to enrich pMHC binding affinity predictions. The integrated model leads to a consistent and significant increase in predictive performance and we demonstrate how this can be utilized to decrease the experimental workload of epitope screens.
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Nordic mcl2-3 trials: mirna-18b overexpression identifies a mantle cell lymphoma subgroup with poor survival and improves mpi-b prediction of prognosis

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“Prevention is better than cure” and when it comes to human health, this strategy translates into many socioeconomic benefits. Practically all the cellular processes, including every step in the flow of genetic information from gene expression to protein synthesis and degradation, can be affected by diet and lifestyle. Similar to the role of pharmaceuticals, nutrients contain a number of different compounds that act as modifiers of network function and stability. However, the level of complexity in nutrition studies is further increased by the simultaneous presence of a variety of nutrients, with diverse chemical structures that can have numerous targets with different affinities and specificities. Obviously, this differentiates the nutritional from the pharmacological studies, where single elements are used at low concentrations and with a relatively high affinity and specificity in a small number of thoroughly selected targets. Our need for fundamental understanding of the building blocks of the complex biological systems had been the main reason for the reductionist approach that was mainly applied in the past to elucidate these systems. Nowadays, it is widely recognized that systems and network biology has the potential to increase our understanding of how small molecules affect metabolic pathways and homeostasis, how this perturbation changes at the disease state, and to what extent individual genotypes contribute to this. A fruitful strategy in approaching and exploring the field of nutritional research is, therefore, to borrow methods that are well established in medical and pharmacological research.

In this thesis, we use advanced data-mining tools for the construction of a database with available, state-of-the-art information concerning the interaction of food and its molecular components with biological systems and their connection to health and disease. The database will be enriched with predicted interactions between food components and protein targets, based on their structural and pharmacophore similarity with known small molecule ligands. Further to this, the associations of bioactive food components with metabolic pathways will be investigated from a chemical-protein network perspective, while their effects in network robustness will be further confirmed by proteome analyses and high-throughput genotype-phenotype characterization.

The first chapter of the thesis is about the development of our data resource. In this work, we applied text mining and Naïve Bayes classification to assemble the knowledge space of foodphytochemical and food-disease associations, where we distinguish between disease prevention/amelioration and disease progression. We subsequently searched for frequently occurring phytochemical-disease pairs and we identified 20,654 phytochemicals from 16,102 plants associated to 1,592 human disease phenotypes. We selected colon cancer as a case study and analyzed our results in three directions; i) one stop legacy knowledge-shop for the effect of food on disease, ii) discovery of novel bioactive compounds
with drug-like properties, and iii) discovery of novel health benefits from foods. This works represents a systematized approach to the association of food with health effect, and provides the phytochemical layer of information for nutritional systems biology research. The paper also shows as a proof-of-concept that a systems biology approach to diet is meaningful and demonstrates some basic principles on how to work with diet systematic.

The second chapter of this thesis we developed the resource NutriChem v1.0. A foodchemical database linking the chemical space of plant-based foods with human disease phenotypes and provides a fundamental foundation for understanding mechanistically the consequences of eating behaviors on health. Dietary components may act directly or indirectly on the human genome and modulate multiple processes involved in disease risk and disease progression. The database has been created from text mining. The database and its content have been made available to the public from our webservr NutriChem: http://cbs.dtu.dk/services/NutriChem-1.0

The third chapter of the thesis is on developing a molecular roadmap of drug-food interactions. Our main hypothesis in the current work is that the complex interference of food on drug pharmacokinetic or pharmacodynamics processes is mainly exerted at the molecular level via natural compounds in food that are biologically active towards a wide range of proteins involved in drug ADME and drug action. Hence, the more information we gather about these natural compounds, such as molecular structure, experimental and predicted bioactivity profile, the greater insight we will gain about the molecular mechanisms dictating drug-food interactions, which will help us identifying, predicting and preventing potential unwanted interactions between foods and marketed- or novel drugs. Unlike drug bioactivity information that has already been made available for system-level analyses, biological activity data and source origin information of natural compounds present in food are scarce and unstructured. To this end, we integrate proteinchemical interaction networks, gene expression signatures and molecular docking to provide the foundation for understanding mechanistically the effect of eating behaviors on therapeutic intervention strategies.

The fourth chapter of the thesis is a case study on diet-colon cancer through candidate molecular interaction networks. The study shows a holistic examination of the dietary components for exploring the mechanisms of action and understanding the nutrient-nutrient interactions. In this paper we used colon cancer as a proof-of-concept for understanding key regulatory sites of diet on the disease pathway. We propose a framework for interrogating the critical targets in colon cancer process and identifying plant-based dietary interventions as important modifiers using a systems chemical biology approach.

The fifth chapter of the thesis is on discovering of novel anti-ovarian cancer compounds from our diet. Ovarian cancer is the leading cause of death from gynecological disorders with an increasingly high incidence, especially in the western world. Epidemiological studies suggest that some dietary factors may play a role in the development of ovarian cancer; so far most studies have shown up inconclusive. In the present study we disclose novel anti-ovarian cancer compounds from our diet with activity against ovarian cancer, through text mining and a systemwide association of phytochemicals, foods and health benefits on human ovarian cancer. We selected several compounds that where predicted to have anti-ovarian cancer activities, using chemoinformatics approaches and evaluated and confirm their activities in vitro.

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**Parent-of-origin-specific allelic associations among 106 genomic loci for age at menarche**

Age at menarche is a marker of timing of puberty in females. It varies widely between individuals, is a heritable trait and is associated with risks for obesity, type 2 diabetes, cardiovascular disease, breast cancer and all-cause mortality(1). Studies of rare human disorders of puberty and animal models point to a complex hypothalamic-pituitary-hormonal regulation(2,3), but the mechanisms that determine pubertal timing and underlie its links to disease risk remain unclear. Here, using genome-wide and custom-genotyping arrays in up to 182,416 women of European descent from 57 studies, we found robust evidence (P ≤ 10(-8)) for 123 signals at 106 genomic loci associated with age at menarche. Many loci were associated with other pubertal traits in both sexes, and there was substantial overlap with genes implicated in body mass index and various diseases, including rare disorders of puberty. Menarche signals were enriched in imprinted regions, with three loci (DLK1-WDR25, MKRN3-MAGEL2 and KCNK9) demonstrating parent-of-origin-specific associations concordant with known parental expression patterns. Pathway analyses implicated nuclear hormone receptors, particularly retinoic acid and gamma-aminobutyric acid-B2 receptor signalling, among novel mechanisms that regulate pubertal timing in humans. Our findings suggest a genetic architecture involving at least hundreds of common variants in the coordinated timing of the pubertal transition.
Patient stratification and identification of adverse event correlations in the space of 1190 drug related adverse events.

New pharmacovigilance methods are needed as a consequence of the morbidity caused by drugs. We exploit fine-grained drug related adverse event information extracted by text mining from electronic medical records (EMRs) to stratify patients based on their adverse events and to determine adverse event co-occurrences. We analyzed the similarity of adverse event profiles of 2347 patients extracted from EMRs from a mental health center in Denmark. The patients were clustered based on their adverse event profiles and the similarities were presented as a network. The set of adverse events in each main patient cluster was evaluated. Co-occurrences of adverse events in patients (p-value < 0.01) were identified and presented as well. We found that each cluster of patients typically had a most distinguishing adverse event. Examination of the co-occurrences of adverse events in patients led to the identification of potentially interesting adverse event correlations that may be further investigated as well as provide further patient stratification opportunities. We have demonstrated the feasibility of a novel approach in pharmacovigilance to stratify patients based on fine-grained adverse event profiles, which also makes it possible to identify adverse event correlations. Used on larger data sets, this data-driven method has the potential to reveal unknown patterns concerning adverse event occurrences.

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Pharmacology profiling of chemicals and proteins

The central tenet in drug-development of one drug selectively interacts with one target is increasingly challenged by the vast amount of data released to the public domain in the past 10-15 years, documenting multiple targets for most of the FDA approved pharmaceuticals [1]. Unintended interactions between pharmaceuticals and proteins in vivo potential leads to unwanted adverse effects, toxicity and reduced half-life, but can also lead to novel therapeutic effects of already approved pharmaceuticals. Hence identification of in vivo targets is of importance in discovery, development and repurposing of pharmaceuticals, a process referred to as pharmacology profiling.

Pharmacology profiling of chemical and protein based pharmaceuticals has been proven valuable in a number studies [2], however missing values in the drug-protein interaction matrix limits the profile for novel or less studied compounds. This limitation complicates adverse effect assessment in the early drug-development phase, thus contributing to drug attrition. Prediction models offer the possibility to close these gaps and provide more complete pharmacology profiles, however improvements in performances are required for these tools to serve as an alternative to experimentally obtained measurements.

Here I present several different tools that aid pharmacology profiling of the two main classes of pharmaceuticals; chemicals (small molecules) and proteins (biopharmaceuticals). Biopharmaceuticals have the inherent risks of eliciting an immune response due to its nonself origin, which potentially alters the pharmacology profile of the substance. The neutralization of biopharmaceuticals by antidrug antibodies (ADAs) is an important element in the immune response cascade, however studies of ADA binding site on biopharmaceuticals, referred to as B-cell epitopes, are complicated by expensive experimental procedures thus making prediction models an
Phytol: A chlorophyll component with anti-inflammatory and metabolic properties

The naturally occurring dipterpenoid molecule Phytol is an alcohol that can be extracted from the chlorophyll of green plants. Phytol has been studied for decades and has been suggested to have both metabolic properties as well as potent anti-inflammatory effects. Phytol represents a molecule derived by nature with lipid regulating properties, in line with today's need for new drugs to control for diseases that follow the westernized diet and lifestyle. The beneficial effects of phytol on inflammatory effects. Phytol is a naturally occurring component in new natural remedies and functional food products to tackle the rapidly increasing global health problems caused by cardiovascular and chronic inflammatory diseases.

In summary, here I present several different tools that can assist researchers in determine essential properties in the pharmacology profile of both protein and small molecule pharmaceuticals and potentially detect adverse effects in drug-discovery and development, thus avoiding unwanted adverse effects.

Finally, the visualization of the pharmacology space is addressed by developing a 2 dimensional zoomable heatmap inspired by country and city maps. Chemicals sharing similar scaffold or features are placed together on the map, thus enabling a more detailed visualization of the pharmacology landscape surrounding one or more chemicals of interest. The tool, presented in chapter 6, enables researchers to couple scaffold and feature hopping with bioactivity data for the use in drug-discovery and development, thus avoiding unwanted adverse effects.

In general, B-cell epitope prediction tools have moderate performances, which to some extent originates from an incomplete understanding of what constitute a B-cell epitope and incomplete datasets used for model building and benchmarking. In the first paper included in this thesis we analyze the B-cell epitopes obtained from co-crystallized antibody-antigen complexes from the PDB database. We were able to describe the epitope area as a flat oblong area residing on the protein surface consisting of a hydrophobic core surrounded by hydrophilic charged residues. This finding prompted us to update the B-cell epitope prediction method DiscoTope [3] by introducing a novel scoring function for describing the spatial neighborhood surrounding each residue as described in paper I of this thesis. Using the developed method we assessed the impact on performance using a more realistic benchmark definition compared to priors studies, by including multiple epitopes for each antigen and the biological unit used for raising the antibody response, when available. On average, the Area Under the roc-Curve(AUC) performance was improved from 0.791 to 0.824 for the 13 proteins were additional information could be obtained, thereby indicating that the performance of B-cell epitope prediction tools in general are under-estimated.

Novel techniques such as Next Generation Sequencing (NGS) and peptide microarray facilitate novel strategies for experimental identification of B-cell epitopes. In chapter 4, a novel method for epitope identification is described, combining NGS with phage-display. Epitopes in peanut allergen ara h1 were successfully detected using sera from peanut allergic patients and confirmed using peptide micro-array technology, demonstrating the applicability of both methods.

Adverse effect of small molecule based pharmaceutical is rarely mediated through an immune response but is predominantly the consequence of interactions with unintended proteins in vivo. To assist researchers in determine the binding profile of chemicals, thus their pharmacology profile, a database of chemical-protein interactions were developed and presented in chapter 5. The database integrates chemical-protein interaction information from 10 different databases as well as disease, functional and pathway mapping of proteins, SNP data through the Ensembl database and prediction tools for filling out gaps in the chemical-protein interaction matrix. Graphical representation of the pharmacology space is accomplished by the use of zoomable heatmaps, which enable traversing from an overview of the entire space to specific pharmacology profiles of a single chemical by zooming on specific areas of the heatmap. The compiled dataset together with the implemented visualization and prediction tools, facilitate pharmacology profiling of chemicals in all development stages, hence potentially enable identification of adverse effects in early drug development or identification of novel treatment paradigms for approved pharmaceuticals.

In summary, here I present several different tools that can assist researchers in determine essential properties in the pharmacology profile of both protein and small molecule pharmaceuticals and potentially detect adverse effects in drug-development.
Polychlorinated dibenzo-p-dioxins, furans, and biphenyls (PCDDs/PCDFs and PCBs) in breast milk and early childhood growth and IGF1.

Experimental studies have shown that dioxin-like chemicals may interfere with aspects of the endocrine system including growth. However, human background population studies are, however, scarce. We aimed to investigate whether early exposure of healthy infants to dioxin-like chemicals was associated with changes in early childhood growth and serum IGF1. In 418 maternal breast milk samples of Danish children (born 1997-2001) from a longitudinal cohort, we measured polychlorinated dibenzo-p-dioxins, polychlorinated dibenzofurans, and polychlorinated biphenyls (pg or ng/g lipid) and calculated total toxic equivalent (total TEQ). SDS and SDS changes over time (ΔSDS) were calculated for height, weight, BMI, and skinfold fat percentage at 0, 3, 18, and 36 months of age. Serum IGF1 was measured at 3 months. We adjusted for confounders using multivariate regression analysis. Estimates (in parentheses) correspond to a fivefold increase in total TEQ. TEQ levels in breast milk increased significantly with maternal age and fish consumption and decreased with maternal birth year, parity, and smoking. Total TEQ was associated with lower fat percentage (-0.45 s.d., CI: -0.89; -0.04), non-significantly with lower weight and length at 0 months, accelerated early height growth (increased ΔSDS) (ΔSDS 0-18 months: +0.77 s.d., CI: 0.34; 1.19) and early weight increase (ΔSDS 0-18: +0.52 s.d., CI: 0.03; 1.00), and increased IGF1 serum levels at 3 months (+13.9 ng/ml, CI: 2.3; 25.5). Environmental exposure to dioxin-like chemicals was associated with being skinny at birth and with higher infant levels of circulating IGF1 as well as accelerated early childhood growth (rapid catch-up growth).
Prediction of Wild-type Enzyme Characteristics

Technological advances within massive parallel data generation techniques in biology have made bioinformatics an increasingly important part of biotechnology research. Data-driven research by means of integration and analysis of large biological data sets provide new opportunities across all areas of biotechnology, including enzyme discovery and characterization. This work presents two articles on sequence-based discovery and functional annotation of enzymes in environmental samples, and two articles on analysis and prediction of enzyme thermostability and cofactor requirements. The first article presents a sequence-based approach to discovery of proteolytic enzymes in metagenomes obtained from the Polar oceans. We show that microorganisms living in these extreme environments of constant low temperature harbour genes encoding novel proteolytic enzymes with potential industrial relevance. The second article presents a web server for the processing and annotation of functional metagenomics sequencing data, tailored to meet the requirements of non-bioinformaticians. The third article presents analyses of the molecular determinants of enzyme thermostability, and a feature-based prediction method of the melting temperature of fungal wild-type enzymes from seven different glycoside hydrolase families. We exemplify family-specific stabilizing protein features, and show that our feature-based algorithm outperforms a sequence similarity-based approach to melting temperature prediction. Finally, the fourth article presents a sequence-based prediction method of the cofactor binding specificity of Rossmann folds. The algorithm predicts the specificity for the cofactors FAD(H2), NAD(H) and NADP(H), and we demonstrate its ability to reflect changes in cofactor preference upon introduction of two or more amino acid substitutions in Rossmann fold sequences.

In summary, this work presents novel methods for prediction of enzyme characteristics, and exemplify the largely untapped potential for discovery of new biocatalysts in environmental samples.
Prehistoric genomes reveal the genetic foundation and cost of horse domestication

Significance The domestication of the horse revolutionized warfare, trade, and the exchange of people and ideas. This at least 5,500-y-long process, which ultimately transformed wild horses into the hundreds of breeds living today, is difficult to reconstruct from archeological data and modern genetics alone. We therefore sequenced two complete horse genomes, predating domestication by thousands of years, to characterize the genetic footprint of domestication. These ancient genomes reveal predomestic population structure and a significant fraction of genetic variation shared with the domestic breeds but absent from Przewalski’s horses. We find positive selection on genes involved in various aspects of locomotion, physiology, and cognition. Finally, we show that modern horse genomes contain an excess of deleterious mutations, likely representing the genetic cost of domestication.

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Pre-natal undernutrition and post-natal overnutrition are associated with permanent changes in hepatic metabolism markers and fatty acid composition in sheep

Determine the impacts of pre- and early-post-natal nutrition on selected markers of hepatic glucose and fat metabolism. Twin-bearing ewes were fed 100% (NORM) or 50% (LOW) of protein and energy requirements during the last 6-weeks of gestation. Twin-lambs received either a high-carbohydrate high-fat (HCHF) or conventional (CONV) diet from 3 days to 6 months of age (around puberty), whereafter lambs from the four subgroups were slaughtered (16 males/3 females). Remaining lambs (19 females) were fed a moderate diet and slaughtered at 2 years of age (young adults). Pre-natal LOW nutrition was associated with increased hepatic triglyceride, ceramide and free fatty acid content in adulthood (not observed in lambs), which was accompanied by up-regulated early-stage insulin signalling as reflected by increased INSRβ and PI3K-p110 protein expression. The HCHF diet increased hepatic triglyceride content in lambs, associated with down-regulated expressions of energy-metabolism-related genes (GLUT1, PPARα, SREBP1c, PEPCK). These post-natal effects were not observed in adult HCHF sheep, after they had received a moderate (body-fat correcting) diet for 1.5 years. Interestingly, pre-natal LOW nutrition induced permanent alterations in hepatic phospholipids’ fatty acid composition. Thus, the amount of linoleic acid (C18 : 2 ∆9,12) was significantly increased and composition of rumen-derived fatty acids were altered, indicating changed composition of rumenal microbiota. Hepatic insulin signalling and linoleic and microbial-derived fatty acid content in phospholipids are targets of foetal programming induced by late-gestation undernutrition. Future studies are required to explain their cause–effect associations with increased risks of developing hepatic steatosis and insulin insensitivity in adulthood.

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Probabilistic Determination of Native State Ensembles of Proteins

The motions of biological macromolecules are tightly coupled to their functions. However, while the study of fast motions has become increasingly feasible in recent years, the study of slower, biologically important motions remains difficult. Here, we present a method to construct native state ensembles of proteins by the combination of physical force fields and experimental data through modern statistical methodology. As an example, we use NMR residual dipolar couplings to determine a native state ensemble of the extensively studied third immunoglobulin binding domain of protein G (GB3). The ensemble accurately describes both local and nonlocal backbone fluctuations as judged by its reproduction of complementary experimental data. While it is difficult to assess precise time-scales of the observed motions, our results suggest that it is possible to construct realistic conformational ensembles of biomolecules very efficiently. The approach may allow for a dramatic reduction in the computational as well as experimental resources needed to obtain accurate conformational ensembles of biological macromolecules in a statistically sound manner.

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Probe design for expression arrays using OligoWiz

Since all measurements from a DNA microarray is dependant on the probes used, a good choice of probes is of vital importance when designing custom micro-arrays. This chapter describes how to design expression arrays using the "OligoWiz" software suite. The general desired features of good probes and the issues which probe design must address are introduced and a conceptual (rather than mathematical) description of how OligoWiz scores the quality of the potential probes is presented. This is followed by a detailed step-by-step guide to designing expression arrays with OligoWiz.

Proteome reference maps of the Lotus japonicus nodule and root

Legume symbiosis with rhizobia results in the formation of a specialized organ, the root nodule, where atmospheric dinitrogen is reduced to ammonia. In Lotus japonicus (Lotus), several genes involved in nodule development or nodule function have been defined using biochemistry, genetic approaches, and high throughput transcriptomics. We have employed proteomics to further understand nodule development. Two developmental stages representing nodules prior to nitrogen fixation (white) and mature nitrogen fixing nodules (red) were compared with roots. In addition, the proteome of a spontaneous nodule formation mutant (snf1) was determined. From nodules and roots, 780 and 790 protein spots from 2D gels were identified and approximately 45% of the corresponding unique gene accessions were common. Including a previous proteomics set from Lotus pod and seed, the common gene accessions were decreased to 7%. Interestingly, an indication of more pronounced post translational modifications in nodules than in roots was determined. Between the two nodule developmental stages, higher levels of pathogen related 10 proteins, HSP's, and proteins involved in redox processes were found in white nodules, suggesting a higher stress level at this developmental stage. In contrast, protein spots corresponding to nodulins such as...
leghemoglobin, asparagine synthetase, sucrose synthase, and glutamine synthetase were prevalent in red nodules. The distinct biochemical state of nodules was further highlighted by the conspicuous presence of several nitrilases, ascorbate metabolic enzymes and putative rhizobial effectors.
Quality scores for 32,000 genomes

Background
More than 80% of the microbial genomes in GenBank are of ‘draft’ quality (12,553 draft vs. 2,679 finished, as of October, 2013). We have examined all the microbial DNA sequences available for complete, draft, and Sequence Read Archive genomes in GenBank as well as three other major public databases, and assigned quality scores for more than 30,000 prokaryotic genome sequences.

Results
Scores were assigned using four categories: the completeness of the assembly, the presence of full-length rRNA genes, tRNA composition and the presence of a set of 102 conserved genes in prokaryotes. Most (~88%) of the genomes had quality scores of 0.8 or better and can be safely used for standard comparative genomics analysis. We compared genomes across factors that may influence the score. We found that although sequencing depth coverage of over 100x did not ensure a better score, sequencing read length was a better indicator of sequencing quality. With few exceptions, most of the 30,000 genomes have nearly all the 102 essential genes.

Conclusions
The score can be used to set thresholds for screening data when analyzing “all published genomes” and reference data is either not available or not applicable. The scores highlighted organisms for which commonly used tools do not perform well. This information can be used to improve tools and to serve a broad group of users as more diverse organisms are sequenced. Unexpectedly, the comparison of predicted tRNAs across 15,000 high quality genomes showed that anticodons beginning with an ‘A’ (codons ending with a ‘U’) are almost non-existent, with the exception of one arginine codon (CGU); this has been noted previously in the literature for a few genomes, but not with the depth found here.

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Rapid whole genome sequencing for the detection and characterization of microorganisms directly from clinical samples. Whole genome sequencing (WGS) is becoming available as a routine tool for clinical microbiology. If applied directly on clinical samples this could further reduce diagnostic time and thereby improve control and treatment. A major bottleneck is the availability of fast and reliable bioinformatics tools. This study was conducted to evaluate the applicability of WGS directly on clinical samples and to develop easy-to-use bioinformatics tools for analysis of the sequencing data. Thirty-five random urine samples from patients with suspected urinary tract infections were examined using conventional microbiology, WGS of isolated bacteria and by directly sequencing on pellets from the urine. A rapid method for analyzing the sequence data was developed. Bacteria were cultivated from 19 samples, but only in pure culture from 17. WGS improved the identification of the cultivated bacteria and almost complete agreement was observed between phenotypic and predicted antimicrobial susceptibility. Complete agreement was observed between species identification, multi-locus-sequence typing and phylogenetic relationship for the Escherichia coli and Enterococcus faecalis isolates when comparing the results of WGS of cultured isolates and directly from the urine samples. Sequencing directly from the urine enabled bacterial identification in polymicrobial samples. Additional putative pathogenic strains were observed in some culture negative samples. WGS directly on clinical samples can provide clinically relevant information and drastically reduce diagnostic time. This may prove very useful, but the need for data analysis is still a hurdle to clinical implementation. To overcome this problem a publicly available bioinformatics tool was developed in this study.

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Real-time whole-genome sequencing for routine typing, surveillance, and outbreak detection of verotoxigenic Escherichia coli.

Fast and accurate identification and typing of pathogens are essential for effective surveillance and outbreak detection. The current routine procedure is based on a variety of techniques, making the procedure laborious, time-consuming, and expensive. With whole-genome sequencing (WGS) becoming cheaper, it has huge potential in both diagnostics and routine surveillance. The aim of this study was to perform a real-time evaluation of WGS for routine typing and surveillance of verocytotoxin-producing Escherichia coli (VTEC). In Denmark, the Statens Serum Institut (SSI) routinely receives all suspected VTEC isolates. During a 7-week period in the fall of 2012, all incoming isolates were concurrently subjected to WGS using IonTorrent PGM. Real-time bioinformatics analysis was performed using web-tools (www.genomicepidemiology.org) for species determination, multilocus sequence type (MLST) typing, and determination of phylogenetic relationship, and a specific VirulenceFinder for detection of E. coli virulence genes was developed as part of this study. In total, 46 suspected VTEC isolates were characterized in parallel during the study. VirulenceFinder proved successful in detecting virulence genes included in routine typing, explicitly verocytotoxin 1 (vtx1), verocytotoxin 2 (vtx2), and intimin (eae), and also detected additional virulence genes. VirulenceFinder is also a robust method for assigning verocytotoxin (vtx) subtypes. A real-time clustering of isolates in agreement with the epidemiology was established from WGS, enabling discrimination between sporadic and outbreak isolates. Overall, WGS typing produced results faster and at a lower cost than the current routine. Therefore, WGS typing is a superior alternative to conventional typing strategies. This approach may also be applied to typing and surveillance of other pathogens.

The phage-shock protein (Psp) system is believed to manage membrane stress in all Enterobacteriaceae and has recently emerged as being important for virulence in several pathogenic species of this phylum. The core of the Psp system consists of the pspA-D operon and the distantly located pspG gene. In Salmonella enterica serovar Typhimurium (S. Typhimurium), it has recently been reported that PspA is essential for systemic infection of mice, but only in NRAMP1(+) mice, signifying that attenuation is related to coping with divalent cation starvation in the intracellular environment. In the present study, we investigated the contribution of individual psp genes to virulence of S. Typhimurium. Interestingly, deletion of the whole pspA-D set of genes caused attenuation in both NRAMP1(+) and NRAMP1(-) mice, indicating that
one or more of the psp genes contribute to virulence independently of NRAMP1 expression in the host. Investigations of single gene mutants showed that knock out of pspB reduced virulence in both types of mice, while deletion of pspA only caused attenuation in NRAMP1(+) mice, and deletion of pspD had a minor effect in NRAMP1(-) mice, while deletions of either pspC or pspG did not affect virulence. Experiments addressed at elucidating the role of PspB in virulence revealed that PspB is dispensable for uptake to and intracellular replication in cultured macrophages and resistance to complement-induced killing. Furthermore, the Psp system of S. Typhimurium was dispensable during pIV-induced secretin stress. In conclusion, our results demonstrate that removal of PspB reduces virulence in S. Typhimurium independently of host NRAMP1 expression, demonstrating that PspB has roles in intra-host survival distinct from the reported contributions of PspA.
Rescue of the highly virulent classical swine fever virus strain "Koslov" from cloned cDNA and first insights into genome variations relevant for virulence

Classical swine fever virus (CSFV) strain "Koslov" is highly virulent with a mortality rate of up to 100% in pigs. In this study, we modified non-functional cDNAs generated from the blood of Koslov virus infected pigs by site-directed mutagenesis, removing non-synonymous mutations step-by-step, thereby producing genomes encoding the consensus amino acid sequence. Viruses rescued from the construct corresponding to the inferred parental form were highly virulent, when tested in pigs, with infected animals displaying pronounced clinical symptoms leading to high mortality. The reconstruction therefore gave rise to a functional cDNA corresponding to the highly virulent Koslov strain of CSFV. It could be demonstrated that two single amino acid changes (S763L and P968H) in the surface structural protein E2 resulted in attenuation in the porcine infection system while another single amino acid change within the nonstructural protein NS3 (D2183G) reduced virus growth within cells in vitro.

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RNA-protein interactions: an overview.

RNA binding proteins (RBPs) are key players in the regulation of gene expression. In this chapter we discuss the main protein-RNA recognition modes used by RBPs in order to regulate multiple steps of RNA processing. We discuss traditional and state-of-the-art technologies that can be used to study RNAs bound by individual RBPs, or vice versa, for both in vitro and in vivo methodologies. To help highlight the biological significance of RBP mediated regulation, online resources on experimentally verified protein-RNA interactions are briefly presented. Finally, we present the major tools to computationally infer RNA binding sites according to the modeling features and to the unsupervised or supervised frameworks that are adopted. Since some RNA binding site search algorithms are derived from DNA binding site search algorithms, we discuss the commonalities and novelties introduced to handle both sequence and structural features uniquely characterizing protein-RNA interactions.

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Robust Estimation of Diffusion-Optimized Ensembles for Enhanced Sampling

The multicanonical, or flat-histogram, method is a common technique to improve the sampling efficiency of molecular simulations. The idea is that free-energy barriers in a simulation can be removed by simulating from a distribution where all values of a reaction coordinate are equally likely, and subsequently reweight the obtained statistics to recover the Boltzmann distribution at the temperature of interest. While this method has been successful in practice, the choice of a flat distribution is not necessarily optimal. Recently, it was proposed that additional performance gains could be obtained by taking the position-dependent diffusion coefficient into account, thus placing greater emphasis on regions diffusing slowly. Although some promising examples of applications of this approach exist, the practical usefulness of the method has been hindered by the difficulty in obtaining sufficiently accurate estimates of the diffusion coefficient. Here, we present a simple, yet robust solution to this problem. Compared to current state-of-the-art procedures, the new estimation method requires an order of magnitude fewer data to obtain reliable estimates, thus broadening the potential scope in which this technique can be applied in practice.
Size of quorum sensing communities

Ensembles of bacteria are able to coordinate their phenotypic behavior in accordance with the size, density, and growth state of the ensemble. This is achieved through production and exchange of diffusible signal molecules in a cell-cell regulatory system termed quorum sensing. In the generic quorum sensor a positive feedback in the production of signal molecules defines the conditions at which the collective behavior switches on. In spite of its conceptual simplicity, a proper measure of biofilm colony “size” appears to be lacking. We establish that the cell density multiplied by a geometric factor which incorporates the boundary conditions constitutes an appropriate size measure. The geometric factor is the square of the radius for a spherical colony or a hemisphere attached to a reflecting surface. If surrounded by a rapidly exchanged medium, the geometric factor is divided by three. For a disk-shaped biofilm the geometric factor is the horizontal dimension multiplied by the height, and the square of the height of the biofilm if there is significant flow above the biofilm. A remarkably simple factorized expression for the size is obtained, which separates the all-or-none ignition caused by the positive feedback from the smoother activation outside the switching region.
Bacteria use small signaling molecules to communicate in a process termed "quorum sensing" (QS), which enables the coordination of survival strategies, such as production of virulence factors and biofilm formation. In Gram-negative bacteria, these signaling molecules are a series of N-acylated L-homoserine lactones. With the goal of identifying non-native compounds capable of modulating bacterial QS, a virtual library of N-dipeptido L-homoserine lactones was screened in silico with two different crystal structures of LasR. The 30 most promising hits were synthesized on HMBA-functionalized PEGA resin and released through an efficient acid-mediated cyclative release mechanism. Subsequent screening for modulation of QS in Pseudomonas aeruginosa and E. coli identified six moderately strong activators. A follow-up library designed from the preliminary derived structure–activity relationships was synthesized and evaluated for their ability to activate the QS system in this bacterium. This resulted in the identification of another six QS activators (two with low micromolar activity) thus illuminating structural features required for QS modulation.
Solving the Problem of Comparing Whole Bacterial Genomes across Different Sequencing Platforms

Whole genome sequencing (WGS) shows great potential for real-time monitoring and identification of infectious disease outbreaks. However, rapid and reliable comparison of data generated in multiple laboratories and using multiple technologies is essential. So far studies have focused on using one technology because each technology has a
systematic bias making integration of data generated from different platforms difficult. We developed two different procedures for identifying variable sites and inferring phylogenies in WGS data across multiple platforms. The methods were evaluated on three bacterial data sets and sequenced on three different platforms (Illumina, 454, Ion Torrent). We show that the methods are able to overcome the systematic biases caused by the sequencers and infer the expected phylogenies. It is concluded that the cause of the success of these new procedures is due to a validation of all informative sites that are included in the analysis. The procedures are available as web tools.

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Scopus rating (2013): SJR 1.74 SNIP 1.147 CiteScore 3.94
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.945 SNIP 1.142 CiteScore 4.15
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 2.369 SNIP 1.23 CiteScore 4.58
ISI indexed (2011): ISI indexed no
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 2.631 SNIP 1.161
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 2.473 SNIP 0.985
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 2.323 SNIP 0.96
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 1.289 SNIP 0.525
Web of Science (2006): Indexed yes
Speciation with gene flow in equids despite extensive chromosomal plasticity

Significance Thirty years after the first DNA fragment from the extinct quagga zebra was sequenced, we set another milestone in equine genomics by sequencing its entire genome, along with the genomes of the surviving equine species. This extensive dataset allows us to decipher the genetic makeup underlying lineage-specific adaptations and reveal the complex history of equine speciation. We find that Equus first diverged in the New World, spread across the Old World 2.1–3.4 Mya, and finally experienced major demographic expansions and collapses coinciding with past climate changes. Strikingly, we find multiple instances of hybridization throughout the equine tree, despite extremely divergent chromosomal structures. This contrasts with theories promoting chromosomal incompatibilities as drivers for the origin of equine species.

General information

State: Published
Organisations: Functional Human Variation, Department of Systems Biology, Center for Biological Sequence Analysis, Metagenomics, University of Copenhagen, University of California, University of Kentucky, Cornell University, King Saud University, Tierpark Berlin, Copenhagen Zoo
Number of pages: 6
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Publication date: 2014
Main Research Area: Technical/natural sciences

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Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 6.767 SNIP 2.682 CiteScore 8.84
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 6.853 SNIP 2.725 CiteScore 8.86
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 6.989 SNIP 2.73 CiteScore 9.5
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
Studies on genetic diversity of bovine viral diarrhea viruses in Danish cattle herds

Scandinavian countries have successfully pursued bovine viral diarrhea virus (BVDV) eradication without the use of vaccines. In Denmark, control and eradication of BVDV were achieved during the last two decades, but occasionally new BVDV infections are detected in some Danish cattle herds. The aim of this study was to determine recent BVDV subtypes isolated from 4 Danish herds (A, B, C, and D) isolated in 2009–2012 and to analyze the genetic variation of these isolates within the same herd and its relation with those of other herds. The results showed that three herds (B, C, D) were BVDV 1-b and only one herd (herd A) was BVDV 1-d, no other subtypes were detected. The deduced E2 amino acids result showed a high identity percent (99–100 %) between isolates originating from the same herd, but with higher variation compared to isolates of the other herds. Some of these new Danish strains have closer relationship to BVDVs from outside Denmark than to older Danish strains indicating that these are new introductions to Denmark. In conclusion, BVDV-1 subtypes recently detected in Denmark were only subtypes 1b and 1d, and BVDV infections established in a herd is genetically stable over a long time period.

General information
State: Published
Synthetic Promoter Library for Modulation of Actinorhodin Production in Streptomyces coelicolor A3(2)

The objective of this study was the application of the synthetic promoter library (SPL) technology for modulation of actinorhodin production in Streptomyces coelicolor A3(2). The SPL technology was used to optimize the expression of a pathway specific positive transcriptional regulator Actl orf4, which activates the transcription of the S. coelicolor actinorhodin biosynthetic gene cluster. The native actl orf4 promoter was replaced with synthetic promoters, generating a S. coelicolor library with a broad range of expression levels of actl orf4. The resulting library was screened based on the yield of actinorhodin. Selected strains were further physiologically characterized. One of the strains from the library, ScoSPL20, showed considerably higher yield of actinorhodin and final actinorhodin titer, compared to S. coelicolor wild type and S. coelicolor with actl orf4 expressed from a strong constitutive promoter. ScoSPL20 demonstrated exceptional productivity despite having a comparatively weak expression from the promoter. Interestingly, the ScoSPL20 promoter was activated at a much earlier stage of growth compared to the wild type, demonstrating the advantage of fine-tuning and temporal tuning of gene expression in metabolic engineering. Transcriptome studies were performed in exponential and actinorhodin-producing phase of growth to compare gene expression between ScoSPL20 and the wild type. To our knowledge, this is the first successful application of the SPL technology for secondary metabolite production in filamentous bacteria.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Integrative Systems Biology, Regulatory Genomics, Chalmers University of Technology
Authors: Sohoni, S. V. (Intern), Fazio, A. (Intern), Workman, C. (Intern), Mijakovic, I. (Ekstern), Eliasson Lantz, A. (Intern)
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Main Research Area: Technical/natural sciences

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Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.414 SNIP 1.131 CiteScore 3.32
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.545 SNIP 1.141 CiteScore 3.54
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.74 SNIP 1.147 CiteScore 3.94
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.945 SNIP 1.142 CiteScore 4.15
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 2.369 SNIP 1.23 CiteScore 4.58
ISI indexed (2011): ISI indexed no
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 2.631 SNIP 1.161
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BFI (2009): BFI-level 1
Scopus rating (2009): SJR 2.473 SNIP 0.985
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 2.323 SNIP 0.96
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 1.289 SNIP 0.525
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Systematic Evaluation of the Prognostic Impact and Intratumour Heterogeneity of Clear Cell Renal Cell Carcinoma Biomarkers

Background: Candidate biomarkers have been identified for clear cell renal cell carcinoma (ccRCC) patients, but most have not been validated. Objective: To validate published ccRCC prognostic biomarkers in an independent patient cohort and to assess intratumour heterogeneity (ITH) of the most promising markers to guide biomarker optimisation. Design, setting, and participants: Cancer-specific survival (CSS) for each of 28 identified genetic or transcriptomic biomarkers was assessed in 350 ccRCC patients. ITH was interrogated in a multiregion biopsy data set of 10 ccRCCs. Outcome measurements and statistical analysis: Biomarker association with CSS was analysed by univariate and multivariate analyses. Results and limitations: A total of 17 of 28 biomarkers (TP53 mutations; amplifications of chromosomes 8q, 12, 20q11.21q13.32, and 20 and deletions of 4p, 9p, 9p21.3p24.1, and 22q; low EDNRB and TSPAN7 expression and six gene expression signatures) were validated as predictors of poor CSS in univariate analysis. Tumour stage and the ccB expression signature were the only independent predictors in multivariate analysis. ITH of the ccB signature was identified in 8 of 10 tumours. Several genetic alterations that were significant in univariate analysis were enriched in samples expressing the ccB signature. The study may be underpowered to validate low-prevalence biomarkers. Conclusions: The ccB signature was the only independent prognostic biomarker. Enrichment of multiple poor prognosis genetic alterations in ccB samples indicated that several events may be required to establish this aggressive phenotype, catalysed in some tumours by chromosomal instability. Multiregion assessment may improve the precision of this biomarker. Patient summary: We evaluated the ability of published biomarkers to predict the survival of patients with clear cell kidney cancer in an independent patient cohort. Only one molecular test adds prognostic information to routine clinical assessments. This marker showed good and poor prognosis results within most individual cancers. Future biomarkers need to consider variation within tumours to improve accuracy.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Cancer Systems Biology, Cancer Research UK, London Research Institute, Royal Marsden Hospital
Authors: Gulati, S. (Ekstern), Martinez, P. (Ekstern), Joshi, T. (Intern), Birkbak, N. J. (Intern), Santos, C. R. (Ekstern), Rowan, A. J. (Ekstern), Pickering, L. (Ekstern), Gore, M. (Ekstern), Larkin, J. (Ekstern), Szallasi, Z. I. (Intern), Bates, P. A. (Ekstern), Swanton, C. (Ekstern), Gerlinger, M. (Ekstern)
Number of pages: 13
Pages: 936-948
Targeting the genetic complexity within adapting RNA virus populations
T-bet and Eomes Are Differentially Linked to the Exhausted Phenotype of CD8+ T Cells in HIV Infection

CD8+ T cell exhaustion represents a major hallmark of chronic HIV infection. Two key transcription factors governing CD8+ T cell differentiation, T-bet and Eomesodermin (Eomes), have previously been shown in mice to differentially regulate T cell exhaustion in part through direct modulation of PD-1. Here, we examined the relationship between these transcription factors and the expression of several inhibitory receptors (PD-1, CD160, and 2B4), functional characteristics and memory differentiation of CD8+ T cells in chronic and treated HIV infection. The expression of PD-1, PD-1, CD160, and 2B4 on total CD8+ T cells was elevated in chronically infected individuals and highly associated with a T-betdimEomeshi expressional profile. Interestingly, both resting and activated HIV-specific CD8+ T cells in chronic infection were almost exclusively T-betdimEomeshi cells, while CMV-specific CD8+ T cells displayed a balanced expression pattern of T-bet and Eomes. The T-betdimEomeshi virus-specific CD8+ T cells did not show features of terminal differentiation, but rather a transitional memory phenotype with poor polyfunctional (effector) characteristics. The transitional and exhausted phenotype of HIV-specific CD8+ T cells was longitudinally related to persistent Eomes expression after antiretroviral therapy (ART) initiation. Strikingly, these characteristics remained stable up to 10 years after ART initiation. This study supports the concept that poor human viral-specific CD8+ T cell functionality is due to an inverse expression balance between T-bet and Eomes, which is not reversed despite long-term viral control through ART. These results aid to explain the inability of HIV-specific CD8+ T cells to control the viral replication post-ART cessation.
Temporal disease trajectories condensed from population-wide registry data covering 6.2 million patients

A key prerequisite for precision medicine is the estimation of disease progression from the current patient state. Disease correlations and temporal disease progression (trajectories) have mainly been analysed with focus on a small number of diseases or using large-scale approaches without time consideration, exceeding a few years. So far, no large-scale studies have focused on defining a comprehensive set of disease trajectories. Here we present a discovery-driven analysis of temporal disease progression patterns using data from an electronic health registry covering the whole population of Denmark. We use the entire spectrum of diseases and convert 14.9 years of registry data on 6.2 million patients into 1,171 significant trajectories. We group these into patterns centred on a small number of key diagnoses such as...
as chronic obstructive pulmonary disease (COPD) and gout, which are central to disease progression and hence important to diagnose early to mitigate the risk of adverse outcomes. We suggest such trajectory analyses may be useful for predicting and preventing future diseases of individual patients.

**General information**

**State:** Published

**Organisations:** Department of Systems Biology, Center for Biological Sequence Analysis, University of New Mexico, University of Gothenburg, University of Copenhagen, Copenhagen University Hospital

**Authors:** Jensen, A. B. (Intern), Moseley, P. (Ekstern), Oprea, T. (Intern), Ellesee, S. G. (Ekstern), Eriksson, R. (Intern), Schmock, H. (Ekstern), Jensen, P. B. (Forskerdatabase), Jensen, L. J. (Intern), Brunak, S. (Intern)

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**Main Research Area:** Technical/natural sciences

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- BFI (2016): BFI-level 2
- Scopus rating (2016): CiteScore 11.8 SJR 6.399 SNIP 2.995
- Web of Science (2016): Indexed yes
- BFI (2015): BFI-level 1
- Scopus rating (2015): SJR 6.364 SNIP 3.053 CiteScore 11.23
- Web of Science (2015): Indexed yes
- BFI (2014): BFI-level 1
- Scopus rating (2014): SJR 6.331 SNIP 3.091 CiteScore 10.77
- Web of Science (2014): Indexed yes
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- Scopus rating (2013): SJR 5.967 SNIP 2.776 CiteScore 9.85
- ISI indexed (2013): ISI indexed yes
- Web of Science (2013): Indexed yes
- Scopus rating (2012): SJR 5.586 SNIP 2.724 CiteScore 8.32
- ISI indexed (2012): ISI indexed yes
- Web of Science (2012): Indexed yes
- Scopus rating (2011): SJR 3.122 SNIP 1.544 CiteScore 4.44
- ISI indexed (2011): ISI indexed no
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**Source-ID:** 2193127482

**Publication:** Research - peer-review › Journal article – Annual report year: 2014

**The comparison of thrombocytosis and platelet-lymphocyte ratio as potential prognostic markers in colorectal cancer**

The aim of the present study was to analyse the preoperative platelet count and the platelet-lymphocyte ratio (PLR) in patients with colorectal cancer (CRC) of different stages and with hepatic metastasis of CRC (mCRC) and to compare these factors as potential prognostic markers. Clinicopathological data of 10 years were collected retrospectively from 336
patients with CRC and 118 patients with mCRC. Both in the CRC and the mCRC group overall survival (OS) was significantly worse in patients who had elevated platelet count (hazard ratio [HR] = 2.2, p <0.001 and HR = 2.9, p = 0.018, respectively). Multivariate analysis indicated that elevated platelet count was an independent prognostic factor of CRC (HR = 1.7, p = 0.035) and mCRC (HR = 3.1, p = 0.017). Disease-free survival (DFS) was significantly worse in patients with elevated platelet count in the CRC group (HR = 2.0, p = 0.011). In the multivariate analysis the PLR was not a prognostic factor in either of the two cohorts (HR = 0.92, p <0.001 and HR = 0.89, p = 0.789, respectively). The platelet count is a valuable prognostic marker for the survival in patients both with CRC and mCRC while the PLR is not prognostic in either group.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Cancer Systems Biology, Harvard University, Semmelweis University, Tumorgenetika Human Biospecimen Collection and Research Company, Uzsoki Memorial Hospital
Authors: Baranyai, Z. (Ekstern), Krzystanek, M. (Intern), Josa, V. (Ekstern), Dede, K. (Ekstern), Ágoston, E. (Ekstern), Szasz, A. M. (Ekstern), Sinko, D. (Ekstern), Szarvas, V. (Ekstern), Salamon, F. (Ekstern), Eklund, A. C. (Intern), Szallasi, Z. I. (Intern), Jakab, F. (Ekstern)
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Main Research Area: Technical/natural sciences

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BFI (2016): BFI-level 1
Scopus rating (2016): SJR 2.099 SNIP 1.32 CiteScore 4.03
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.106 SNIP 1.343 CiteScore 4.19
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.84 SNIP 1.287 CiteScore 3.74
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 2.409 SNIP 1.51 CiteScore 4.94
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 2.485 SNIP 1.654 CiteScore 4.88
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 2.046 SNIP 1.444 CiteScore 4.03
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.829 SNIP 1.272
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.752 SNIP 1.274
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 1.672 SNIP 1.149
Scopus rating (2007): SJR 1.422 SNIP 1.1
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 1.299 SNIP 1.058
Scopus rating (2005): SJR 1.205 SNIP 1.033
Scopus rating (2004): SJR 1.536 SNIP 1.186
Scopus rating (2003): SJR 1.678 SNIP 1.468
The effect of a short-term high-fat overfeeding on plasma levels of amino acids in young, healthy men with low or normal birth weight

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Duke University, Copenhagen University Hospital
Publication date: 2014
Main Research Area: Technical/natural sciences
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Publication: Research - peer-review › Conference abstract for conference – Annual report year: 2014

The effect of a short-term high-fat overfeeding on plasma levels of amino acids in young, healthy men with low or normal birth weight

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Duke University, Copenhagen University Hospital
Publication date: 2014
Main Research Area: Technical/natural sciences
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Publication: Research - peer-review › Conference abstract for conference – Annual report year: 2014

The genetic prehistory of the New World Arctic
The New World Arctic, the last region of the Americas to be populated by humans, has a relatively well-researched archaeology, but an understanding of its genetic history is lacking. We present genome-wide sequence data from ancient and present-day humans from Greenland, Arctic Canada, Alaska, Aleutian Islands, and Siberia. We show that Paleo-Eskimos (similar to 3000 BCE to 1300 CE) represent a migration pulse into the Americas independent of both Native American and Inuit expansions. Furthermore, the genetic continuity characterizing the Paleo-Eskimo period was interrupted by the arrival of a new population, representing the ancestors of present-day Inuit, with evidence of past gene flow between these lineages. Despite periodic abandonment of major Arctic regions, a single Paleo-Eskimo metapopulation likely survived in near-isolation for more than 4000 years, only to vanish around 700 years ago.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Behavioral Phenomics, Metagenomics, University of Copenhagen, Pennsylvania State University, Harvard Medical School, National Museum of Denmark, University of Toronto, National Museum of Natural History, Smithsonian Institution, Uppsala University, Aarhus University, University of California, Irvine, Max Planck Institute, Memorial University of Newfoundland, University of Western Ontario, University of Cambridge, University of Aberdeen, University of Tartu, Washington State University,
The genome of a Late Pleistocene human from a Clovis burial site in western Montana.

Clovis, with its distinctive biface, blade and osseous technologies, is the oldest widespread archaeological complex defined in North America, dating from 11,100 to 10,700 (14)C years before present (bp) (13,000 to 12,600 calendar years bp). Nearly 50 years of archaeological research point to the Clovis complex as having developed south of the North American ice sheets from an ancestral technology. However, both the origins and the genetic legacy of the people who manufactured Clovis tools remain under debate. It is generally believed that these people ultimately derived from Asia and were directly related to contemporary Native Americans. An alternative, Solutrean, hypothesis posits that the Clovis predecessors emigrated from southwestern Europe during the Last Glacial Maximum. Here we report the genome sequence of a male infant (Anzick-1) recovered from the Anzick burial site in western Montana. The human bones date to 10,705 ± 35 (14)C years bp (approximately 12,707-12,556 calendar years bp) and were directly associated with Clovis tools. We sequenced the genome to an average depth of 14.4× and show that the gene flow from the Siberian Upper Palaeolithic Mal’ta population into Native American ancestors is also shared by the Anzick-1 individual and thus happened before 12,600 years bp. We also show that the Anzick-1 individual is more closely related to all indigenous American populations than to any other group. Our data are compatible with the hypothesis that Anzick-1 belonged to a population directly ancestral to many contemporary Native Americans. Finally, we find evidence of a deep divergence in Native American populations that predates the Anzick-1 individual.
The Genome of the Chicken DT40 Bursal Lymphoma Cell Line

The chicken DT40 cell line is a widely used model system in the study of multiple cellular processes due to the efficiency of homologous gene targeting. The cell line was derived from a bursal lymphoma induced by avian leukosis virus infection. In this study we characterized the genome of the cell line using whole genome shotgun sequencing and single nucleotide polymorphism array hybridization. The results indicate that wild-type DT40 has a relatively normal karyotype, except for whole chromosome copy number gains, and no karyotype variability within stocks. In a comparison to two domestic chicken genomes and the Gallus gallus reference genome, we found no unique mutational processes shaping the DT40 genome except for a mild increase in insertion and deletion events, particularly deletions at tandem repeats. We mapped coding sequence mutations that are unique to the DT40 genome; mutations inactivating the PIK3R1 and ATRX genes likely contributed to the oncogenic transformation. In addition to a known avian leukosis virus integration in the MYC gene, we detected further integration sites that are likely to de-regulate gene expression. The new findings support the hypothesis that DT40 is a typical transformed cell line with a relatively intact genome; therefore, it is well-suited to the role of a model system for DNA repair and related processes. The sequence data generated by this study, including a searchable de novo genome assembly and annotated lists of mutated genes, will support future research using this cell line.

General information
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Hungarian Academy of Sciences, Eötvös Loránd University, Cancer Research UK, London Research Institute
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BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.441 SNIP 0.633 CiteScore 2.05
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.792 SNIP 0.746 CiteScore 2.48
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.425 SNIP 0.728 CiteScore 2.03
ISI indexed (2013): ISI indexed yes
Scopus rating (2012): SJR 1.617 SNIP 0.667
Original language: English
Electronic versions: 2231.full.pdf
The interplay of sequence conservation and T cell immune recognition
Predicting which peptides can elicit a T cell response (i.e. are immunogenic) is of great importance for many immunological studies. While it is clear that MHC binding is a necessary requirement for peptide immunogenicity, other variables exist that are incompletely understood. In this study we examined the hypothesis that conservation of a peptide in bacteria that are part of the healthy human microbiome leads to a reduced level of immunogenicity due to tolerization of T cells to the commensal bacteria. This was done by comparing experimentally characterized T cell epitope recognition data from the Immune Epitope Database with their conservation in the human microbiome. Indeed, we did see a lower immunogenicity for conserved peptides conserved. While many aspects how this conservation comparison is done require further optimization, this is a first step towards a better understanding T cell recognition of peptides in bacterial pathogens is influenced by their conservation in commensal bacteria. If the further work proves that this approach is successful, the degree of overlap of a peptide with the human proteome or microbiome could be added to the arsenal of tools available to assess peptide immunogenicity.

The microbiome of New World vultures
Vultures are scavengers that fill a key ecosystem niche, in which they have evolved a remarkable tolerance to bacterial toxins in decaying meat. Here we report the first deep metagenomic analysis of the vulture microbiome. Through face and gut comparisons of 50 vultures representing two species, we demonstrate a remarkably conserved low diversity of gut microbial flora. The gut samples contained an average of 76 operational taxonomic units (OTUs) per specimen, compared with 528 OTUs on the facial skin. Clostridia and Fusobacteria, widely pathogenic to other vertebrates, dominate the vulture's gut microbiota. We reveal a likely faecal-oral-gut route for their origin. DNA of prey species detectable on facial swabs was completely degraded in the gut samples from most vultures, suggesting that the gastrointestinal tracts of vultures are extremely selective. Our findings show a strong adaption of vultures and their bacteria to their food source, exemplifying a specialized host-microbial alliance.
This review discusses the role of extracellular matrix (ECM) quality in the pathogenesis of pulmonary fibrosis (PF). In PF, the highly ordered structure of collagens and elastin within the ECM of the lung is severely disrupted and lacks its original tissue quality. Discussions about the ECM have focused on the role of protein quantity in relation to the progression of PF, while the importance of lung ECM quality, defined by the levels of ECM protein modifications and by the protein distribution in lung tissue, has not been properly addressed. The quality and function of proteins may be altered by different post-translational modifications (PTMs), such as crosslinking, proteolytic cleavage, citrullination, misfolding and glycosylation. This paper is the first to review key data from the literature related to the lung ECM at the molecular level, relate these to changes observed at a macroscopic level and evaluate which PTMs most likely contribute to PF. This paper also reviews the role of novel neo-epitope-specific biomarkers in the early diagnosis and prognosis of fibrotic disorders. We discuss and argue that the altered quality of the individual ECM proteins contributes to the progression of PF and may also lead to the increased quantity of lung proteins. Thus, both quantity and quality appear to be of utmost importance.
The Role of the st313-td Gene in Virulence of Salmonella Typhimurium ST313

Multidrug-resistant Salmonella enterica serovar Typhimurium ST313 has emerged in sub-Saharan Africa causing severe infections in humans. Therefore, it has been speculated that this specific sequence type, ST313, carries factors associated with increased pathogenicity. We assessed the role in virulence of a gene with a yet unknown function, st313-td, detected in ST313 through comparative genomics. Additionally, the structure of the genomic island ST313-GI, harbouring the gene was determined. The gene st313-td was cloned into wild type S. Typhimurium 4/74 (4/74-C) as well as knocked out in S. Typhimurium ST313 02-03/002 (Delta st313-td) followed by complementation (02-03/002-C). Delta st313-td was less
virulent in mice following i.p. challenge than the wild type and this phenotype could be partly complemented in trans, indicating that st313-td plays a role during systemic infection. The gene st313-td was shown not to affect invasion of cultured epithelial cells, while the absence of the gene significantly affects uptake and intracellular survival within macrophages. The gene st313-td was proven to be strongly associated to invasiveness, harboured by 92.5% of S. Typhimurium blood isolates (n = 82) and 100% of S. Dublin strains (n = 50) analysed. On the contrary, S. Typhimurium isolates of animal and food origin (n = 82) did not carry st313-td. Six human, non-blood isolates of S. Typhimurium from Belarus, China and Nepal harboured the gene and belonged to sequence types ST398 and ST19. Our data showed a global presence of the st313-td gene and in other sequence types than ST313. The gene st313-td was shown to be expressed during logarithmic phase of growth in 14 selected Salmonella strains carrying the gene. This study reveals that st313-td plays a role in S. Typhimurium ST313 pathogenesis and adds another chapter to understanding of the virulence of S. Typhimurium and in particular of the emerging sequence type ST313.

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The transcriptome of corona radiata cells from individual MII oocytes that after ICSI developed to embryos selected for transfer: PCOS women compared to healthy women

Corona radiata cells (CRCs) refer to the fraction of cumulus cells just adjacent to the oocyte. The CRCs are closely connected to the oocyte throughout maturation and their gene expression profiles might reflect oocyte quality. Polycystic ovary syndrome (PCOS) is a common cause of infertility. It is controversial whether PCOS associate with diminished oocyte quality. The purpose of this study was to compare individual human CRC samples between PCOS patients and controls.

All patients were stimulated by the long gonadotropin-releasing hormone (GnRH) agonist protocol. The CRC samples originated from individual oocytes developing into embryos selected for transfer. CRCs were isolated in a two-step denudation procedure, separating outer cumulus cells from the inner CRCs. Extracted RNA was amplified and transcriptome profiling was performed with Human Agilent® arrays.

The transcriptomes of CRCs showed no individual genes with significant differential expression between PCOS and controls, but gene set enrichment analysis identified several cell cycle- and DNA replication pathways overexpressed in PCOS CRCs (FDR < 0.05). Five of the genes contributing to the up-regulated cell cycle pathways in the PCOS CRCs were selected for qRT-PCR validation in ten PCOS and ten control CRC samples. qRT-PCR confirmed significant up-regulation in PCOS CRCs of cell cycle progression genes HIST1H4C (FC = 2.7), UBE2C (FC = 2.6) and cell cycle related transcription factor E2F4 (FC = 2.5).

The overexpression of cell cycle-related genes and cell cycle pathways in PCOS CRCs could indicate a disturbed or delayed final maturation and differentiation of the CRCs in response to the human chorionic gonadotropin (hCG) surge. However, this had no effect on the in vitro development of the corresponding embryos. Future studies are needed to clarify whether the up-regulated cell cycle pathways in PCOS CRCs have any clinical implications.

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Thrombocytosis portends adverse prognostic significance in patients with stage II colorectal carcinoma

Thrombocytosis portends adverse prognostic significance in many types of cancers including ovarian and lung carcinoma. In this study, we determined the prevalence and prognostic significance of thrombocytosis (defined as platelet count in excess of 400 K/μl) in patients with colorectal cancer. We performed a retrospective analysis of 310 consecutive patients diagnosed at our institution between 2004 and 2013. The patients (48.7% male and 51.3% female) had a mean age of 69.9 years (+/- 12.7 years) at diagnosis. Thrombocytosis was found in a total of 25 patients, with a higher incidence in those with stage III and IV disease (14.4% of patients). Although the mean platelet count increased with the depth of tumor invasion (pT), its values remained within normal limits in the whole patient cohort. No patient with stage I cancer (n=57) had elevated platelet count at diagnosis. By contrast, five of the 78 patients (6.4%) with stage II cancer showed thrombocytosis, and four of these patients showed early recurrence and/or metastatic disease, resulting in shortened survival (they died within one year after surgery). The incidence of thrombocytosis increased to 12.2% and 20.6%, respectively, in patients with stage III and IV disease. The overall survival rate of patients with thrombocytosis was lower than those without thrombocytosis in the stage II and III disease groups, but this difference disappeared in patients with stage IV cancer who did poorly regardless of their platelet count. We concluded that thrombocytosis at diagnosis indicates adverse clinical outcome in colorectal cancer patients with stage II or III disease. This observation is especially intriguing in stage II patients because the clinical management of these patients is controversial. If our data are confirmed in larger studies, stage II colon cancer patients with thrombocytosis should be upstaged and treated as stage III/IV disease patients.
Tolerance of Whole-Genome Doubling Propagates Chromosomal Instability and Accelerates Cancer Genome Evolution

The contribution of whole-genome doubling to chromosomal instability (CIN) and tumor evolution is unclear. We use long-term culture of isogenic tetraploid cells from a stable diploid colon cancer progenitor to investigate how a genome-doubling event affects genome stability over time. Rare cells that survive genome doubling demonstrate increased tolerance to chromosome aberrations. Tetraploid cells do not exhibit increased frequencies of structural or numerical CIN per chromosome. However, the tolerant phenotype in tetraploid cells, coupled with a doubling of chromosome aberrations per cell, allows chromosome abnormalities to evolve specifically in tetraploids, recapitulating chromosomal changes in genomically complex colorectal tumors. Finally, a genome-doubling event is independently predictive of poor relapse-free survival in early-stage disease in two independent cohorts in multivariate analyses [discovery data: hazard ratio (HR), 4.70, 95% confidence interval (CI), 1.04–21.37; validation data: HR, 1.59, 95% CI, 1.05–2.42]. These data highlight an important role for the tolerance of genome doubling in driving cancer genome evolution.
The importance of intratumour genetic and functional heterogeneity is increasingly recognised as a driver of cancer progression and survival outcome. Understanding how tumour clonal heterogeneity impacts upon therapeutic outcome, however, is still an area of unmet clinical and scientific need. TRACERx (TRAcking non-small cell lung Cancer Evolution through therapy [Rx]), a prospective study of patients with primary non-small cell lung cancer (NSCLC), aims to define the evolutionary trajectories of lung cancer in both space and time through multiregion and longitudinal tumour sampling and genetic analysis. By following cancers from diagnosis to relapse, tracking the evolutionary trajectories of tumours in relation to therapeutic interventions, and determining the impact of clonal heterogeneity on clinical outcomes, TRACERx may help to identify novel therapeutic targets for NSCLC and may also serve as a model applicable to other cancer types.

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Translating inter-individual genetic variation to biological function in complex phenotypes

The key objectives of this thesis work are to decipher and prioritise observed variations among different phenotypes. With advancements in high throughput technology leading to a surge in biological data, it is imperative to analyse and interpret this information. Consequently, this thesis work examines epigenetic, genetic, transcriptomic and proteomic variations within different multifactorial diseases and this pivotal information is then annotated and associated to its corresponding phenotype. Childhood asthma and obesity are the two main phenotypic themes in this thesis.

In the first section, Chapter 1 provides an introduction to various methodologies utilised in this thesis work. Subsequently,
chapters 2, 3 and 4 in the second section, address finding causal variations in childhood asthma. Chapter 2 focuses on a genome wide association study (GWAS) performed on asthma exacerbation case cohort. This study reports a new susceptibility locus within the gene CDHR3 for exacerbation phenotype of childhood asthma. Chapter 3 of the thesis presents a pilot study, which aims at designing a candidate gene panel for childhood asthma to identify the causal variants from known asthma genes. Chapter 4 describes artificial neural network (ANN) based methodology of selecting genetic and clinical features with predictive power for childhood asthma. The goal of these studies is to understand the complex genetics of childhood asthma.

The third part of this thesis (chapters 5 and 6) focuses on various mechanisms involved in adipose depots, which is a major tissue implicated in obesity. Chapter 5 sheds light on different mechanisms that result in the replacement of metabolism efficient brown fat with the storage-type white fat in large mammals (including human) especially within the first few months following birth. The project work discussed in chapter 6 is aimed towards understanding the various underlying differences in obesity responses in fat cells from different white adipose tissue depots under diet-induced and genetic obesity by decoding the global epigenetic modifications.

The fourth section of this thesis work (chapter 7) comprises of two studies that are aimed towards genotype to phenotype mapping. The first section of chapter 7, details the usage of variations from the Danish pan-genome pilot project to comprehend the common phenotypes of the population and attempt to establish its kinship with European populations. Next, the second portion of this chapter describes a personalised genome study of an ancient genome which was conducted by calculating the genetic risk scores to unravel phenotypes.

Appendix section (Chapter 8) comprises of an integrative functional analysis study of the changing proteome and phosphor-proteome in chemotherapy resistant breast cancer cell lines with high TIMP-1 gene expression. In summary, this thesis work demonstrates applications of various omic variations at different levels of complexity and their integration using systems biology based methodologies to associate them to multifactorial phenotypes. These studies help in revealing pivotal mechanistic details concerning the phenotypes, which can be further utilized in drug designing and disease management.

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**Two ancient human genomes reveal Polynesian ancestry among the indigenous Botocudos of Brazil**
Understanding the peopling of the Americas remains an important and challenging question. Here, we present 14C dates, and morphological, isotopic and genomic sequence data from two human skulls from the state of Minas Gerais, Brazil, part of one of the indigenous groups known as ‘Botocudos’. We find that their genomic ancestry is Polynesian, with no detectable Native American component. Radiocarbon analysis of the skulls shows that the individuals had died prior to the beginning of the 19th century. Our findings could either represent genomic evidence of Polynesians reaching South America during their Pacific expansion, or European-mediated transport.

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Two randomized cross-over trials assessing the impact of dietary gluten or wholegrain on the gut microbiome and host metabolic health

Background: Gut microbiota composition and activity may be changed by dietary factors and possibly affect metabolic health. Dietary gluten and wholegrain are suggested to influence metabolism in a negative and positive direction, respectively.

Objective: Describe the design and rational as well as baseline characteristics of two human intervention studies, within the Gut, Grain and Greens (3G) Center, investigating the effects of a gluten-poor and wholegrain-rich diet on microbiota composition and metabolic health.

Design: The gluten and wholegrain studies had a randomized, controlled, cross-over design each comprising two eight-week dietary intervention periods, separated by a six-week wash-out period. Each trial included 60 men and women.
exhibiting an increased metabolic risk. In the gluten study a gluten-poor diet was compared with a gluten-rich dietary fiber-controlled diet, and in the wholegrain study a wholegrain-rich diet was compared with a refined grain diet. The control diet was identical in both studies, being concomitantly high in gluten and refined. Participants substituted all cereal products with provided intervention products which they consumed ad libitum. Before and after each intervention period, fecal samples for quantitative metagenomic analyses were collected and an examination day was conducted. The primary outcome of the gluten intervention study was changes in the gut microbiota composition, while insulin sensitivity was an additional primary outcome of the wholegrain study. Further, a number of secondary outcomes were investigated.

Results: 52 and 50 participants completed the gluten and wholegrain intervention study, respectively. Participants had slightly elevated fasting glucose levels and increased waist circumference. Biological outcomes of the two studies will be published elsewhere.

Conclusion: The studies have the potential to provide new insights into the interplay of gut microbiota and metabolic health in individuals with increased risk of developing metabolic disorders.

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Uncovering the Peptide-Binding Specificities of HLA-C: A General Strategy To Determine the Specificity of Any MHC Class I Molecule

MHC class I molecules (HLA-I in humans) present peptides derived from endogenous proteins to CTLs. Whereas the peptide-binding specificities of HLA-A and -B molecules have been studied extensively, little is known about HLA-C specificities. Combining a positional scanning combinatorial peptide library approach with a peptide-HLA-I dissociation assay, in this study we present a general strategy to determine the peptide-binding specificity of any MHC class I molecule. We applied this novel strategy to 17 of the most common HLA-C molecules, and for 16 of these we successfully generated matrices representing their peptide-binding motifs. The motifs prominently shared a conserved C-terminal primary anchor with hydrophobic amino acid residues, as well as one or more diverse primary and auxiliary anchors at P1, P2, P3, and/or P7. Matrices were used to generate a large panel of HLA-C-specific peptide-binding data and update our pan-specific NetMHCpan predictor, whose predictive performance was considerably improved with respect to peptide binding to HLA-C. The updated predictor was used to assess the specificities of HLA-C molecules, which were found to cover a more limited sequence space than HLA-A and -B molecules. Assessing the functional significance of these new tools, HLA-C*07:01 transgenic mice were immunized with stable HLA-C*07:01 binders; six of six tested stable peptide binders were immunogenic. Finally, we generated HLA-C tetramers and labeled human CD8(+) T cells and NK cells. These new resources should support future research on the biology of HLA-C molecules. The data are deposited at the Immune Epitope Database, and the updated NetMHCpan predictor is available at the Center for Biological Sequence Analysis and the Immune Epitope Database.
Upper Palaeolithic Siberian genome reveals dual ancestry of Native Americans

The origins of the First Americans remain contentious. Although Native Americans seem to be genetically most closely related to east Asians, there is no consensus with regard to which specific Old World populations they are closest to. Here we sequence the draft genome of an approximately 24,000-year-old individual (MA-1), from Mal’ta in south-central Siberia, to an average depth of 1×. To our knowledge this is the oldest anatomically modern human genome reported to date. The MA-1 mitochondrial genome belongs to haplogroup U, which has also been found at high frequency among Upper Palaeolithic and Mesolithic European hunter-gatherers, and the Y chromosome of MA-1 is basal to modern-day western Eurasians and near the root of most Native American lineages. Similarly, we find autosomal evidence that MA-1 is basal to modern-day western Eurasians and genetically closely related to modern-day Native Americans, with no close affinity to east Asians. This suggests that populations related to contemporary western Eurasians had a more north-easterly distribution 24,000 years ago than commonly thought. Furthermore, we estimate that 14 to 38% of Native American ancestry may originate through gene flow from this ancient population. This is likely to have occurred after the divergence of Native American ancestors from east Asian ancestors, but before the diversification of Native American populations in the New World. Gene flow from the MA-1 lineage into Native American ancestors could explain why several crania from the First Americans have been reported as bearing morphological characteristics that do not resemble those of east Asians. Sequencing of another south-central Siberian, Afontova Gora-2 dating to approximately 17,000 years ago, revealed similar autosomal genetic signatures as MA-1, suggesting that the region was continuously occupied by humans throughout the Last Glacial Maximum. Our findings reveal that western Eurasian genetic signatures in modern-day Native Americans derive not only from post-Columbian admixture, as commonly thought, but also from a mixed ancestry of the First Americans.
Use of "one-pot, mix-and-read" peptide-MHC class I tetramers and predictive algorithms to improve detection of cytotoxic T lymphocyte responses in cattle

Peptide-major histocompatibility complex (p-MHC) class I tetramer complexes have facilitated the early detection and functional characterisation of epitope specific CD8(+) cytotoxic T lymphocytes (CTL). Here, we report on the generation of seven recombinant bovine leukocyte antigens (BoLA) and recombinant bovine beta 2-microglobulin from which p-MHC class I tetramers can be derived in similar to 48 h. We validated a set of p-MHC class I tetramers against a panel of CTL lines specific to seven epitopes on five different antigens of Theileria parva, a protozoan pathogen causing the lethal bovine disease East Coast fever. One of the p-MHC class I tetramers was tested in ex vivo assays and we detected T. parva specific CTL in peripheral blood of cattle at day 15-17 post-immunization with a live parasite vaccine. The algorithm NetMHCpan predicted alternative epitope sequences for some of the T. parva CTL epitopes. Using an ELISA assay to measure peptide-BoLA monomer formation and p-MHC class I tetramers of new specificity, we demonstrate that a predicted alternative epitope Tp2(29-37) rather than the previously reported Tp2(27-37) epitope is the correct Tp2 epitope presented by BoLA-6*04101. We also verified the prediction by NetMHCpan that the Tp5(87-95) epitope reported as BoLA-T5 restricted can also be presented by BoLA-1*02301, a molecule similar in sequence to BoLA-T5. In addition, Tp5(87-95) specific bovine CTL were simultaneously stained by Tp5-BoLA-1*02301 and Tp5-BoLA-T5 tetramers suggesting that one T cell receptor can bind to two different BoLA MHC class I molecules presenting the Tp5(87-95)...
epitope and that these BoLA molecules fall into a single functional supertype.

**General information**

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We have compared chromosome-specific genes in a set of 18 finished Vibrio genomes, and, in addition, also calculated the pan- and core-genomes from a data set of more than 250 draft Vibrio genome sequences. These genomes come from 9 known species and 2 unknown species. Within the finished chromosomes, we find a core set of 1269 encoded protein families for chromosome 1, and a core of 252 encoded protein families for chromosome 2. Many of these core proteins are also found in the draft genomes (although which chromosome they are located on is unknown.) Of the chromosome specific core protein families, 1169 and 153 are uniquely found in chromosomes 1 and 2, respectively. Gene ontology (GO) terms for each of the protein families were determined, and the different sets for each chromosome were compared. A total of 363 different "Molecular Function" GO categories were found for chromosome 1 specific protein families, and these include several broad activities: pyridoxine 5' phosphate synthetase, glucosylceramidase, heme transport, DNA ligase, amino acid binding, and ribosomal components; in contrast, chromosome 2 specific protein families have only 66 Molecular Function GO terms and include many membrane-associated activities, such as ion channels, transmembrane transporters, and electron transport chain proteins. Thus, it appears that whilst there are many "housekeeping systems" encoded in chromosome 1, there are far fewer core functions found in chromosome 2. However, the presence of many membrane-associated encoded proteins in chromosome 2 is surprising.
Whole-genome analyses resolve early branches in the tree of life of modern birds

To better determine the history of modern birds, we performed a genome-scale phylogenetic analysis of 48 species representing all orders of Neoaves using phylogenomic methods created to handle genome-scale data. We recovered a highly resolved tree that confirms previously controversial sister or close relationships. We identified the first divergence in Neoaves, two groups we named Passerea and Columbea, representing independent lineages of diverse and convergently evolved land and water bird species. Among Passerea, we infer the common ancestor of core landbirds to have been an apex predator and confirm independent gains of vocal learning. Among Columbea, we identify pigeons and flamingoes as belonging to sister clades. Even with whole genomes, some of the earliest branches in Neoaves proved challenging to resolve, which was best explained by massive protein-coding sequence convergence and high levels of incomplete lineage sorting that occurred during a rapid radiation after the Cretaceous-Paleogene mass extinction event about 66 million years ago.
Escherichia coli (E. coli) is of huge importance in global health both as a commensal organism living within its host or as a pathogen causing millions of infections each year. Infections occur both sporadic and as outbreaks with sometimes up to thousands of infected people. To limit the number of infections it is important to monitor pathogenic E. coli in order to
detect outbreaks as quickly as possible and find the source of the outbreak. The effectiveness of monitoring and tracking of pathogens is very dependent on the typing methods that are employed. Classical typing methods employed for E. coli is in general expensive and to some extent unreliable. Next generation sequencing has quickly become a tool widely available and has enabled even smaller laboratories to do whole genome sequencing (WGS). Having the entire genome available provides the opportunity to create the ultimate typing method. This PhD thesis attempts to take the first steps toward such a method.

In Kaas I all publicly available E. coli genomes sequenced (186) are analyzed. 1,702 core genes were found in all genomes. 3,051 genes were found in 95% of the genomes. The pan genome was found to consist of 16,373 genes. The overall phylogeny was inferred from the core genome and also set into context of the Escherichia genus. The variance within each gene cluster was calculated in order to compare the variance between genes and possibly identify typing targets for further study. The variance scores calculated was also used to compare the three MLST schemes that exist for E. coli.

It quickly became clear that single nucleotide polymorphism (SNP) analysis was becoming the method of choice for inferring the phylogeny of bacterial outbreaks. However, the method remained unavailable to many people due to technical obstacles. In Kaas II we describe the SNP method and the validation behind a web server that we set up in order to overcome some of the technical obstacles faced by many people and thereby making the method more available. The method briefly, calls SNPs against a specified reference sequence, creates an alignment (pseudosequence) of all the SNPs, and uses the maximum likelihood (ML) method to create a tree. The most important detail in the method is the assumption made about “missing” SNPs. Meaning SNPs called in one strain but not in another. It was assumed that SNPs not found in a position was due to that nucleotide being identical to the one in the reference sequence. The assumption is in general valid if all the genomes compared are closely related and the sequencing data is of good quality.

In Kaas III we sought to overcome the assumption mentioned above but most important of all we wanted to create a method that could handle sequence data obtained from different sequencing technologies. The method from Kaas II was completely rewritten and a new web server (CSI Phylogeny) was published that could handle sequence data of all kinds and no longer made assumptions about missing SNPs. Very briefly, the method differs from Kaas II mainly by validating all the locations in all the genomes in which a SNP has been called in any genome. In parallel to the development of a new SNP method another method was also developed that briefly, relies on counting nucleotide differences (ND) between each genome pair, while also validating each position analyzed and ignoring the positions that cannot be validated thereby creating a distance matrix that is used as input to an UPGMA method that creates the final phylogeny. The ND method was also implemented as a web server and published.

If whole genome sequencing is to be used for routine monitoring and tracking of E. coli pathogens, it is crucial to have an idea of how large the difference is between isolates from the same outbreak, compared to the difference to other non-outbreak isolates, in order to do reliable distinctions. In Kaas IV we analyzed ten different outbreaks. Seven of the outbreaks were sequenced for the study and three of the outbreaks were obtained from published studies. Several background isolates that resembled the outbreak isolates were also sequenced. Five different bioinformatic methods were evaluated against the 10 outbreaks. The five different methods were based on SNP, ND, core genes, k-mers, and average nucleotide identity (ANI). Only the ANI method was not able to cluster all outbreaks correctly. The pairwise distance between all isolates were also calculated by each method and compared. Most methods showed lower distance between isolates in the same outbreak compared to the background strains, but only the SNP method was able to set one common threshold for outbreak isolates versus non-outbreak isolates for the entire dataset.

Whole genome sequencing is a powerful but also a rather new tool. This PhD thesis has hopefully shed some light on how we can continue development of whole genome sequence typing and also made WGS more available to a broader audience.

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Whole Genome Epidemiological Typing of Salmonella
Salmonella is one of the most common foodborne pathogens worldwide. In the US alone, salmonellosis was estimated to cause 1.4 million cases effecting 17,000 hospitalization and almost 600 deaths each year. Particularly, Salmonella enterica is a common cause of minor and large food borne outbreaks. Technological advances and effective price in high throughput genome sequencing are making whole genome sequencing (WGS) available as a routine tool for bacterial
Typing of Salmonella, especially sub-typing within the same serotype or even the same clone, the genetic variation of the target genes being used for typing is crucial for successful discrimination. The core genes or the genes that are conserved in all members of a genus or species are potentially good candidates for investigating genomic variation in phylogeny and epidemiology. A total of 2,882 core genes have been observed among 73 available Salmonella enterica genomes (accessed in April 2011). A consensus tree based on variation of the core genes gives better resolution than 16S rRNA and MLST that rarely provide separation between closely related strains. The performance of the pan-genome tree which is based on the presence/absence of all genes across genomes, is similar to the consensus tree but with higher branching confidence value. The core genes can be divided into two categories: a few highly variable genes and a larger set of conserved core genes, with low variance. These core genes are useful for investigating molecular evolution and remain useful as candidate genes for bacterial genome typing- even if they cannot be expected to differentiate highly clonal isolates e.g. outbreak cases of Salmonella [I].

To achieve successful ‘real-time’ monitoring and identification of outbreaks, rapid and reliable sub-typing is essential. A collection of thirty-four human S. Typhimurium strains from six different outbreaks together with background strains plus eight S. Enteritidis isolates from two outbreaks and five S. Derby isolates from a single outbreak were used to evaluate the strengths and drawbacks of different WGS approaches compared to the traditional typing, PFGE, for retrospectively outbreak typing of Salmonella. The resulting outcome showed that SNP analysis and nucleotide difference approach seem to be the superior methods for outbreak detection compared to other phylogenetic analytic approaches of WGS. Furthermore, WGS approaches were also superior to the more classical typing method, PFGE. Meanwhile, k-mer method constructs a tree in high speed and giving high accuracy in clade level [II].

SNP analysis has successfully applied in recent epidemiological studies of Salmonella. Currently, there are different tools and methods to identify SNPs including various cut-off values. In addition, all the tools require bioinformatics skill. In order to apply WGS in routine typing, an automatic and user-friendly tool is needed. Therefore, snpTree has been developed as a server for online-automatic SNP analysis. snpTree can identify SNPs and construct phylogenetic tree from WGS raw reads as well as from assembled genomes or contigs. The tool is freely accessible at http://cge.cbs.dtu.dk/services/snpTree/ [III].

Globally, Salmonella enterica serovar Typhimurium is the most commonly isolated serovar. S. Typhimurium consists of a number of subtypes that conventionally have been divided by phagetyping. During the last three decades, S. Typhimurium phage type DT104 emerged as the most prevalent phage type and one of the best-studied because of its rapid global dissemination. Nonetheless, the origin and transmission route of this particular phage type have not been revealed. To bridge the gaps in epidemiology of DT104, WGS and temporally structured sequence analysis within Bayesian framework have been incorporated for reconstructing temporal and spatial phylogenies, estimating rate of mutation and divergence time of global and local S. Typhimurium DT104 isolates sampled from 1969 to 2012 from twenty-one countries in six continents. The DT104 was estimated to initially emerge as antimicrobial-susceptible strains in ~1946 (1931-1959) and further became multidrug-resistant (MDR) DT104 in ~1974 (1966-1981) through horizontal transfer of 13-kb SGI1 MDR region into SGI1-contained susceptible strains. Changes in population size over time supported global occurrences of MDR DT104. Besides, using WGS is capable to confirm local epidemiology especially the transmission between animal herds of DT104 isolates from Denmark. Interestingly, the demographic history of Danish MDR DT104 provided an evidence for the accomplishment of an eradicating program across pig herds in Denmark during 1996 to 2000 [IV]. Overall, this Ph.D. thesis has assessed the usefulness of WGS epidemiological typing in Salmonella as well as evaluated the different WGS approaches for outbreak investigation compared to the traditional typing, PFGE. An online tool to construct phylogenetic tree based on SNPs has also been developed. Furthermore, it has revealed the application of WGS in epidemiological study of global and local occurrences of S. Typhimurium DT104.
45p deciphering patterns of chromosomal aberrations in breast cancer patients: how defects in specific DNA repair genes affect the accumulation of gross DNA aberrations in the cancer genome

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Scopus rating (2006): SJR 1.893 SNIP 1.744
Scopus rating (2005): SJR 1.628 SNIP 1.58
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Accurate prediction of secondary metabolite gene clusters in filamentous fungi.
Biosynthetic pathways of secondary metabolites from fungi are currently subject to an intense effort to elucidate the genetic basis for these compounds due to their large potential within pharmaceutics and synthetic biochemistry. The preferred method is methodical gene deletions to identify supporting enzymes for key synthases one cluster at a time. In this study, we design and apply a DNA expression array for Aspergillus nidulans in combination with legacy data to form a comprehensive gene expression compendium. We apply a guilt-by-association-based analysis to predict the extent of the biosynthetic clusters for the 58 synthases active in our set of experimental conditions. A comparison with legacy data shows the method to be accurate in 13 of 16 known clusters and nearly accurate for the remaining 3 clusters. Furthermore, we apply a data clustering approach, which identifies cross-chemistry between physically separate gene clusters (superclusters), and validate this both with legacy data and experimentally by prediction and verification of a supercluster consisting of the synthase AN1242 and the prenyltransferase AN11080, as well as identification of the product compound nidulanin A. We have used A. nidulans for our method development and validation due to the wealth of available biochemical data, but the method can be applied to any fungus with a sequenced and assembled genome, thus supporting further secondary metabolite pathway elucidation in the fungal kingdom.

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A computational approach to chemical etiologies of diabetes.

Computational meta-analysis can link environmental chemicals to genes and proteins involved in human diseases, thereby elucidating possible etiologies and pathogeneses of non-communicable diseases. We used an integrated computational systems biology approach to examine possible pathogenetic linkages in type 2 diabetes (T2D) through genome-wide associations, disease similarities, and published empirical evidence. Ten environmental chemicals were found to be potentially linked to T2D, the highest scores were observed for arsenic, 2,3,7,8-tetrachlorodibenzo-p-dioxin, hexachlorobenzene, and perfluorooctanoic acid. For these substances we integrated disease and pathway annotations on top of protein interactions to reveal possible pathogenetic pathways that deserve empirical testing. The approach is general and can address other public health concerns in addition to identifying diabetogenic chemicals, and offers thus promising guidance for future research in regard to the etiology and pathogenesis of complex diseases.

General information
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Southern Denmark
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A conceptual model linking functional gene expression and reductive dechlorination rates of chlorinated ethenes in clay rich groundwater sediment

We used current knowledge of cellular processes involved in reductive dechlorination to develop a conceptual model to describe the regulatory system of dechlorination at the cell level; the model links bacterial growth and substrate consumption to the abundance of messenger RNA of functional genes involved in the dechlorination process. The applicability of the model was tested on a treatability study of biostimulated and bioaugmented microcosms. Using quantitative real time PCR, high-resolution expression profiles of the functional reductive dehalogenase genes bvcA and vcrA were obtained during two consecutive dechlorination events of trichloroethene, cis-dichloroethene and vinyl chloride. Up-regulation of the bvcA (for the biostimulated microcosms) and vcrA (for the bioaugmented microcosms) gene expression fitted well with high rates of dechlorination of vinyl chloride, while no known transcripts could be measured during trichloroethene and cis-dichloroethene dechlorination. Maximum concentrations of 2.1 and 1.7 transcripts per gene of the bvcA and vcrA genes, respectively, were measured at the same time points as maximum dechlorination rates were observed. The developed model compared well with the experimental data for both biostimulated and bioaugmented microcosms under non-steady state conditions and was supported by results from a recently published study under steady state conditions.

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Organisations: Center for Biological Sequence Analysis, Novo Nordisk Foundation Center for Biosustainability, CFB - Metagenomic Systems Biology, Department of Environmental Engineering, Residual Resource Engineering, Water Resources Engineering, Geological Survey of Denmark and Greenland, University of Copenhagen
Authors: Bælum, J. (Intern), Chambon, J. C. C. (Intern), Scheutz, C. (Intern), Binning, P. J. (Intern), Laier, T. (Ekstern), Bjerg, P. L. (Intern), Jacobsen, C. (Forskerdatabase)
Adipose tissue trans fatty acids and changes in body weight and waist circumference

Previous studies have suggested that intake of trans fatty acids (TFA) may play a role in the development of obesity. For fatty acids not synthesized endogenously in humans, such as TFA, the proportions in adipose tissue tend to correlate well with the habitual dietary intake. Biomarkers may provide a more accurate measure of habitual TFA intake than dietary questionnaires. Our objective was to investigate the associations between specific TFA in adipose tissue and subsequent changes in body weight and waist circumference (WC).

A fast and robust method for full genome sequencing of Porcine Reproductive and Respiratory Syndrome Virus (PRRSV) Type 1 and Type 2

PRRSV is a positive-sense RNA virus with a high degree of genetic variability among isolates. For diagnostic sensitivity and vaccine design it is essential to monitor PRRSV genetic diversity. However, to date only a few full genome sequences of PRRSV isolates have been made publicly available. In the present study, fast and robust methods for long range RT-PCR amplification and subsequent next generation sequencing (NGS) were developed and validated on nine Type 1 and nine Type 2 PRRSV viruses. The methods generated robust and reliable sequences both on primary material and cell culture adapted viruses and the protocols performed well on all three NGS platforms tested (Roche 454 FLX, Illumina HiSeq2000, and Ion Torrent PGM™ Sequencer). These methods will greatly facilitate the generation of more full genome PRRSV sequences globally.
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BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
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Scopus rating (2016): SJR 0.87 SNIP 0.736 CiteScore 1.78
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BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.868 SNIP 0.799 CiteScore 1.68
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.893 SNIP 0.952 CiteScore 1.87
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 0.861 SNIP 0.91 CiteScore 1.99
ISI indexed (2013): ISI indexed yes
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Scopus rating (2010): SJR 0.892 SNIP 0.998
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 0.964 SNIP 1.061
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Scopus rating (2008): SJR 0.918 SNIP 1.082
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Web of Science (2007): Indexed yes
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Web of Science (2005): Indexed yes
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Web of Science (2003): Indexed yes
Scopus rating (2002): SJR 0.736 SNIP 1.059
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Amino Acid Usage Is Asymmetrically Biased in AT- and GC-Rich Microbial Genomes.

Introduction: Genomic base composition ranges from less than 25% AT to more than 85% AT in prokaryotes. Since only a small fraction of prokaryotic genomes is not protein coding even a minor change in genomic base composition will induce profound protein changes. We examined how amino acid and codon frequencies were distributed in over 2000 microbial genomes and how these distributions were affected by base compositional changes. In addition, we wanted to know how genome-wide amino acid usage was biased in the different genomes and how changes to base composition and mutations affected this bias. To carry this out, we used a Generalized Additive Mixed-effects Model (GAMM) to explore non-linear associations and strong data dependences in closely related microbes; principal component analysis (PCA) was used to examine genomic amino acid- and codon frequencies, while the concept of relative entropy was used to analyze genomic mutation rates. Results: We found that genomic amino acid frequencies carried a stronger phylogenetic signal than codon frequencies, but that this signal was weak compared to that of genomic %AT. Further, in contrast to codon usage bias (CUB), amino acid usage bias (AAUB) was differently distributed in AT- and GC-rich genomes in the sense that AT-rich genomes did not prefer specific amino acids over others to the same extent as GC-rich genomes. AAUB was also associated with relative entropy; genomes with low AAUB contained more random mutations as a consequence of relaxed purifying selection than genomes with higher AAUB. Conclusion: Genomic base composition has a substantial effect on both amino acid- and codon frequencies in bacterial genomes. While phylogeny influenced amino acid usage more in GC-rich genomes, AT-content was driving amino acid usage in AT-rich genomes. We found the GAMM model to be an excellent tool to analyze the genomic data used in this study.
Analyzing Plasmodium falciparum erythrocyte membrane protein 1 gene expression by a next generation sequencing based method

Plasmodium falciparum is responsible for most cases of severe malaria and causes >1 million deaths every year. The particular virulence of this Plasmodium species is highly associated with the expression of certain members of the Plasmodium falciparum erythrocyte membrane protein 1 (PfEMP1) family, encoded by ~60 highly variable ‘var’ genes per haploid genome. PfEMP1 is exported to the surface of infected erythrocytes and is thought to be fundamental to immune evasion by adhesion to host and parasite factors. The highly variable nature has constituted a roadblock in var expression studies aimed at identifying PfEMP1 features associated with high virulence. Here we present the first effective method for sequence analysis of var genes expressed in field samples: a sequential PCR and next generation sequencing based technique applied on expressed var sequence tags and subsequently on long range PCR amplicons of the expressed vars. The results obtained with this method supports quantitative PCR data showing PfEMP1 of the group A and domain cassettes 8 and 13 types being expressed at particularly high levels in severe childhood malaria.

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BFI (2013): BFI-level 2
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Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 1.539 SNIP 1.252 CiteScore 2.82
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 1.563 SNIP 1.145 CiteScore 2.78
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 1.491 SNIP 1.265
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 1.258 SNIP 1.282
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 1.212 SNIP 1.153
Scopus rating (2007): SJR 1.584 SNIP 1.516
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 1.378 SNIP 1.384
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A Nondegenerate Code of Deleterious Variants in Mendelian Loci Contributes to Complex Disease Risk

Although countless highly penetrant variants have been associated with Mendelian disorders, the genetic etiologies underlying complex diseases remain largely unresolved. By mining the medical records of over 110 million patients, we examine the extent to which Mendelian variation contributes to complex disease risk. We detect thousands of associations between Mendelian and complex diseases, revealing a nondegenerate, phenotypic code that links each complex disorder to a unique collection of Mendelian loci. Using genome-wide association results, we demonstrate that common variants associated with complex diseases are enriched in the genes indicated by this "Mendelian code." Finally, we detect hundreds of comorbidity associations among Mendelian disorders, and we use probabilistic genetic modeling to demonstrate that Mendelian variants likely contribute nonadditively to the risk for a subset of complex diseases. Overall, this study illustrates a complementary approach for mapping complex disease loci and provides unique predictions concerning the etiologies of specific diseases.
A Novel Domain Cassette Identifies *Plasmodium falciparum* PfEMP1 Proteins Binding ICAM-1 and Is a Target of Cross-Reactive, Adhesion-Inhibitory Antibodies

Cerebral *Plasmodium falciparum* malaria is characterized by adhesion of infected erythrocytes (IEs) to the cerebral microvasculature. This has been linked to parasites expressing the structurally related group A subset of the *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) family of IE adhesion ligands and to IEs with affinity for ICAM-1. However, recent evidence has cast doubt on both these associations, tempering hopes of the feasibility of developing a vaccine based on ICAM-1-binding PfEMP1. In this study, we report the identification of a domain cassette (DC) present in group A var genes from six genetically distinct *P. falciparum* parasites. The three domains in the cassette, which we call DC4, had a high level of sequence identity and cluster together phylogenetically. Erythrocytes infected by these parasites and selected in vitro for expression of DC4 adhered specifically to ICAM-1. The ICAM-1-binding capacity of DC4 was mapped to the C-terminal third of its Duffy-binding-like beta 3 domain. DC4 was the target of broadly cross-reactive and adhesion-inhibitory IgG Abs, and levels of DC4-specific and adhesion-inhibitory IgG increased with age among *P. falciparum*-exposed children. Our study challenges earlier conclusions that group A PfEMP1 proteins are not central to ICAM-1-specific IE adhesion and support the feasibility of developing a vaccine preventing cerebral malaria by inhibiting cerebral IE sequestration. The Journal of Immunology, 2013, 190: 240-249.
cerebral malaria Malaria, Cerebral (MeSH) nervous system disease, parasitic disease, Primates Mammalia Vertebrata
Chordata Animalia (Animals, Chordates, Humans, Mammals, Primates, Vertebrates) - Hominidae [86215] HEK293F cell
line cell_line human embryonic kidney cells, Protozoa Invertebrata Animalia (Animals, Invertebrates, Microorganisms,
Protozoans) - Sporozoa [35400] Plasmodium falciparum species parasite strain-3D7, strain-BM057, Plasmodium falciparum var gene [Sporozoa], ICAM-1, Plasmodium falciparum erythrocyte membrane protein 1 PIEMP1, 02506,
Cytology - Animal, 02508, Cytology - Human, 03506, Genetics - Animal, 03508, Genetics - Human, 10064, Biochemistry
studies - Proteins, peptides and amino acids, 15002, Blood - Blood and lymph studies, 15004, Blood - Blood cell studies,
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ATAF1 transcription factor directly regulates abscisic acid biosynthetic gene NCED3 in Arabidopsis thaliana.

ATAF1, an Arabidopsis thaliana NAC transcription factor, plays important roles in plant adaptation to environmental stress and development. To search for ATAF1 target genes, we used protein binding microarrays and chromatin-immunoprecipitation (ChIP). This identified T[A,C,G]CGT[A,G] and T[T,A,C,G]CGT as ATAF1 consensus binding sequences. Co-expression analysis across publicly available microarray experiments identified 25 genes co-expressed with ATAF1. The promoter regions of ATAF1 co-expressors were significantly enriched for ATAF1 binding sites, and TTGGCGTA was identified in the promoter of the key abscisic acid (ABA) phytohormone biosynthetic gene NCED3. ChIP-qPCR and expression analysis showed that ATAF1 binding to the NCED3 promoter correlated with increased NCED3 expression and ABA hormone levels. These results indicate that ATAF1 regulates ABA biosynthesis.

Ataxia, Dementia, and Hypogonadotropism Caused by Disordered Ubiquitination

The combination of ataxia and hypogonadism was first described more than a century ago, but its genetic basis has remained elusive.

METHODS

We performed whole-exome sequencing in a patient with ataxia and hypogonadotropic hypogonadism, followed by targeted sequencing of candidate genes in similarly affected patients. Neurologic and reproductive endocrine phenotypes were characterized in detail. The effects of sequence variants and the presence of an epistatic interaction were tested in a zebrafish model.
RESULTS
Digenic homozygous mutations in RNF216 and OTUD4, which encode a ubiquitin E3 ligase and a deubiquitinase, respectively, were found in three affected siblings in a consanguineous family. Additional screening identified compound heterozygous truncating mutations in RNF216 in an unrelated patient and single heterozygous deleterious mutations in four other patients. Knockdown of rnf216 or otud4 in zebrafish embryos induced defects in the eye, optic tectum, and cerebellum; combinatorial suppression of both genes exacerbated these phenotypes, which were rescued by nonmutant, but not mutant, human RNF216 or OTUD4 messenger RNA. All patients had progressive ataxia and dementia. Neuronal loss was observed in cerebellar pathways and the hippocampus; surviving hippocampal neurons contained ubiquitin-immunoreactive intranuclear inclusions. Defects were detected at the hypothalamic and pituitary levels of the reproductive endocrine axis.

CONCLUSIONS
The syndrome of hypogonadotropic hypogonadism, ataxia, and dementia can be caused by inactivating mutations in RNF216 or by the combination of mutations in RNF216 and OTUD4. These findings link disordered ubiquitination to neurodegeneration and reproductive dysfunction and highlight the power of whole-exome sequencing in combination with functional studies to unveil genetic interactions that cause disease.
A Unified Model of the GABA(A) Receptor Comprising Agonist and Benzodiazepine Binding Sites

We present a full-length a1b2c2 GABA receptor model optimized for agonists and benzodiazepine (BZD) allosteric modulators. We propose binding hypotheses for the agonists GABA, muscimol and THIP and for the allosteric modulator diazepam (DZP). The receptor model is primarily based on the glutamate-gated chloride channel (GluCl) from C. elegans and includes additional structural information from the prokaryotic ligand-gated ion channel ELIC in a few regions. Available mutational data of the binding sites are well explained by the model and the proposed ligand binding poses. We suggest a GABA binding mode similar to the binding mode of glutamate in the GluCl X-ray structure. Key interactions are predicted with residues a1R66, b2T202, a1T129, b2E155, b2Y205 and the backbone of b2S156. Muscimol is predicted to bind similarly, however, with minor differences rationalized with quantum mechanical energy calculations. Muscimol key interactions are predicted to be a1R66, b2T202, a1T129, b2E155, b2Y205 and b2F200. Furthermore, we argue that a water molecule could mediate further interactions between muscimol and the backbone of b2S156 and b2Y157. DZP is predicted to bind with interactions comparable to those of the agonists in the orthosteric site. The carbonyl group of DZP is predicted to interact with two threonines a1T206 and c2T142, similar to the acidic moiety of GABA. The chlorine atom of DZP is placed near the important a1H101 and the N-methyl group near a1Y159, a1T206, and a1Y209. We present a binding mode of DZP in which the pending phenyl moiety of DZP is buried in the binding pocket and thus shielded from solvent exposure. Our full length GABAA receptor is made available as Model S1.

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, National Food Institute, Division of Toxicology and Risk Assessment, Novo Nordisk A/S, University of Sydney, University of Copenhagen
Authors: Kongsbak, K. G. (Intern), Bergmann, R. (Ekstern), Sørensen, P. L. (Ekstern), Sander, T. (Ekstern), Balle, T. (Ekstern)
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Bacterial natural transformation by highly fragmented and damaged DNA.

DNA molecules are continuously released through decomposition of organic matter and are ubiquitous in most environments. Such DNA becomes fragmented and damaged (often <100 bp) and may persist in the environment for more than half a million years. Fragmented DNA is recognized as nutrient source for microbes, but not as potential substrate for bacterial evolution. Here, we show that fragmented DNA molecules (&ge;20 bp) that additionally may contain abasic sites, cross-links, or miscoding lesions are acquired by the environmental bacterium Acinetobacter baylyi through natural transformation. With uptake of DNA from a 43,000-y-old woolly mammoth bone, we further demonstrate that such natural transformation events include ancient DNA molecules. We find that the DNA recombination is RecA recombinase independent and is directly linked to DNA replication. We show that the adjacent nucleotide variations generated by uptake of short DNA fragments escape mismatch repair. Moreover, doublenucleotide polymorphisms appear more common among genomes of transformable than nontransformable bacteria. Our findings reveal that short and damaged, including truly ancient, DNA molecules, which are present in large quantities in the environment, can be acquired by bacteria through natural transformation. Our findings open for the possibility that natural genetic exchange can occur with DNA up to several hundreds of thousands years old.

**General information**

State: Published

Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Novo Nordisk Foundation Center for Biosustainability, CFB - Metagenomic Systems Biology, University of Tromsø - University of Canterbury, Carl von Ossietzky Universität Oldenburg, University of Oxford, University of California, University of Copenhagen
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- **BFI (2016):** BFI-level 2
- **Scopus rating (2016):** CiteScore 8.56 SJR 6.321 SNIP 2.629
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- **BFI (2015):** BFI-level 2
- **Scopus rating (2015):** SJR 6.767 SNIP 2.682 CiteScore 8.84
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- **BFI (2014):** BFI-level 2
- **Scopus rating (2014):** SJR 6.853 SNIP 2.725 CiteScore 8.86
  - **Web of Science (2014):** Indexed yes
- **BFI (2013):** BFI-level 2
- **Scopus rating (2013):** SJR 6.989 SNIP 2.73 CiteScore 9.5
  - **ISI indexed (2013):** ISI indexed yes
  - **Web of Science (2013):** Indexed yes
- **BFI (2012):** BFI-level 2
- **Scopus rating (2012):** SJR 6.792 SNIP 2.682 CiteScore 9.49
  - **ISI indexed (2012):** ISI indexed yes
  - **Web of Science (2012):** Indexed yes
- **BFI (2011):** BFI-level 2
- **Scopus rating (2011):** SJR 6.771 SNIP 2.636 CiteScore 9.31
  - **ISI indexed (2011):** ISI indexed yes
  - **Web of Science (2011):** Indexed yes
- **BFI (2010):** BFI-level 2
- **Scopus rating (2010):** SJR 6.769 SNIP 2.529
  - **Web of Science (2010):** Indexed yes
- **BFI (2009):** BFI-level 2
- **Scopus rating (2009):** SJR 6.913 SNIP 2.544
  - **Web of Science (2009):** Indexed yes
- **BFI (2008):** BFI-level 2
- **Scopus rating (2008):** SJR 6.899 SNIP 2.445
  - **Web of Science (2008):** Indexed yes
- **Scopus rating (2007):** SJR 6.766 SNIP 2.441
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- **Scopus rating (2005):** SJR 6.784 SNIP 2.551
  - **Web of Science (2005):** Indexed yes
- **Scopus rating (2004):** SJR 7.026 SNIP 2.622
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**Main Research Area:** Technical/natural sciences
Biasogram: visualization of confounding technical bias in gene expression data.

Gene expression profiles of clinical cohorts can be used to identify genes that are correlated with a clinical variable of interest such as patient outcome or response to a particular drug. However, expression measurements are susceptible to technical bias caused by variation in extraneous factors such as RNA quality and array hybridization conditions. If such technical bias is correlated with the clinical variable of interest, the likelihood of identifying false positive genes is increased. Here we describe a method to visualize an expression matrix as a projection of all genes onto a plane defined by a clinical variable and a technical nuisance variable. The resulting plot indicates the extent to which each gene is correlated with the clinical variable or the technical variable. We demonstrate this method by applying it to three clinical trial microarray data sets, one of which identified genes that may have been driven by a confounding technical variable. This approach can be used as a quality control step to identify data sets that are likely to yield false positive results.
Biochemical and kinetic characterisation of a novel xylooligosaccharide-upregulated GH43 β-d-xylosidase/α-l-arabinofuranosidase (BXA43) from the probiotic Bifidobacterium animalis subsp. lactis BB-12

The Bifidobacterium animalis subsp. lactis BB-12 gene BIF_00092, assigned to encode a β-d-xylosidase (BXA43) of glycoside hydrolase family 43 (GH43), was cloned with a C-terminal His-tag and expressed in Escherichia coli. BXA43 was purified to homogeneity from the cell lysate and found to be a dual-specificity exo-hydrolase active on para-nitrophenyl-β-d-xylopyranoside (pNPX), para-nitrophenyl-α-L-arabinofuranoside (pNPA), β-(1 → 4)-xylopyranosyl oligomers (XOS) of degree of polymerisation (DP) 2–4, and birchwood xylan. A phylogenetic tree of the 92 characterised GH43 enzymes displayed five distinct groups (I – V) showing specificity differences. BXA43 belonged to group IV and had an activity ratio for pNPA:pNPX of 1:25. BXA43 was stable below 40°C and at pH 4.0–8.0 and showed maximum activity at pH 5.5 and 50°C. Km and kcat for pNPX were 15.6 ± 4.2 mM and 60.6 ± 10.8 s⁻¹, respectively, and substrate inhibition became apparent above 18 mM pNPX. Similar kinetic parameters and catalytic efficiency values were reported for β-d-xylosidase (XynB3) from Geobacillus stearothermophilus T–6 also belonging to group IV. The activity of BXA43 for xylooligosaccharides increased with the size and was 2.3 and 5.6 fold higher, respectively for xylobiose and xylotetraose compared to pNPX. BXA43 showed clearly metal inhibition for Zn²⁺ and Ag⁺, which is different to its close homologues. Multiple sequence alignment and homology modelling indicated that Arg¹⁵⁰ Tyr¹⁵⁶ present in BXA43 are probably important for binding to xylotetraose at subsite +3 and occur only in GH43 from the Bifidobacterium genus.

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Organisations: Department of Systems Biology, Enzyme and Protein Chemistry, Center for Biological Sequence Analysis, Chr. Hansen A/S
Number of pages: 8
Bioinformatics Identification of Antigenic Peptide: Predicting the Specificity of Major MHC Class I and II Pathway Players.

Bioinformatics methods for immunology have become increasingly used over the last decade and now form an integrated part of most epitope discovery projects. This wide usage has led to the confusion of defining which of the many methods to use for what problems. In this chapter, an overview is given focusing on the suite of tools developed at the Technical University of Denmark.
Bioprospecting and Functional Analysis of Neglected Environments

Advances in Next Generation Sequencing technologies made it possible to sequence DNA extracted from environments and organisms at a reasonable cost allowing research fields such as metagenomics and whole transcriptome sequencing (RNA-seq) to be established. These techniques allow the study of functional relationships in single organisms and environments. The sequencing data can also be mined for novel compounds and enzymes. The process of exploiting biological resources for commercial use is known as bioprospecting.

This PhD thesis describes the concept of bioprospecting in the post genomic era (Chapter 1) and introduces the research fields of metagenomics and RNA-seq (Chapter 2) as concepts to access and analyze biological resources. When attempting to discover and commercialize such biological resources, legal obligations have to be met, which is generally governed by the Convention on Biological Diversity (explained in Chapter 3). Proteolytic enzymes – described in Chapter 4 – are the target for bioprospecting due to their high market value. Section II describes methods used for the analysis of metagenomic and RNA-seq datasets, including Manuscript I, which includes the taxonomic annotation of a late Pleistocene horse metagenome and the functional annotation of the donkey genome. The functional analysis and the identification of novel proteolytic enzymes in the polar marine environment and the full transcriptome analysis of the carnivorous plant Dionaea muscipula is also presented.

The polar seas are unique, extreme habitat with constant low temperatures and no light penetration in the deep. Water samples at varying depth (40 m – 4,300 m) were collected during the Galathea III and LOMROG II polar expeditions. The sample DNA was extracted and sequenced. Comparative functional analysis of arctic marine metagenomes reveals bacterial strategies for deep sea persistence (Manuscript II). Furthermore, this extreme environment is a fertile ground to mine for novel proteolytic enzymes. Manuscript III presents a bioinformatics approach to identify sequences for potential commercialization.

Carnivory is a rare trait in the plant kingdom, and only few species are able to trap and digest prey. The sequencing, assembly and functional annotation of a normalized transcriptome of the most famous carnivorous plant, the Venus flytrap (Dionaea muscipula), is presented in Manuscript IV.

Chapter 12 summarizes the thesis and includes final remarks on the future perspectives on the presented research. In summary, this thesis demonstrates how biological resources can be exploited for commercial use. Furthermore, the findings give a better understanding of the microbial community’s persistence in the deep sea. Lastly, the transcriptome data of the Venus flytrap provide a public resource for unveiling features of the carnivorous syndrome such as digestion.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Metagenomics
Authors: Vogt, J. K. (Intern), Sicheritz-Pontén, T. (Intern)
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BlockLogo: Visualization of peptide and sequence motif conservation
BlockLogo is a web-server application for the visualization of protein and nucleotide fragments, continuous protein sequence motifs, and discontinuous sequence motifs using calculation of block entropy from multiple sequence alignments. The user input consists of a multiple sequence alignment, selection of motif positions, type of sequence, and output format definition. The output has BlockLogo along with the sequence logo, and a table of motif frequencies. We deployed BlockLogo as an online application and have demonstrated its utility through examples that show visualization of T-cell epitopes and B-cell epitopes (both continuous and discontinuous). Our additional example shows a visualization and analysis of structural motifs that determine the specificity of peptide binding to HLA-DR molecules. The BlockLogo server also employs selected experimentally validated prediction algorithms to enable on-the-fly prediction of MHC binding affinity to 15 common HLA class I and class II alleles as well as visual analysis of discontinuous epitopes from multiple sequence alignments. It enables the visualization and analysis of structural and functional motifs that are usually described as regular expressions. It provides a compact view of discontinuous motifs composed of distant positions within biological sequences. BlockLogo is available at: http://research4.dfci.harvard.edu/cvc/blocklogo/ and http://met-hilab.bu.edu/blocklogo/.

General information
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Dana-Farber Cancer Institute, Harvard Medical School, Kyushu Institute of Technology
Cancer signaling networks and their implications for personalized medicine

Amongst the unique features of cancer cells perhaps the most crucial one is the change in the cellular decision-making process. While both non-cancer and cancer cells are constantly integrating different external cues that reach them and computing cellular decisions (e.g. proliferation or apoptosis) based on the integration of these cues; this integration and consequently the cellular decisions taken by cancer cells are arguably very distinct from the decisions that would be expected from non-cancer cells. Since cellular signaling networks and its different states are the computational circuits that determine cellular outcome, it is clear to many that these networks will be highly dysregulated in cancer cells. Thus, developing and applying methods that will be capable of mapping and predicting how cancer mutations translate into signaling network perturbations, which could explain cancer development as well as cancer resistance to treatment, represent not only a huge challenge, but also one with potentially extreme benefit for our understanding of the disease and for patients. This thesis summarizes my efforts during the last years in contributing positively to overcome this challenge. This thesis is divided into six parts. Starting with a brief introduction to the history and some basic concepts of cancer, signaling networks and human protein kinases (part I), we quickly move on to describing existing methods to analyze cancer signaling networks, including methods proposed by us, as well as three of the articles that are part of this PhD thesis (part II). In part III, we illustrate with an article that has been submitted recently, how next-generation sequencing data and mass spectrometry data can be combined to uncover genome-specific signaling networks. In part IV, I describe the two computational methods that I have developed and how they can be integrated with the aim of predicting how signaling networks will be dysregulated in cancer. As a matter of fact, the following part (part V) proves the usefulness of the method by identifying a functional mutation in a group of ovarian clear cell carcinoma cell lines that could cause their resistance to cisplatin treatment. Part VI closes the thesis by summarizing its main points and proposing some future perspectives for the work presented here.

All in all, this work establishes a new framework for the prediction of mechanisms underlying cancer development and evolution which, one would hope, should help close the gap between cancer genotype and phenotype.
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- Web of Science (2016): Indexed yes
- BFI (2015): BFI-level 2
- Scopus rating (2015): SJR 7.239 SNIP 2.639 CiteScore 9.48
- Web of Science (2015): Indexed yes
- BFI (2014): BFI-level 2
- Scopus rating (2014): SJR 6.576 SNIP 2.568 CiteScore 8.74
- Web of Science (2014): Indexed yes
- BFI (2013): BFI-level 2
- Scopus rating (2013): SJR 6.582 SNIP 2.266 CiteScore 8.46
- ISI indexed (2013): ISI indexed yes
- Web of Science (2013): Indexed yes
- BFI (2012): BFI-level 2
- Scopus rating (2012): SJR 6.13 SNIP 2.392 CiteScore 8.62
- ISI indexed (2012): ISI indexed yes
- Web of Science (2012): Indexed yes
- BFI (2011): BFI-level 2
- Scopus rating (2011): SJR 5.758 SNIP 2.172 CiteScore 7.86
- ISI indexed (2011): ISI indexed yes
- Web of Science (2011): Indexed yes
- BFI (2010): BFI-level 2
- Scopus rating (2010): SJR 5.24 SNIP 2.034
- Web of Science (2010): Indexed yes
- BFI (2009): BFI-level 2
- Scopus rating (2009): SJR 5.571 SNIP 1.869
- BFI (2008): BFI-level 2
- Scopus rating (2008): SJR 4.641 SNIP 1.557
- Web of Science (2008): Indexed yes
- Scopus rating (2007): SJR 4.86 SNIP 1.787
- Web of Science (2007): Indexed yes
- Scopus rating (2006): SJR 4.55 SNIP 2.04
- Web of Science (2006): Indexed yes
- Scopus rating (2005): SJR 4.992 SNIP 2.152
- Web of Science (2005): Indexed yes
- Scopus rating (2004): SJR 4.809 SNIP 1.971
- Web of Science (2004): Indexed yes
- Scopus rating (2003): SJR 0.108 SNIP 1.862
- Web of Science (2003): Indexed yes
- Scopus rating (2002): SJR 0.12 SNIP 1.535
- Scopus rating (2001): SJR 0.131 SNIP 1.402
- Scopus rating (2000): SJR 0.141 SNIP 1.672
- Web of Science (2000): Indexed yes
- Scopus rating (1999): SJR 0.149 SNIP 1.562
ChemProt: A disease chemical biology database
The integration of chemistry, biology, and informatics to study drug actions across multiple biological targets, pathways, and biological systems is an emerging paradigm in drug discovery. Rather than reducing a complex system to simplistic models, fields such as chemogenomics and translational informatics are seeking to build a holistic model for a better understanding of the drug pharmacology and clinical effects. Here we will present a webserver called ChemProt that can assist, in silico, the drug actions in the context of cellular and disease networks and contribute in the field of disease chemical biology, drug repurposing, and off-target effects prediction.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of New Mexico
Authors: Taboureau, O. (Intern), Oprea, T. I. (Ekstern)
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CMG-Biotools, a Free Workbench for Basic Comparative Microbial Genomics.
This paper shows the strength and diverse use of the CMG-biotools system. The system can be installed on a wide range of host operating systems and utilizes as much of the host computer as desired. It allows the user to compare multiple genomes, from various sources using standardized data formats and intuitive visualizations of results. The examples presented here clearly show that users with limited computational experience can perform complicated analysis without much training.

General information
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Department of Electrical Engineering, Electromagnetic Systems
Authors: Vesth, T. C. (Intern), Lagesen, K. (Intern), Acar, Ö. (Intern), Ussery, D. (Intern)
Pages: e60120
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Main Research Area: Technical/natural sciences

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Colorectal cancer cell lines made resistant to SN38-and Oxaliplatin: Roles of altered ion transporter function in resistance?

Colorectal cancer (CRC) is the 3rd most common cancer globally, with 5-year survival rates of ~50%. Response rates to standard treatments (irinotecan (SN38) or Oxaliplatin (Oxp)) are 31–56% and drug resistance is a major problem. Thus, we established in vitro CRC models to investigate SN38 and Oxp resistance in HCT-116, HT-29 and LoVo cells. Microarray analysis and qPCR validation showed that mRNA expression of glutamate transporters SLC1A1 and SLC1A3 were markedly altered in resistant cells. Remarkably, mRNA levels of SLC1A3 were increased by ~40- and ~2500-fold in SN38- and Oxp-resistant HT29 cells, respectively. Studies are ongoing to assess glutamate uptake in parental and resistant CRC cells and the effect of inhibition/knockdown of SLC1A1 and -3 on SN38- and Oxp resistance.

In conclusion, SN38- and Oxp-resistance in CRC cells is associated with SLC1A1 and -3 dysregulation. As these transporters have not previously been implicated in SN38 or Oxp resistance and are generally restricted to the CNS, they are potential novel biomarkers for resistance and interesting candidates for therapeutic targeting.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Integrative Systems Biology, Behavioral Phenomics, Functional Human Variation, Metagenomics, University of Copenhagen
Comparison of two Next Generation sequencing platforms for full genome sequencing of Classical Swine Fever Virus

Next Generation Sequencing (NGS) is becoming more adopted into viral research and will be the preferred technology in the years to come. We have recently sequenced several strains of Classical Swine Fever Virus (CSFV) by NGS on both Genome Sequencer FLX (GS FLX) and Iontorrent PGM platforms. In this study, we analyzed NGS data of virus rescued from a CSFV C-strain vaccine strain cDNA clone. The virus analyzed was obtained from a 4th and a 12th passage of rescued virus in SFT cell culture, which had shown a difference in growth kinetics between the passages, and NGS analysis was chosen in order to look for molecular differences. Identical RT-PCR products were run on both GS FLX and an Iontorrent PGM platform for comparison. The NGS data was compared by quality and the percentage mapped reads. Results showed good quality of reads for both platforms and a close to 100% of the reads mapped to the consensus sequence. Additionally, we got an average sequence depth for the genome of 4000 for the Iontorrent PGM and 400 for the FLX platform making the mapping suitable for single nucleotide variant (SNV) detection. The analysis revealed a single non-silent SNV A10665G leading to the amino acid change D3431G in the RNAdependent RNA polymerase NS5B. This SNV was present at 100% frequency in the 12th passage and only at 55% in the 4th passage, which could explain the difference in growth kinetics between the passages.

General information
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Organisations: Molecular Evolution, National Veterinary Institute, Section for Virology, Department of Systems Biology, Center for Biological Sequence Analysis, Behavioral Phenomics, Friedrich Loeffler Institute
Authors: Fahnøe, U. (Intern), Pedersen, A. G. (Intern), Höper, D. (Ekstern), Beer, M. (Ekstern), Rasmussen, T. B. (Intern)
Number of pages: 1
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Complete genes may pass from food to human blood

Our bloodstream is considered to be an environment well separated from the outside world and the digestive tract. According to the standard paradigm large macromolecules consumed with food cannot pass directly to the circulatory system. During digestion proteins and DNA are thought to be degraded into small constituents, amino acids and nucleic acids, respectively, and then absorbed by a complex active process and distributed to various parts of the body through the circulation system. Here, based on the analysis of over 1000 human samples from four independent studies, we report evidence that meal-derived DNA fragments which are large enough to carry complete genes can avoid degradation and through an unknown mechanism enter the human circulation system. In one of the blood samples the relative concentration of plant DNA is higher than the human DNA. The plant DNA concentration shows a surprisingly precise log-normal distribution in the plasma samples while non-plasma (cord blood) control sample was found to be free of plant DNA.
Computational approaches to identify functional genetic variants in cancer genomes.

The International Cancer Genome Consortium (ICGC) aims to catalog genomic abnormalities in tumors from 50 different cancer types. Genome sequencing reveals hundreds to thousands of somatic mutations in each tumor but only a minority of these drive tumor progression. We present the result of discussions within the ICGC on how to address the challenge of identifying mutations that contribute to oncogenesis, tumor maintenance or response to therapy, and recommend computational techniques to annotate somatic variants and predict their impact on cancer phenotype.
Computational optimisation of targeted DNA sequencing for cancer detection.

Despite recent progress thanks to next-generation sequencing technologies, personalised cancer medicine is still hampered by intra-tumour heterogeneity and drug resistance. As most patients with advanced metastatic disease face poor survival, there is need to improve early diagnosis. Analysing circulating tumour DNA (ctDNA) might represent a non-invasive method to detect mutations in patients, facilitating early detection. In this article, we define reduced gene panels from publicly available datasets as a first step to assess and optimise the potential of targeted ctDNA scans for early tumour detection. Dividing 4,467 samples into one discovery and two independent validation cohorts, we show that up to 76% of 10 cancer types harbour at least one mutation in a panel of only 25 genes, with high sensitivity across most tumour types. Our analyses demonstrate that targeting "hotspot" regions would introduce biases towards in-frame mutations and would compromise the reproducibility of tumour detection.
Concordance of gene expression in human protein complexes reveals tissue specificity and pathology

Disease-causing variants in human genes usually lead to phenotypes specific to only a few tissues. Here, we present a method for predicting tissue specificity based on quantitative deregulation of protein complexes. The underlying assumption is that the degree of coordinated expression among proteins in a complex within a given tissue may pinpoint tissues that will be affected by a mutation in the complex and coordinated expression may reveal the complex to be active in the tissue. We identified known disease genes and their protein complex partners in a high-quality human interactome. Each susceptibility gene's tissue involvement was ranked based on coordinated expression with its interaction partners in a non-disease global map of human tissue-specific expression. The approach demonstrated high overall area under the curve (0.78) and was very successfully benchmarked against a random model and an approach not using protein complexes. This was illustrated by correct tissue predictions for three case studies on leptin, insulin-like-growth-factor 2 and the inhibitor of NF-κB kinase subunit gamma that show high concordant expression in biologically relevant tissues. Our method identifies novel gene-phenotype associations in human diseases and predicts the tissues where associated phenotypic effects may arise.

General information
Content and distribution of phytanic acid diastereomers in organic milk as affected by feed composition

Phytanic acid (PA) is a bioactive compound found in milk that is derived from the phytol chain of chlorophyll, and the content of PA in milk fat depends on the availability of phytol from feed. In this study, the content of PA diastereomers was analyzed in milk sampled from five organic herds twice during the grazing season (May and September). The total content of PA was higher in September compared to May, but was not affected by breed (Danish Holstein or Danish Jersey). Total PA could not be directly related to intake of green feed items. The distribution between diastereomers was closely related to the amount of grazed clovers, where a higher intake resulted in a higher share of the RRR isomer. © 2012 American Chemical Society.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Aarhus University
Authors: Che, B. N. (Forskerdatabase), Kristensen, T. (Ekstern), Nebel, C. (Forskerdatabase), Dalsgaard, T. (Forskerdatabase), Hellgren, L. (Intern), Young, J. F. (Forskerdatabase), Larsen, M. K. (Ekstern)
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Scopus rating (2015): SJR 1.236 SNIP 1.253 CiteScore 3.23
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 1.278 SNIP 1.421 CiteScore 3.25
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 1.423 SNIP 1.479 CiteScore 3.44
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
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Scopus rating (2012): SJR 1.43 SNIP 1.471 CiteScore 3.2
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
This thesis presents the work carried out at the Center for Biological Sequence Analysis, Technical University of Denmark. The thesis includes four articles describing large-scale data integration and methods for the prediction of drug side-effects. Chapter 2 presents ChemProt, a novel disease chemical biology database. ChemProt integrates different chemical-protein annotation resources for disease-associated proteins and protein-protein interaction data. ChemProt is developed to assist in silico evaluation of environmental chemicals, natural products and approved drugs, as well as to aid the selection of new compounds based on their activity profiles against biological targets. The latest update of ChemProt database includes a new visual interface, which enables easy navigation through the pharmacological space. Additionally, new search methods for chemical, protein, disease and side-effect data have been implemented.

Chapter 3 presents two articles that showcase the application of systems chemical biology approaches to understand and model drug side-effect data. The first approach applies machine learning methods to cluster side-effects, drugs, proteins and clinical outcomes in networks. This work demonstrates the power of a strategy that uses clinical data mining in association with chemical biology in order to reduce the search space and aid identification of novel drug actions. The second article described in chapter 3 outlines a high confidence side-effect-drug interaction dataset. We estimated based on the placebo-controlled studies from DailyMed that only approximately 20% of the drug-side-effect associations are significant. With the ChemProt database we linked drugs with their biological targets and applied a scoring function in order to capture frequently encountered side-effect-protein associations. We then built a computational chemical biology model, which revealed side-effect predictive capabilities for 55% of the 133 drugs in the SIDER database. Further validation was performed on withdrawn drugs stored in DrugBank and many side-effects were confirmed through literature search. This work demonstrates the importance of using high-confidence drug-side-effect data in deciphering the effect of small molecules in humans.
In summary, this thesis presents computational systems chemical biology approaches that can help identify clinical effects of small molecules through large-scale data integration. These approaches also serve to pave the way into a variety of chemogenomics, polypharmacology and systems chemical biology studies.

General information
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis
Authors: Kjærulf, S. K. (Intern), Brunak, S. (Intern), Taboureau, O. (Intern), Kouskoumvekaki, I. (Intern)
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Deconvoluting complex tissues for expression quantitative trait locus-based analyses
Breast cancer genome-wide association studies have pinpointed dozens of variants associated with breast cancer pathogenesis. The majority of risk variants, however, are located outside of known protein-coding regions. Therefore, identifying which genes the risk variants are acting through presents an important challenge. Variants that are associated with mRNA transcript levels are referred to as expression quantitative trait loci (eQTLs). Many studies have demonstrated that eQTL-based strategies provide a direct way to connect a trait-associated locus with its candidate target gene. Performing eQTL-based analyses in human samples is complicated because of the heterogeneous nature of human tissue. We addressed this issue by devising a method to computationally infer the fraction of cell types in normal human breast tissues. We then applied this method to 13 known breast cancer risk loci, which we hypothesized were eQTLs. For each risk locus, we took all known transcripts within a 2 Mb interval and performed an eQTL analysis in 100 reduction mammoplasty cases. A total of 18 significant associations were discovered (eight in the epithelial compartment and 10 in the stromal compartment). This study highlights the ability to perform large-scale eQTL studies in heterogeneous tissues.

General information
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Deep phenotyping of the unselected COPSAC2010 birth cohort study

We hypothesize that perinatal exposures, in particular the human microbiome and maternal nutrition during pregnancy, interact with the genetic predisposition to cause an abnormal immune modulation in early life towards a trajectory to chronic inflammatory diseases such as asthma and others. The aim of this study is to explore these interactions by conducting a longitudinal study in an unselected cohort of pregnant women and their offspring with emphasis on deep clinical phenotyping, exposure assessment, and biobanking. Exposure assessments focus on the human microbiome. Nutritional intervention during pregnancy in randomized controlled trials are included in the study to prevent disease and to be able to establish causal relationships. Pregnant women from eastern Denmark were invited during 2008–2010 to a novel unselected ‘COPSAC2010’ cohort. The women visited the clinic during pregnancy weeks 24 and 36. Their children were followed at the clinic with deep phenotyping and collection of biological samples at nine regular visits until the age of 3 and at acute symptoms. Randomized controlled trials of high-dose vitamin D and fish oil supplements were conducted during pregnancy, and a trial of azithromycin for acute lung symptoms was conducted in the children with recurrent wheeze. Seven hundred and thirty-eight mothers were recruited from week 24 of gestation, and 700 of their children were included in the birth cohort. The cohort has an over-representation of atopic parents. The participant satisfaction was high and the adherence equally high with 685 children (98%) attending the 1 year clinic visit and 667 children (95%) attending the 2 year clinic visit. The COPSAC2010 birth cohort study provides longitudinal clinical follow-up with highly specific end-points, exposure assessments, and biobanking. The cohort has a high adherence rate promising strong data to elucidate the interaction between genomics and the exposome in perinatal life leading to lifestyle-related chronic inflammatory disorders such as asthma.
Detection of serological biomarkers by proximity extension assay for detection of colorectal neoplasias in symptomatic individuals

Although the potential of biomarkers to aid in early detection of colorectal cancer (CRC) is recognized and numerous biomarker candidates have been reported in the literature, to date only few molecular markers have been approved for daily clinical use.

In order to improve the translation of biomarkers from the bench to clinical practice we initiated a biomarker study focusing on a novel technique, the proximity extension assay, with multiplexing capability and the possible additive effect obtained from biomarker panels. We performed a screening of 74 different biomarkers in plasma derived from a case–control sample set consisting of symptomatic individuals representing CRC patients, patients with adenoma, patients with non-neoplastic large bowel diseases and healthy individuals.

After statistical evaluation we found 12 significant indicators of CRC and the receiver operating characteristic (ROC) curve of Carcinoembryonic antigen (CEA), Transferrin Receptor-1 (TFRC), Macrophage migration inhibitory factor (MIF), Osteopontin (OPN/SPP1) and cancer antigen 242 (CA242) showed additive effect. This biomarker panel identified CRC patients with a sensitivity of 56% at 90% specificity and thus the performance is sufficiently high to further investigate this combination of five proteins as serological biomarkers for detection of CRC. Furthermore, when applying the indicators to identify early-stage CRC a combination of CEA, TFRC and CA242 resulted in a ROC curve with an area under the curve of 0.861.

General information
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Scopus rating (2015): SJR 1.734 SNIP 1.094 CiteScore 4.23
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Scopus rating (2014): SJR 1.774 SNIP 1.175 CiteScore 4.1
BFI (2013): BFI-level 1
Biocides are chemical compounds with antimicrobial properties and they are widely used for disinfection, antiseptic and preservation purposes. Biocides have been applied for centuries due to early empirical approaches, such as cleansing of wounds with wine, vinegar and honey and salting of fish and meat. Today, large amounts of biocides are used for disinfection to achieve a satisfactory level of hygiene in various settings and use of biocides has become an integrated part of the industrialized world.

Despite the widespread use and application of biocides knowledge about their exact mechanisms of action, especially at sub-inhibitory concentrations, and the bacterial response to such exposure, is relatively limited. The increasing use of biocides has within recent years lead to concerns about development and emergence of biocide resistant microorganisms that might make the task of eradication of pathogenic bacteria more difficult. Furthermore, it has been suggested that use of biocides may contribute to the development of resistance in bacteria to antimicrobial agents used in human and animal therapy. So far, it is evident that cross- and co-resistance mechanisms to antimicrobials agents and biocides exist. However, much less is known about the potential effect of biocides on development of antimicrobial resistance in bacteria by promoting the horizontal transfer of resistance genes or by inducing the mutation rate. Even though biocides are commonly used at working concentrations way above the lethal bacterial dose, the efficacy of these compounds can be significantly reduced by incorrect use or the presence of residual concentrations hence, bacterial exposure to sub-inhibitory concentrations of biocides is likely to occur.

The overall objective of this study was to examine if natural bacterial isolates become less susceptible to biocides used in their environment and if this can lead to spread of antimicrobial resistant clones due to co-selection. Furthermore, the objective was to examine if exposure to subinhibitory concentrations of biocides induce development of resistance to antimicrobial agents.

So far, only few studies have investigated the susceptibility of livestock-associated isolates to biocides used in their environment. Pigs are increasingly recognised as a potential reservoir of community-acquired methicillin resistant Staphylococcus aureus (CA-MRSA), especially clones belonging to clonal complex (CC) 398. Recently, methicillin resistant S. aureus (MRSA) isolates belonging to CC30 was for the first time detected among Danish pigs. The susceptibility of 79 porcine S. aureus isolates belonging to C398 or CC30 to commonly used biocides in pig farming was
Dictionary construction and identification of possible adverse drug events in Danish clinical narrative text

Objective Drugs have tremendous potential to cure and relieve disease, but the risk of unintended effects is always present. Healthcare providers increasingly record data in electronic patient records (EPRs), in which we aim to identify possible adverse events (AEs) and, specifically, possible adverse drug events (ADEs). Materials and methods Based on the undesirable effects section from the summary of product characteristics (SPC) of 7446 drugs, we have built a Danish ADE dictionary. Starting from this dictionary we have developed a pipeline for identifying possible ADEs in unstructured clinical narrative text. We use a named entity recognition (NER) tagger to identify dictionary matches in the text and post-coordination rules to construct ADE compound terms. Finally, we apply post-processing rules and filters to handle, for example, negations and sentences about subjects other than the patient. Moreover, this method allows synonyms to be merged to allow appropriate grouping of effects in the same location. Results The method identified 1 970 731 (35 477 unique) possible ADEs in a large corpus of 6011 psychiatric hospital patient records. Validation was performed through manual inspection of possible ADEs, resulting in precision of 89% and recall of 75%. Discussion The presented dictionary-building method could be used to construct other ADE dictionaries. The complication of compound words in Germanic languages was addressed. Additionally, the synonym and
anatomical location collapse improve the method. Conclusions The developed dictionary and method can be used to identify possible ADEs in Danish clinical narratives.
Full agonists to the peroxisome proliferator-activated receptor (PPARγ), such as Rosiglitazone, have been associated with a series of undesired side effects, such as weight gain, fluid retention, cardiac hypertrophy, and hepatotoxicity. Nevertheless, PPARγ is involved in the expression of genes that control glucose and lipid metabolism and is an important target for drugs against type 2 diabetes, dyslipidemia, atherosclerosis, and cardiovascular disease. In an effort to identify novel PPARγ ligands with an improved pharmacological profile, emphasis has shifted to selective ligands with partial agonist binding properties. Toward this end we applied an integrated in silico/in vitro workflow, based on pharmacophore- and structure-based virtual screening of the ZINC library, coupled with competitive binding and transactivation assays, and adipocyte differentiation and gene expression studies. Hit compound 9 was identified as the most potent ligand (IC50 = 0.3 μM) and a relatively poor inducer of adipocyte differentiation. The binding mode of compound 9 was confirmed by molecular dynamics simulation, and the calculated free energy of binding was -8.4 kcal/mol. A novel functional group, the carbonitrile group, was identified to be a key substituent in the ligand-protein interactions. Further studies on the transcriptional regulation properties of compound 9 revealed a gene regulatory profile that was to a large extent unique, however functionally closer to that of a partial agonist. © 2013 American Chemical Society.
Scopus rating (2011): SJR 1.323 SNIP 1.332 CiteScore 4.3
ISI indexed (2011): ISI indexed yes
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Docosahexaenoic acid status at 9 months is inversely associated with communicative skills in 3-year-old girls
The objective of the present observational study was to investigate if the docosahexaenoic acid (DHA) status assessed in infant erythrocytes (RBC) at 9 months was associated with the age when the infants reach developmental milestones and their psychomotor function at 3 years of age. Three hundred eleven healthy Danish children were followed from 9 months to 3 years of age (the SKOT cohort). RBC fatty acid composition was analysed by gas chromatography in 272 of the children. Milestone age was collected by questionnaires at 9 and 18 months and psychomotor development at 3 years of age was assessed by the parents using third edition of the Ages and Stages Questionnaire (ASQ-3). RBC DHA levels ranged from 2.2% to 12.6% of the RBC fatty acids. The age of reaching milestones correlated with psychomotor development, particularly with gross motor function at 3 years. An association between milestones and later personal and social skills was also observed, but only for girls. In girls, RBC-DHA was found to be inversely correlated with communication at 3 years of age (odds ratio = 0.69, 95% confidence interval: 0.56-0.86, P = 0.001), but no other associations with psychomotor development or milestones were found. The results from study indicate that DHA status at 9 months may not have a pronounced beneficial effect on psychomotor development in early childhood and that communicative skills at 3 years of age may even be inversely associated with early RBC-DHA levels in girls.

General information
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Effect of gestation on obesity-induced hepatic and placental inflammation in mice

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Effects of butter from mountain-pasture grazing cows on risk markers of the metabolic syndrome compared with conventional Danish butter: a randomized controlled study.

There is considerable interest in dairy products from low-input systems, such as mountain-pasture grazing cows, because these products are thought to be healthier than products from high-input conventional systems. This may be due to a higher content of bioactive components, such as phytic acid, a PPAR-agonist derived from chlorophyll. However, the effects of such products on human health have been poorly investigated. Objective: To compare the effect of milk-fat from mountain-pasture grazing cows (G) and conventionally fed cows (C) on risk markers of the metabolic syndrome. Design:
In a double-blind, randomized, 12-week, parallel intervention study, 38 healthy subjects replaced part of their habitual dietary fat intake with 39 g fat from test butter made from milk from mountain-pasture grazing cows or from cows fed conventional winter fodder. Glucose-tolerance and circulating risk markers were analysed before and after the intervention. Results: No differences in blood lipids, lipoproteins, hsCRP, insulin, glucose or glucose-tolerance were observed. Interestingly, strong correlations between phytanic acid at baseline and total (P
Effects of maternal energy intake during gestation and lactation on leptin levels in the young and adult pups

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Efficient generation of recombinant RNA viruses using targeted recombination-mediated mutagenesis of bacterial artificial chromosomes containing full-length cDNA

Background
Infectious cDNA clones are a prerequisite for directed genetic manipulation of RNA viruses. Here, a strategy to facilitate manipulation and rescue of classical swine fever viruses (CSFVs) from full-length cDNAs present within bacterial artificial chromosomes (BACs) is described. This strategy allows manipulation of viral cDNA by targeted recombination-mediated mutagenesis within bacteria.

Results
A new CSFV-BAC (pBeloR26) derived from the Riems vaccine strain has been constructed and subsequently modified in the E2 coding sequence, using the targeted recombination strategy to enable rescue of chimeric pestiviruses (vR26_E2gif and vR26_TAV) with potential as new marker vaccine candidates. Sequencing of the BACs revealed a high genetic stability during passages within bacteria. The complete genome sequences of rescued viruses, after extensive passages in mammalian cells showed that modifications in the E2 protein coding sequence were stably maintained. A single amino acid substitution (D3431G) in the RNA dependent RNA polymerase was observed in the rescued viruses vR26_E2gif and vR26, which was reversion to the parental Riems sequence.

Conclusions
These results show that targeted recombination-mediated mutagenesis provides a powerful tool for expediting the construction of novel RNA genomes and should be applicable to the manipulation of other RNA viruses.

General information
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Organisations: National Veterinary Institute, Section for Virology, Molecular Evolution, Friedrich Loeffler Institute
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Web of Science (2010): Indexed yes
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Scopus rating (2008): SJR 2.067 SNIP 1.005
Web of Science (2008): Indexed yes
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Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 1.431 SNIP 0.895
Web of Science (2006): Indexed yes
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Web of Science (2005): Indexed yes
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Web of Science (2004): Indexed yes
Scopus rating (2003): SJR 1.909 SNIP 0.561
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Scopus rating (2002): SJR 1.342 SNIP 0.532
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Emerging trends in the discovery of natural product antibacterials
This article highlights current trends and advances in exploiting natural sources for the deployment of novel and potent anti-infective countermeasures. The key challenge is to therapeutically target bacterial pathogens that exhibit a variety of puzzling and evolutionarily complex resistance mechanisms. Special emphasis is given to the strengths, weaknesses, and opportunities in the natural product antibacterial drug discovery arena, and to emerging applications driven by advances in bioinformatics, chemical biology, and synthetic biology in concert with exploiting bacterial phenotypes. These efforts have identified a critical mass of natural product antibacterial lead compounds and discovery technologies with high probability of successful implementation against emerging bacterial pathogens.

General information
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BFI (2013): BFI-level 1
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Scopus rating (2005): SJR 2.286 SNIP 1.251
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NetMHCIIpan-3.0, a common pan-specific MHC class II prediction method including all three human MHC class II isotypes, HLA-DR, HLA-DP and HLA-DQ

Major histocompatibility complex class II (MHCII) molecules play an important role in cell-mediated immunity. They present specific peptides derived from endosomal proteins for recognition by T helper cells. The identification of peptides that bind to MHCII molecules is therefore of great importance for understanding the nature of immune responses and identifying T cell epitopes for the design of new vaccines and immunotherapies. Given the large number of MHC variants, and the costly experimental procedures needed to evaluate individual peptide–MHC interactions, computational predictions have become particularly attractive as first-line methods in epitope discovery. However, only a few so-called pan-specific prediction methods capable of predicting binding to any MHC molecule with known protein sequence are currently available, and all of them are limited to HLA-DR. Here, we present the first pan-specific method capable of predicting peptide binding to any HLA class II molecule with a defined protein sequence. The method employs a strategy common for HLA-DR, HLA-DP and HLA-DQ molecules to define the peptide-binding MHC environment in terms of a pseudo sequence. This strategy allows the inclusion of new molecules even from other species. The method was evaluated in several benchmarks and demonstrates a significant improvement over molecule-specific methods as well as the ability to predict peptide binding of previously uncharacterised MHCII molecules. To the best of our knowledge, the NetMHCIIpan-3.0 method is the first pan-specific predictor covering all HLA class II molecules with known sequences including HLA-DR, HLA-DP, and HLA-DQ. The NetMHCpan-3.0 method is available at http://www.cbs.dtu.dk/services/NetMHCIIpan-3.0.

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Web of Science (2015): Indexed yes
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Web of Science (2014): Indexed yes
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Epithelial entry rather than the ensuing systemic immune response determines the pathogenicity of two Salmonella enterica serovar Typhimurium strains in a mouse model

Most studies of Salmonella enterica serovar Typhimurium infection focus only on the pathogenicity of one strain. We investigated whether differences in pathogenicity of two wild-type S. Typhimurium strains, DT120 and SL1344, were related to gut invasion or the resulting immune response. Oral administration of a ten-fold lower number of SL1344 (106 CFU) as compared to DT120 (107 CFU) resulted in higher bacterial counts in liver and lymph nodes, and led to massive neutrophil infiltration of the spleen, while DT120 administration did not. In contrast, administration of the same dose (103 CFU) of the two strains intravenously resulted in the same levels of bacteria and neutrophils in spleen and bone marrow. Oral administration of SL1344 led to an increase in neutrophil apoptosis in both spleen and bone marrow and four out of five mice died before Day 8, while in DT120 mice, no increase in neutrophil apoptosis was observed and all mice survived until Day 8. This study reveals that two wild-type S. Typhimurium strains, despite evoking highly comparable immune responses upon intravenous injection, exhibit diverse pathogenicity in mice and thus suggests that differences in their invasiveness and survival during gut passage determines the success of the ensuing immune response.
Major histocompatibility complex (MHC) molecules play a crucial role in adaptive immunity by sampling peptides from self and non-self proteins to be recognised by the immune system. MHC molecules present peptides on cell surfaces for recognition by CD8+ and CD4+ T lymphocytes that can initiate immune responses. Therefore, it is of great importance to be able to identify peptides that bind to MHC molecules, in order to understand the nature of immune responses and discover T cell epitopes useful for designing new vaccines and immunotherapies. MHC molecules in humans, referred to as human leucocyte antigen (HLA) molecules, are encoded by extremely polymorphic genes on chromosome 6. Due to this polymorphism, thousands of different MHC molecules exist, making the experimental identification of peptide-MHC interactions a very costly procedure. This has primed the need for in silico peptide-MHC prediction methods, and over the last decade several such methods have been successfully developed and used for epitope discovery purposes.

My PhD project has been dedicated to improve methods for predicting peptide-MHC interactions by developing new strategies for training prediction algorithms based on machine learning techniques.
Several MHC class I binding prediction algorithms have been developed and due to their high accuracy they are used by many immunologists to facilitate the conventional experimental process of epitope discovery. However, the accuracy of these methods depends on data defining the MHC molecule in question, making it difficult for the non-expert end-user to choose the most suitable predictor. The first paper in this thesis presents a new, publicly available, consensus method for MHC class I predictions. The NetMHCcons predictor combines three state-of-the-art prediction tools and provides the most accurate predictions for any given MHC molecule.

While the methods for MHC class I binding have reached a very high accuracy and are widely used for immunological research, the case of MHC class II is less clear. The open binding groove of MHC class II molecules and differences in polymorphism among MHC encoding genes makes predictions of peptide binding to MHC class II molecules a complicated problem. We addressed these issues in order to develop the first pan-specific predictor common for all three human class II isoatypes: HLA-DR, HLA-DP and HLA-DQ. The second paper introduces the NetMHCIIpan-3.0 predictor based on artificial neural networks, which is capable of giving binding affinities to any human MHC class II molecule.

Chapter 4 of this thesis gives an overview of bioinformatics tools developed by the Immunological Bioinformatics group at Center for Biological Sequence Analysis. The chapter provides detailed explanations on how to use different methods for T cell epitope discovery research, explaining how input should be given as well as how to interpret the output.

In the last chapter, I present the results of a bioinformatics analysis of epitopes from the yellow fever virus. The analysis demonstrated the absence of distinct regions of higher epitope density within the virus polyprotein. Also, the density of epitopes among different proteins was demonstrated to mostly depend on protein length and amino acid composition, underlining the importance of identifying peptide-MHC interactions. Furthermore, using yellow fever virus epitopes, we demonstrated the power of the %Rank score when compared with the binding affinity score of MHC prediction methods, suggesting that this score should be considered to be used for selecting potential T cell epitopes.

In summary, this thesis presents methods for prediction of peptides that bind to both MHC class I and class II molecules, which is important for driving immunological research within the field of T cell epitope discovery and for general understanding of the cellular responses.

General information
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Functional Human Variation, Immunological Bioinformatics
Authors: Karosiene, E. (Intern), Nielsen, M. (Intern), Lund, O. (Intern)
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Publication: Research › Ph.D. thesis – Annual report year: 2013

Evaluation of peptide selection approaches for epitope-based vaccine design
A major challenge in epitope-based vaccine (EV) design stems from the vast genomic variation of pathogens and the diversity of the host cellular immune system. Several computational approaches have been published to assist the selection of potential T cell epitopes for EV design. So far, no thorough comparison between the current methods has been realized. Using human immunodeficiency virus as test case, different EV selection algorithms were evaluated with respect to their ability to select small peptides sets with broad coverage of allelic and pathogenic diversity. The methods were compared in terms of in silico measurements simulating important vaccine properties like the ability of inducing protection against a multivariant pathogen in a population; the predicted immunogenicity; pathogen, allele, and population coverage; as well as the conservation of selected epitopes. Additionally, we evaluate the use of human leukocyte antigen (HLA) supertypes with regards to their applicability for population-spanning vaccine design. The results showed that in terms of induced protection methods that simultaneously aim to optimize pathogen and HLA coverage significantly outperform methods focusing on pathogen coverage alone. Moreover, supertype-based approaches for coverage of HLA diversity were showed to yield only satisfying results in populations in which the supertype representatives are prevalent.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Immunological Bioinformatics, Eberhard Karls University
Authors: Schubert, B. (Ekstern), Lund, O. (Intern), Nielsen, M. (Intern)
Pages: 243–251
Publication date: 2013
Main Research Area: Technical/natural sciences

Publication information
Exome mutation burden predicts clinical outcome in ovarian cancer carrying mutated BRCA1 and BRCA2 genes

Reliable biomarkers predicting resistance or sensitivity to anti-cancer therapy are critical for oncologists to select proper therapeutic drugs in individual cancer patients. Ovarian and breast cancer patients carrying germline mutations in BRCA1 or BRCA2 genes are often sensitive to DNA damaging drugs and relative to non-mutation carriers present a favorable clinical outcome following therapy. Genome sequencing studies have shown a high number of mutations in the tumor genome in patients carrying BRCA1 or BRCA2 mutations (mBRCA). The present study used exome-sequencing and SNP 6 array data of The Cancer Genome Atlas (TCGA) to correlate the total exome mutation number (Nmut) to progression-free survival (PFS) and overall survival (OS) in the patients (n = 316) with high grade serous ovarian cancer (HGSOC) after debulking surgery and platinum-based chemotherapy. HGSOC in 70 patients of this cohort had either germlines or
somatic mutations of BRCA1 or BRCA2 genes. The results revealed that the Nmut was significantly lower in the chemotherapy-resistant mBRCA HGSOc defined by progression within 6 months after completion of first line platinum-based chemotherapy. We found a significant association between low Nmut and shorter PFS and OS in mBRCA HGSOc by Cox regression and Kaplan-Meier analyses. The association was also significant when the analysis was limited to germline BRCA1 or BRCA2 mutated patients with SNP array-determined loss of heterozygosity of the BRCA1 or BRCA2 locus in the tumors. In the mBRCA HGSOc tumors, Nmut was correlated with the genome fraction with loss of heterozygosity and with number of telomeric allelic imbalance, genomic measures evaluating chromosomal instability. However, no significant association between Nmut and PFS or OS was found in HGSOc carrying wild-type BRCA1 and BRCA2 genes. These results suggest that in cancers with DNA repair deficiency caused by functional BRCA loss, higher versus lower Nmut may reflect the status of deficiency or rescue by alternative mechanism(s) for DNA repair, with lower Nmut predicting for resistance to DNA-damaging drugs in mBRCA HGSOc. Our observations are consistent with the new concept that BRCA1/2 critically regulate error-free repair of nucleotide damage to suppress mutation formation, and may imply an activation of alternative repair mechanism(s) capable of bypassing the BRCA defect and restoring error-free DNA repair.
FADS genotype and diet are important determinants of DHA status: a cross-sectional study in Danish infants

Background: Infant docosahexaenoic acid (DHA) status is supported by the DHA content of breast milk and thus can decrease once complementary feeding begins. Furthermore, it is unclear to what extent endogenous DHA synthesis contributes to status. Objective: We investigated several determinants, including FADS genotypes on DHA status at 9 mo and 3 y. Design: This was a cross-sectional study with Danish infants from 2 prospective studies [Essentielle Fedtsyrer i Overgangskostøn (EFION) and the Småbørns Kost Og Trivsel (SKOT) cohort] in which we measured red blood cell (RBC) DHA status at 9 mo (n = 409) and 3 y (n = 176) and genotyped 4 FADS tag single nucleotide polymorphisms (SNPs): rs3834458, rs1535, rs174575, and rs174448 (n = 401). Information about breastfeeding was obtained by using questionnaires, and fish intake was assessed by using 7-d precoded food diaries. Results: FADS genotype, breastfeeding, and fish intake explained 25% of the variation in infant RBC DHA status [mean ± SD: 6.6 ± 1.9% of fatty acids (FA%)]. Breastfeeding explained most of the variation (~20%), and still being breastfed at 9 mo was associated with a 0.7 FA% higher DHA compared with no longer being breastfed (P < 0.001). The FADS SNPs rs1535 and rs3834458 were highly correlated (r = 0.98). Homozygous carriers of the minor allele of rs1535 had a DHA increase of 1.8 FA% (P = 0.001) relative to those with the wild-type allele, whereas minor allele carriers of rs174448 and rs174575 had a decrease of 1.1 FA% (P = 0.005) and 2.0 FA% (P = 0.001), respectively. Each 10-g increment in fish intake was associated with an increased DHA status of 0.3 FA%. At 3 y, fish intake was the only significant determinant of DHA status (0.2 FA%/10 g). Conclusion: Breastfeeding, FADS genotype, and fish intake are important determinants of DHA status in late infancy. The EFION study was registered at clinicaltrials.gov as NCT 00631046.
From essential to persistent genes: a functional approach to constructing synthetic life

A central undertaking in synthetic biology (SB) is the quest for the 'minimal genome'. However, 'minimal sets' of essential genes are strongly context-dependent and, in all prokaryotic genomes sequenced to date, not a single protein-coding gene is entirely conserved. Furthermore, a lack of consensus in the field as to what attributes make a gene truly essential adds another aspect of variation. Thus, a universal minimal genome remains elusive. Here, as an alternative to defining a minimal genome, we propose that the concept of gene persistence can be used to classify genes needed for robust long-term survival. Persistent genes, although not ubiquitous, are conserved in a majority of genomes, tend to be expressed at high levels, and are frequently located on the leading DNA strand. These criteria impose constraints on genome organization, and these are important considerations for engineering cells and for creating cellular life-like forms in SB.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Max Planck Institute, Yale University, International Dialogue and Conflict Management, University of Hong Kong
Authors: Acevedo-Rocha, C. G. (Ekstern), Fang, G. (Ekstern), Schmidt, M. (Ekstern), Ussery, D. (Intern), Danchin, A. (Ekstern)
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BFI (2015): BFI-level 2
Scopus rating (2015): SJR 7.676 SNIP 2.361 CiteScore 9.03
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 8.409 SNIP 2.279 CiteScore 9.09
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 9.296 SNIP 2.322 CiteScore 10.75
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 8.161 SNIP 2.46 CiteScore 9.85
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 7.945 SNIP 2.578 CiteScore 9.59
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 8.548 SNIP 2.634
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 7.238 SNIP 2.552
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 6.905 SNIP 2.179
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 7.15 SNIP 2.146
Scopus rating (2006): SJR 7.217 SNIP 2.171
From viral genome to specific peptide epitopes: methods for identifying porcine T cell epitopes based on in silico predictions, in vitro identification and ex vivo verification

The affinity with which major histocompatibility complex (MHC) class I molecules bind peptides is instrumental to presentation of viral epitopes to cytotoxic T lymphocytes (CTLs). We analyzed three swine leukocyte antigen (SLA) molecules for complete nonamer peptide-based binding matrices in order to predict likely candidates for peptide-SLA binding. These results were combined with binding predictions generated by the algorithm, NetMHCpan (http://www.cbs.dtu.dk/services/NetMHCpan/) in order to select peptide candidates for in vitro analysis. The correlation between high affinity and high stability was determined using luminescence oxygen channeling (LOCI) and scintillation proximity assay (SPA) for peptides bound by the commonly occurring SLA molecules, SLA-1*0401, SLA-2*0401, and SLA-3*0401. Using these tools, peptides bound by SLA with high affinity and stability were identified from a library of 10,000 peptides. T cell epitopes were identified using peptide-SLA complexes assembled into fluorescent tetramers to stain swine influenza specific CTLs derived from immunized animals and MHC-defined pigs vaccinated against foot-and-mouth disease virus. These results demonstrate the broad applicability of methods originally developed for analysis of human leukocyte antigen (HLA) presentation of peptides. The methods presented provide a timely and cost-effective approach to CTL epitope discovery that can be applied to diseases of swine and of other mammalian species of interest.

General information
State: Published
Organisations: National Veterinary Institute, Section for Immunology and Vaccinology, Department of Systems Biology, Center for Biological Sequence Analysis, Immunological Bioinformatics, Agricultural Research Service, University of Copenhagen
Authors: Pedersen, L. E. (Intern), Rasmussen, M. (Ekstern), Harndah, M. (Ekstern), Patch, J. (Ekstern), Nielsen, M. (Intern), Buus, S. (Ekstern), Golde, W. (Ekstern), Jungersen, G. (Intern)
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Main Research Area: Technical/natural sciences
Functional Similarities and Disparities in Inflammation-Promoting Abilities of Gut-Derived Escherichia coli Strains from Patients with Inflammatory Bowel Diseases and Healthy Individuals

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Statens Serum Institut, Technical University of Denmark, University Hospital Herlev, University of Copenhagen
Authors: Jensen, S. R. (Intern), Mirsepasi, H. (Ekstern), Thysen, A. (Ekstern), Brynskov, J. (Ekstern), Krogfelt, K. (Ekstern), Petersen, A. M. (Ekstern), Pedersen, A. E. (Ekstern), Pedersen, S. B. (Intern)
Pages: 266-267
Publication date: 2013
Conference: 41st Meeting and Summer School of the Scandinavian-Society-for-Immunology, Copenhagen, Denmark, 14/04/2013 - 14/04/2013
Genetic and antigenic characterization of influenza A virus circulating in Danish swine during the past decade

Influenza A virus has been endemic in Danish swine for the last 30 years, with H1N1 and H1N2 being the dominating subtypes. The purpose of this study was to investigate the genetic and antigenic evolution of the influenza viruses found in Danish swine during the last 10 years. A total of 78 samples were isolated in MDCK cells, RNA extracted and the hemagglutinin and neuraminidase genes full length sequenced. In addition, the isolates were tested in hemagglutination inhibition (HI) tests against a panel of known antisera raised against a range of European swine influenza virus isolates. Phylogenetic analysis of the HA and NA genes revealed continuous evolutionary drift as expected for RNA viruses with low mutational selection pressure. Estimated selection pressures indicated that more purifying and less diversifying selection controlled the H1 evolution. The mean rates of synonymous and non-synonymous substitutions for H1, N1 and N2 were found to be in agreement with previously observed values for Eurasian swine lineages. Calculation of possible glycosylation sites in the hemagglutinin gene revealed that the H1N2 and H1N1 subtypes had three well conserved glycosylation sites in common. The results of the HI tests were analysed by antigenic cartography to quantify the antigenic relationship between the virus isolates. The antigenic cartography map showed that most of the Danish viruses were antigenic very similar, with only a few outliers. In conclusion, this study provided an important contribution to the complex epidemiology of circulating swine influenza virus in Denmark and indicates that vaccine development targeted against Danish H1N1 and H1N2 need only to include few components for the induction of cross protection against the predominant strains.

The study was supported by grants from “European surveillance network for influenza in pigs (ESNIP) 3” (http://www.esnip3.eu) and The Danish Veterinary and Food Administration.

General information

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Organisations: National Veterinary Institute, Section for Virology, Department of Systems Biology, Integrative Systems Biology, Molecular Evolution, Section for Public sector service and commercial diagnostics, University of Cambridge Authors: Fobian, K. (Intern), Kirk, I. K. (Intern), Breum, S. Ø. (Intern), Lewis, N. (Ekstern), Hjulsager, C. K. (Intern), Larsen, L. E. (Intern)
Number of pages: 1
Publication date: 2013
Event: Abstract from Influenza2013, Oxford, United Kingdom.
Main Research Area: Technical/natural sciences
Swine influenza, Phylogeny, Antigenic cartography
Electronic versions:
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Podium presentation.
Source: dtu
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Publication: Research - peer-review › Conference abstract for conference – Annual report year: 2013

Genome-scale cold stress response regulatory networks in ten Arabidopsis thaliana ecotypes

BACKGROUND: Low temperature leads to major crop losses every year. Although several studies have been conducted focusing on diversity of cold tolerance level in multiple phenotypically divergent Arabidopsis thaliana (A. thaliana) ecotypes, genome-scale molecular understanding is still lacking. RESULTS: In this study, we report genome-scale transcript response diversity of 10 A. thaliana ecotypes originating from different geographical locations to non-freezing cold stress (10°C). To analyze the transcriptional response diversity, we initially compared transcriptome changes in all 10 ecotypes using Arabidopsis NimbleGen ATH6 microarrays. In total 6061 transcripts were significantly cold regulated (p <0.01) in 10 ecotypes, including 498 transcription factors and 315 transposable elements. The majority of the transcripts (75%) showed ecotype specific expression pattern. By using sequence data available from Arabidopsis thaliana 1001 genome project, we further investigated sequence polymorphisms in the core cold stress regulon genes. Significant numbers of non-synonymous amino acid changes were observed in the coding region of the CBF regulon genes. CONCLUSIONS: A. thaliana ecotypes exhibit considerable variation in transcriptome level responses to non-freezing cold stress treatment. Ecotype specific transcripts and related gene ontology (GO) categories were identified to delineate natural variation of cold stress regulated differential gene expression in the model plant A. thaliana. The predicted regulatory network model was able to identify new ecotype specific transcription factors and their regulatory interactions, which might be crucial for their local geographic adaptation to cold temperature. Additionally, since the approach presented here is general, it could be adapted to study networks regulating biological process in any biological systems.

General information
Genome Sequencing Identifies Two Nearly Unchanged Strains of Persistent Listeria monocytogenes Isolated at Two Different Fish Processing Plants Sampled 6 Years Apart

Listeria monocytogenes is a food-borne human-pathogenic bacterium that can cause infections with a high mortality rate. It has a remarkable ability to persist in food processing facilities. Here we report the genome sequences for two L. monocytogenes strains (N53-1 and La111) that were isolated 6 years apart from two different Danish fish processors. Both strains are of serotype 1/2a and belong to a highly persistent DNA subtype (random amplified polymorphic DNA [RAPD] type 9). We demonstrate using in silico analyses that both strains belong to the multilocus sequence typing (MLST) type ST121 that has been isolated as a persistent subtype in several European countries. The purpose of this study was to use genome analyses to identify genes or proteins that could contribute to persistence. In a genome comparison, the two persistent strains were extremely similar and collectively differed from the reference lineage II strain, EGD-e. Also, they differed markedly from a lineage I strain (F2365). On the proteome level, the two strains were almost identical, with a predicted protein homology of 99.94%, differing at only 2 proteins. No single-nucleotide polymorphism (SNP) differences were seen between the two strains; in contrast, N53-1 and La111 differed from the EGD-e reference strain by 3,942 and 3,471 SNPs, respectively. We included a persistent L. monocytogenes strain from the United States (F6854) in our comparisons. Compared to nonpersistent strains, all three persistent strains were distinguished by two genome deletions: one, of 2,472 bp, typically contains the gene for inlF, and the other, of 3,017 bp, includes three genes potentially related to bacteriocin production and transport (lmo2774, lmo2775, and the 3′-terminal part of lmo2776). Further studies of highly persistent strains are required to determine if the absence of these genes promotes persistence. While the genome comparison did not point to a clear physiological explanation of the persistent phenotype, the remarkable similarity between the two strains indicates that subtypes with specific traits are selected for in the food processing environment and that particular genetic and physiological factors are responsible for the persistent phenotype.

General information
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Organisations: National Food Institute, Department of Systems Biology, Center for Biological Sequence Analysis, Allegheny College, U.S. Department of Agriculture
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- BFI (2017): BFI-level 2
- Web of Science (2017): Indexed yes
- BFI (2016): BFI-level 2
- Scopus rating (2016): CiteScore 4.08
- Web of Science (2016): Indexed yes
- BFI (2015): BFI-level 2
- Scopus rating (2015): SJR 1.891 SNIP 1.308 CiteScore 4.14
- Web of Science (2015): Indexed yes
- BFI (2014): BFI-level 2
Genome-wide assessment of the association of rare and common copy number variations to testicular germ cell cancer.

Testicular germ cell cancer (TGCC) is one of the most heritable forms of cancer. Previous genome-wide association studies have focused on single nucleotide polymorphisms, largely ignoring the influence of copy number variants (CNVs). Here we present a genome-wide study of CNV on a cohort of 212 cases and 437 controls from Denmark, which was genotyped at ~1.8 million markers, half of which were non-polymorphic copy number markers. No association of common variants were found, whereas analysis of rare variants (present in less than 1% of the samples) initially indicated a single gene with significantly higher accumulation of rare CNVs in cases as compared to controls, at the gene PTPN1 (P = 3.8 × 10^-2, 0.9% of cases and 0% of controls). However, the CNV could not be verified by qPCR in the affected samples. Further, the CNV calling of the array-data was validated by sequencing of the GSTM1 gene, which showed that the CNV...
frequency was in complete agreement between the two platforms. This study therefore disconfirms the hypothesis that there exists a single CNV locus with a major effect size that predisposes to TGCC. Genome-wide pathway association analysis indicated a weak association of rare CNVs related to cell migration (false-discovery rate = 0.021, 1.8% of cases and 1.1% of controls). Dysregulation during migration of primordial germ cells has previously been suspected to be a part of TGCC development and this set of multiple rare variants may thereby have a minor contribution to an increased susceptibility of TGCCs.

**General information**

State: Published

Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Copenhagen University Hospital


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**Publication information**

Journal: Frontiers in Endocrinology

Volume: 4

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Scopus rating (2016): SJR 1.772 SNIP 1.078 CiteScore 3.72

BFI (2015): BFI-level 1

Scopus rating (2015): SJR 1.808 SNIP 1.004 CiteScore 3.69

BFI (2014): BFI-level 1

Scopus rating (2014): SJR 1.411 SNIP 0.832 CiteScore 3.21

BFI (2013): BFI-level 1

Scopus rating (2013): SJR 0.99 SNIP 0.604 CiteScore 2.35

ISI indexed (2013): ISI indexed no

Scopus rating (2012): SJR 0.298 SNIP 0.277 CiteScore 0.79

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**Genome-wide meta-analysis identifies new susceptibility loci for migraine.**

Migraine is the most common brain disorder, affecting approximately 14% of the adult population, but its molecular mechanisms are poorly understood. We report the results of a meta-analysis across 29 genome-wide association studies, including a total of 23,285 individuals with migraine (cases) and 95,425 population-matched controls. We identified 12 loci associated with migraine susceptibility (P <5 × 10(-8)). Five loci are new: near AJAP1 at 1p36, near TSPAN2 at 1p13, within FHL5 at 6q16, near C7orf10 at 7p14 and near MMP16 at 8q21. Three of these loci were identified in disease subgroup analyses. Brain tissue expression quantitative trait locus analysis suggests potential functional candidate genes at four loci: APOA1BP, TBC1D7, FUT9, STAT6 and ATP5B.

**General information**

State: Published

Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Integrative Systems Biology

Authors: Anttila, V. (Ekstern), Winsvold, B. S. (Ekstern), Gormley, P. (Ekstern), Kurth, T. (Ekstern), Bettella, F. (Ekstern), McMahon, G. (Ekstern), Kallida, M. (Ekstern), Malik, R. (Ekstern), de Vries, B. (Ekstern), Terwindt, G. (Ekstern), Medland, S. E. (Ekstern), Todt, U. (Ekstern), McArdle, W. L. (Ekstern), Quaye, L. (Ekstern), Koiranen, M. (Ekstern), Ikram, M. A.
Genomics of an emerging clone of Salmonella serovar Typhimurium ST313 from Nigeria and the Democratic Republic of Congo.

We showed in a limited number of isolates that S. Typhimurium ST313 is a prevalent sequence-type causing gastrointestinal diseases and septicemia in patients from Nigeria and DRC. We found three distinct phylogenetic clusters based on the origin of isolation suggesting some spatial evolution. Comparative genomics showed an interesting putative virulence fragment (ST313-TD) unique to S. Typhimurium ST313 and invasive S. Dublin.

General information
State: Published
Organisations: Comparative Microbial Genomics, National Food Institute, Division of Epidemiology and Microbial Genomics, Center for Biological Sequence Analysis, Immunological Bioinformatics, Division of Microbiology and Risk Assessment, Translational Genomics Research Institute, University of Ibadan, Saint-Pierre University Hospital
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Scopus rating (2016): SJR 0.681 SNIP 0.917 CiteScore 1.56
Scopus rating (2015): SJR 0.68 SNIP 0.897 CiteScore 1.34
Scopus rating (2014): SJR 0.665 SNIP 1.083 CiteScore 1.44
Web of Science (2014): Indexed yes
Scopus rating (2013): SJR 0.701 SNIP 1.169 CiteScore 1.65
Genotyping using whole-genome sequencing is a realistic alternative to surveillance based on phenotypic antimicrobial susceptibility testing

Objectives: Antimicrobial susceptibility testing of bacterial isolates is essential for clinical diagnosis, to detect emerging problems and to guide empirical treatment. Current phenotypic procedures are sometimes associated with mistakes and may require further genetic testing. Whole-genome sequencing (WGS) may soon be within reach even for routine surveillance and clinical diagnostics. The aim of this study was to evaluate WGS as a routine tool for surveillance of antimicrobial resistance compared with current phenotypic procedures.

Methods: Antimicrobial susceptibility tests were performed on 200 isolates originating from Danish pigs, covering four bacterial species. Genomic DNA was purified from all isolates and sequenced as paired-end reads on the Illumina platform. The web servers ResFinder and MLST (www.genomicepidemiology.org) were used to identify acquired antimicrobial resistance genes and MLST types (where MLST stands for multilocus sequence typing). ResFinder results were compared with phenotypic antimicrobial susceptibility testing results using EUCAST epidemiological cut-off values and MLST types.

Results: A total of 3051 different phenotypic tests were performed; 482 led to the categorizing of isolates as resistant and 2569 as susceptible. Seven cases of disagreement between tested and predicted susceptibility were observed, six of which were related to spectinomycin resistance in Escherichia coli. Correlation between MLST type and resistance profiles was only observed in Salmonella Typhimurium, where isolates belonging to sequence type (ST) 34 were more resistant than ST19 isolates.

Conclusions: High concordance (99.74%) between phenotypic and predicted antimicrobial susceptibility was observed. Thus, antimicrobial resistance testing based on WGS is an alternative to conventional phenotypic methods. 

General information
State: Published
Organisations: Center for Biological Sequence Analysis, National Food Institute, Division of Epidemiology and Microbial Genomics, Center for Systems Microbiology, Division of Food Microbiology, Department of Systems Biology
Authors: Zankari, E. (Intern), Hasman, H. (Intern), Kaas, R. S. (Intern), Seyfarth, A. M. (Intern), Agersø, Y. (Intern), Lund, O. (Intern), Larsen, M. V. (Intern), Aarestrup, F. M. (Intern)
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Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 4.21 SJR 2.24 SNIP 1.527
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.203 SNIP 1.513 CiteScore 4.06
Gestation reverses obesity-induced hepatic inflammation in mice

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Cambridge

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Gestation reverses obesity-induced hepatic inflammation in mice

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Scopus rating (2016): SJR 1.148 SNIP 1.213 CiteScore 1.84
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.229 SNIP 1.19 CiteScore 1.9
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.197 SNIP 1.294 CiteScore 2
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.092 SNIP 1.136 CiteScore 1.82
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 0.897 SNIP 1.012 CiteScore 1.62
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 0.952 SNIP 1.077 CiteScore 1.72
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 0.911 SNIP 1.009
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 0.896 SNIP 1.028
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 0.736 SNIP 0.923
Scopus rating (2007): SJR 0.796 SNIP 0.972
Scopus rating (2006): SJR 0.887 SNIP 1.014
Scopus rating (2005): SJR 0.902 SNIP 1.148
Global characterization of signalling networks associated with tamoxifen resistance in breast cancer

Acquired resistance to the anti-estrogen tamoxifen remains a significant challenge in breast cancer management. In this study, we used an integrative approach to characterize global protein expression and tyrosine phosphorylation events in tamoxifen-resistant MCF7 breast cancer cells (TamR) compared with parental controls. Quantitative mass spectrometry and computational approaches were combined to identify perturbed signalling networks, and candidate regulatory proteins were functionally interrogated by siRNA-mediated knockdown. Network analysis revealed that cellular metabolism was perturbed in TamR cells, together with pathways enriched for proteins associated with growth factor, cell–cell and cell matrix-initiated signalling. Consistent with known roles for Ras/MAPK and PI3-kinase signalling in tamoxifen resistance, tyrosine-phosphorylated MAPK1, SHC1 and PIK3R2 were elevated in TamR cells. Phosphorylation of the tyrosine kinase Yes and expression of the actin-binding protein myristoylated alanine-rich C-kinase substrate (MARCKS) were increased two- and eightfold in TamR cells respectively, and these proteins were selected for further analysis. Knockdown of either protein in TamR cells had no effect on anti-estrogen sensitivity, but significantly decreased cell motility. MARCKS expression was significantly higher in breast cancer cell lines than normal mammary epithelial cells and in ER-negative versus ER-positive breast cancer cell lines. In primary breast cancers, cytoplasmic MARCKS staining was significantly higher in basal-like and HER2 cancers than in luminal cancers, and was independently predictive of poor survival in multivariate analyses of the whole cohort (P <0.0001) and in ER-positive patients (P = 0.0005). These findings provide network-level insights into the molecular alterations associated with the tamoxifen-resistant phenotype, and identify MARCKS as a potential biomarker of therapeutic responsiveness that may assist in stratification of patients for optimal therapy.
Glucagon-Like Peptide-1 Protects Human Islets against Cytokine-Mediated β-Cell Dysfunction and Death: A Proteomic Study of the Pathways Involved

Glucagon-like peptide-1 (GLP-1) has been shown to protect pancreatic β-cells against cytokine-induced dysfunction and destruction. The mechanisms through which GLP-1 exerts its effects are complex and still poorly understood. The aim of this study was to analyze the protein expression profiles of human islets of Langerhans treated with cytokines (IL-1β and IFN-γ) in the presence or absence of GLP-1 by 2D difference gel electrophoresis and subsequent protein interaction network analysis to understand the molecular pathways involved in GLP-1-mediated β-cell protection. Co-incubation of cytokine-treated human islets with GLP-1 resulted in a marked protection of β-cells against cytokine-induced apoptosis and significantly attenuated cytokine-mediated inhibition of glucose-stimulated insulin secretion. The cytoprotective effects of GLP-1 coincided with substantial alterations in the protein expression profile of cytokine-treated human islets, illustrating a counteracting effect on proteins from different functional classes such as actin cytoskeleton, chaperones, metabolic proteins, and islet regenerating proteins. In summary, GLP-1 alters in an integrated manner protein networks in cytokine-exposed human islets while protecting them against cytokine-mediated cell death and dysfunction. These data illustrate the beneficial effects of GLP-1 on human islets under immune attack, leading to a better understanding of the underlying mechanisms involved, a prerequisite for improving therapies for diabetic patients.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, KU Leuven, University of Pisa
Authors: Rondas, D. (Ekstern), Bugliani, M. (Ekstern), D’Hertog, W. (Ekstern), Hansen, K. L. (Intern), Masini, M. (Ekstern), Waelkens, E. (Ekstern), Marchetti, P. (Ekstern), Mathieu, C. (Ekstern), Overbergh, L. (Ekstern)
Pages: 204193–4206
Publication date: 2013
Main Research Area: Technical/natural sciences

Publication information
Journal: Journal of Proteome Research
Volume: 12
Issue number: 9
ISSN (Print): 1535-3893
Ratings:
BFI (2018): BFI-level 2
BFI (2017): BFI-level 2
Web of Science (2017): Indexed yes
Gut Mucosal Regulation of Distinct Macrophage and Dendritic Cell Subsets During Early Stage Salmonella Infection

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, National Food Institute, Division of Food Microbiology
Authors: Sørensen, R. B. (Intern), Petersen, A. (Ekstern), Larsen, J. M. (Intern), Licht, T. R. (Intern), Pedersen, S. B. (Intern)
Pages: 262-263
Publication date: 2013
Conference: 41st Meeting and Summer School of the Scandinavian-Society-for-Immunology, Copenhagen, Denmark, 14/04/2013 - 14/04/2013
Main Research Area: Technical/natural sciences
HELQ promotes RAD51 paralogue-dependent repair to avert germ cell loss and tumorigenesis

Repair of interstrand crosslinks (ICLs) requires the coordinated action of the intra-S-phase checkpoint and the Fanconi anaemia pathway, which promote ICL incision, translesion synthesis and homologous recombination (reviewed in refs 1, 2). Previous studies have implicated the 3'-5' superfamily 2 helicase HELQ in ICL repair in Drosophila melanogaster (MUS301 (ref. 3)) and Caenorhabditis elegans (HELQ-1 (ref. 4)). Although in vitro analysis suggests that HELQ preferentially unwinds synthetic replication fork substrates with 3’ single-stranded DNA overhangs and also disrupts protein-DNA interactions while translocating along DNA, little is known regarding its functions in mammalian organisms. Here we report that HELQ helicase-deficient mice exhibit subfertility, germ cell attrition, ICL sensitivity and tumour predisposition, with Helq heterozygous mice exhibiting a similar, albeit less severe, phenotype than the null, indicative of haploinsufficiency. We establish that HELQ interacts directly with the RAD51 paralogue complex BCDX2 and functions in parallel to the Fanconi anaemia pathway to promote efficient homologous recombination at damaged replication forks. Thus, our results reveal a critical role for HELQ in replication-coupled DNA repair, germ cell maintenance and tumour suppression in mammals.
HExpoChem: a systems biology resource to explore human exposure to chemicals

Summary: Humans are exposed to diverse hazardous chemicals daily. Although an exposure to these chemicals is suspected to have adverse effects on human health, mechanistic insights into how they interact with the human body are still limited. Therefore, acquisition of curated data and development of computational biology approaches are needed to assess the health risks of chemical exposure. Here we present HExpoChem, a tool based on environmental chemicals and their bioactivities on human proteins with the objective of aiding the qualitative exploration of human exposure to chemicals. The chemical–protein interactions have been enriched with a quality-scored human protein–protein interaction network, a protein–protein association network and a chemical–chemical interaction network, thus allowing the study of environmental chemicals through formation of protein complexes and phenotypic outcomes enrichment. Availability: HExpoChem is available at http://www.cbs.dtu.dk/services/HExpoChem-1.0/. Contact: karine@cbs.dtu.dk Supplementary information: Supplementary data are available at Bioinformatics online.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology
Pages: 1231-1232
Publication date: 2013
Main Research Area: Technical/natural sciences

Publication information
Journal: Bioinformatics
Volume: 29
Issue number: 9
ISSN (Print): 1367-4803
Ratings:
BFI (2018): BFI-level 2
BFI (2017): BFI-level 2
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 6.42
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): CiteScore 6.06
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): CiteScore 5.5
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): CiteScore 5.78
High-Mannose Glycosylation of Infectious HIV-1 gp120 and Immune Regulation in Human Plasmacytoid Dendritic Cells

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Statens Serum Institut
Authors: Søndergaard, J. N. (Intern), Vinner, L. (Ekstern), Pedersen, S. B. (Intern)
Pages: 264-265
Publication date: 2013
Conference: 41st Meeting and Summer School of the Scandinavian-Society-for-Immunology , Copenhagen, Denmark, 14/04/2013 - 14/04/2013
Main Research Area: Technical/natural sciences

Publication information
Journal: Scandinavian Journal of Immunology
Volume: 77
Issue number: 4
ISSN (Print): 0300-9475
Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.03 SJR 0.951 SNIP 0.646
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.93 SNIP 0.684 CiteScore 1.97
Web of Science (2015): Indexed yes
Identification of a novel immunoregulatory signaling pathway exploited by M. tuberculosis in dendritic cells

The causative agent of tuberculosis, Mycobacterium tuberculosis, has infected over a third of the world's population and poses a massive burden to health care systems and human well-being. Most M. tuberculosis infections are latent and are not cleared fully by the host immune system due to the highly sophisticated infectious machinery employed by the bacterium. The dendritic cell (DC) plays a crucial role in shaping the nature of the immune response after exposure to pathogens, and the interaction between M. tuberculosis and the dendritic cell is of profound importance for the course of infection. During their interaction, the DC is exposed to multiple M. tuberculosis-derived ligands recognized by a range of pattern recognition receptors, but the result is typically an immune response that is not very effective at clearing the bacteria from the host. The reason why the induced immune response is ineffective at clearing the bacteria is not fully understood, but clues may be given in the signaling pathways induced in DCs upon M. tuberculosis-exposure.

General information
Identification of a novel immunoregulatory signaling pathway exploited by M. tuberculosis in dendritic cells

The causative agent of tuberculosis, Mycobacterium tuberculosis, has infected over a third of the world's population and poses a massive burden to health care systems and human well-being. Most M. tuberculosis infections are latent and are not cleared fully by the host immune system due to the highly sophisticated infectious machinery employed by the bacterium. The dendritic cell (DC) plays a crucial role in shaping the nature of the immune response after exposure to pathogens, and the interaction between M. tuberculosis and the dendritic cell is of profound importance for the course of infection. During their interaction, the DC is exposed to multiple M. tuberculosis-derived ligands recognized by a range of pattern recognition receptors, but the result is typically an immune response that is not very effective at clearing the bacteria from the host. The reason why the induced immune response is ineffective at clearing the bacteria is not fully understood, but clues may be given in the signaling pathways induced in DCs upon M. tuberculosis-exposure.
Identification of A Novel Immunoregulatory Signaling Pathway Exploited by Mycobacterium tuberculosis in Dendritic Cells

General information
State: Published
Identification of LasR Ligands through a Virtual Screening Approach

With the widespread occurrence of bacterial resistance to antibiotics, the development of new strategies beyond conventional treatments is a pursuit taken by public health institutions worldwide. LasR, a transcription factor that controls quorum sensing in Pseudomonas aeruginosa, has emerged as an attractive therapeutic target for the next generation of antimicrobial agents. In the present study, a virtual screening workflow combining pharmacophore- and structure-based approaches was used to identify new LasR ligands. Five novel inducers and three inhibitors of LasR activity were validated experimentally by use of a cell-based assay. Interestingly, these compounds are molecularly distinct from the native signal molecule, N-3-oxododecanoyl-L-homoserine lactone (OHN), and may serve as lead structures for the design of new drugs. The binding modes of these compounds to the OHN binding site in LasR were predicted and used to identify the key interactions that contribute to the induction and inhibition of LasR activity.

General information
State: Published
Organisations: Organic Chemistry, Department of Chemistry, Center for Biological Sequence Analysis, Department of Systems Biology, University of Copenhagen, Technical University of Denmark
Pages: 157-163
Publication date: 2013
Main Research Area: Technical/natural sciences

Publication information
Journal: ChemMedChem
Volume: 8
Issue number: 1
ISSN (Print): 1860-7179
Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): SJR 1.13 SNIP 0.906 CiteScore 3.11
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.148 SNIP 0.905 CiteScore 3
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.11 SNIP 0.907 CiteScore 2.83
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.142 SNIP 0.845 CiteScore 2.93
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.125 SNIP 0.814 CiteScore 2.87
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.263 SNIP 0.928 CiteScore 3.24
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.264 SNIP 0.923
Identification of peptides from foot-and-mouth disease virus structural proteins bound by class I swine leukocyte antigen (SLA) alleles, SLA-1*0401 and SLA-2*0401

Characterization of the peptide-binding specificity of swine leukocyte antigen (SLA) class I and II molecules is critical to the understanding of adaptive immune responses of swine toward infectious pathogens. Here, we describe the complete binding motif of the SLA-2*0401 molecule based on a positional scanning combinatorial peptide library approach. By combining this binding motif with data achieved by applying the NetMHCpan peptide prediction algorithm to both SLA-1*0401 and SLA-2*0401, we identified high-affinity binding peptides. A total of 727 different 9mer and 726 different 10mer peptides within the structural proteins of foot-and-mouth disease virus (FMDV), strain A24 were analyzed as candidate T-cell epitopes. Peptides predicted by the NetMHCpan were tested in ELISA for binding to the SLA-1*0401 and SLA-2*0401 major histocompatibility complex class I proteins. Four of the 10 predicted FMDV peptides bound to SLA-2*0401, whereas five of the nine predicted FMDV peptides bound to SLA-1*0401. These methods provide the characterization of T-cell epitopes in response to pathogens in more detail. The development of such approaches to analyze vaccine performance will contribute to a more accelerated improvement of livestock vaccines by virtue of identifying and focusing analysis on bona fide T-cell epitopes.

General information
State: Published
Organisations: National Veterinary Institute, Section for Immunology and Vaccinology, Department of Systems Biology, Center for Biological Sequence Analysis, United States Department of Agriculture, University of Copenhagen
Authors: Pedersen, L. E. (Intern), Harndahl, M. (Forskerdatabase), Nielsen, M. (Intern), Patch, J. R. (Ekstern), Jungersen, G. (Intern), Buus, S. (Ekstern), Golde, W. T. (Ekstern)
Number of pages: 8
Pages: 251-258
Publication date: 2013
Main Research Area: Technical/natural sciences

Publication information
Journal: Animal Genetics
Volume: 44
Issue number: 3
ISSN (Print): 0268-9146
Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 1.64 SJR 0.732 SNIP 0.803
BFI (2015): BFI-level 1
Identification of Y-Chromosomally Encoded Minor Histocompatibility Antigens Using a Reverse Immunology Approach

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Copenhagen University Hospital, University of Copenhagen
Authors: Mortensen, B. K. (Forskerdatabase), Brændstrup, P. (Forskerdatabase), Larsen, M. E. (Intern), Larsen, M. V. (Intern), Lund, O. (Intern), Rasmussen, M. (Ekstern), Buus, S. (Ekstern), Stryhn, A. (Ekstern), Vindeløv, L. (Forskerdatabase)
Pages: S335
Publication date: 2013
Conference: 2013 BMT Tandem Meetings, Salt Lake City, Utah, United States, 13/02/2013 - 13/02/2013
Main Research Area: Technical/natural sciences

Publication information
Journal: Biology of Blood and Marrow Transplantation
Volume: 19
Issue number: 2
ISSN (Print): 1083-8791
Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Identificiation of Y-Chromosomally Encoded Minor Histocompatibility Antigens Using a Reverse Immunology Approach

General information

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Immunological Bioinformatics, Copenhagen University Hospital, University of Copenhagen
Authors: Mortensen, B. K. (Ekstern), Brændstrup, P. (Ekstern), Larsen, M. E. (Intern), Larsen, M. V. (Intern), Lund, O. (Intern), Rasmussen, M. (Ekstern), Buus, S. (Ekstern), Stryhn, A. (Ekstern), Vindeløv, L. (Ekstern)
Pages: 317-318
Publication date: 2013
Conference: 41st Meeting and Summer School of the Scandinavian-Society-for-Immunology, Copenhagen, Denmark, 14/04/2013 - 14/04/2013
Main Research Area: Technical/natural sciences

Publication information
Inconsistency in large pharmacogenomic studies

Two large-scale pharmacogenomic studies were published recently in this journal. Genomic data are well correlated between studies; however, the measured drug response data are highly discordant. Although the source of inconsistencies remains uncertain, it has potential implications for using these outcome measures to assess gene-drug associations or select potential anticancer drugs on the basis of their reported results.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Montreal, Harvard Medical School, Dana-Farber Cancer Institute
Authors: Haibe-Kains, B. (Ekstern), El-Hachem, N. (Ekstern), Birkbak, N. J. (Intern), Jin, A. C. (Ekstern), Beck, A. H. (Ekstern), Aerts, H. J. W. L. (Ekstern), Quackenbush, J. (Ekstern)
Pages: 389–393
Publication date: 2013
Main Research Area: Technical/natural sciences

Publication information
Journal: Nature
Volume: 504
Issue number: 7480
ISSN (Print): 0028-0836
Ratings:
BFI (2018): BFI-level 3
BFI (2017): BFI-level 2
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 13.33
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): CiteScore 14.38
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): CiteScore 14.22
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): CiteScore 14.96
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): CiteScore 14.01
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): CiteScore 13.96
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Web of Science (2010): Indexed yes
In silico peptide-binding predictions of passerine MHC class I reveal similarities across distantly related species, suggesting convergence on the level of protein function

The major histocompatibility complex (MHC) genes are the most polymorphic genes found in the vertebrate genome, and they encode proteins that play an essential role in the adaptive immune response. Many songbirds (passerines) have been shown to have a large number of transcribed MHC class I genes compared to most mammals. To elucidate the reason for this large number of genes, we compared 14 MHC class I alleles (α1–α3 domains), from great reed warbler, house sparrow and tree sparrow, via phylogenetic analysis, homology modelling and in silico peptide-binding predictions to investigate their functional and genetic relationships. We found more pronounced clustering of the MHC class I allomorphs (allele specific proteins) in regards to their function (peptide-binding specificities) compared to their genetic relationships (amino acid sequences), indicating that the high number of alleles is of functional significance. The MHC class I allomorphs from house sparrow and tree sparrow, species that diverged 10 million years ago (MYA), had overlapping peptide-binding specificities, and these similarities across species were also confirmed in phylogenetic analyses based on amino acid sequences. Notably, there were also overlapping peptide-binding specificities in the allomorphs from house sparrow and great reed warbler, although these species diverged 30 MYA. This overlap was not found in a tree based on amino acid sequences. Our interpretation is that convergent evolution on the level of the protein function, possibly driven by selection from shared pathogens, has resulted in allomorphs with similar peptide-binding repertoires, although trans-species evolution in combination with gene conversion cannot be ruled out.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Lund University
Authors: Follin, E. (Ekstern), Karlsson, M. (Ekstern), Lundegaard, C. (Intern), Nielsen, M. (Intern), Wallin, S. (Ekstern), Paulsson, K. M. (Forskerdatabase), Westerdahl, H. (Ekstern)
Pages: 299-311
Publication date: 2013
Main Research Area: Technical/natural sciences

Publication information
Journal: Immunogenetics
Volume: 65
Issue number: 4
ISSN (Print): 0093-7711
Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.2 SJR 1.231 SNIP 0.703
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.551 SNIP 0.819 CiteScore 2.47
Integrative Annotation of Variants from 1092 Humans: Application to Cancer Genomics

Identifying Important Identifiers

Each of us has millions of sequence variations in our genomes. Signatures of purifying or negative selection should help identify which of those variations is functionally important. Khurana et al. (1235587) used sequence polymorphisms from 1092 humans across 14 populations to identify patterns of selection, especially in noncoding regulatory regions. Noncoding regions under very strong negative selection included binding sites of some chromatin and general transcription factors (TFs) and core motifs of some important TF families. Positive selection in TF binding sites tended to occur in network hub promoters. Many recurrent somatic cancer variants occurred in noncoding regulatory regions and thus might indicate mutations that drive cancer.
Internet-Based Solutions for Analysis of Next-Generation Sequence Data

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis
Authors: Larsen, M. V. (Intern)
Pages: 3162-3162
Publication date: 2013
Main Research Area: Technical/natural sciences

Publication information
Journal: Journal of Clinical Microbiology
Volume: 51
Issue number: 9
ISSN (Print): 0095-1137
Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.57 SJR 2.14 SNIP 1.417
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.204 SNIP 1.448 CiteScore 3.56
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.205 SNIP 1.538 CiteScore 3.84
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 2.414 SNIP 1.646 CiteScore 4.18
Web of Science (2013): Indexed yes
In Vivo SILAC-Based Proteomics Reveals Phosphoproteome Changes during Mouse Skin Carcinogenesis

SILAC technology in combination with high-resolution mass spectrometry (MS) can be successfully used to measure phosphoproteomes in vivo. Here, Zanivan, Mann, and colleagues have applied SILAC-based MS to investigate phosphoproteomic changes during skin carcinogenesis, using the DMBA/TPA two-stage mouse model. Using this approach, the authors have revealed the phosphoproteomic dynamics that accompany skin cancer progression and predict specific kinase activities associated with tumor malignancy.

General information

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Beatson Institute for Cancer Research, Mayo Clinic College of Medicine, Max Planck Institute, National Institute of Environmental Health Sciences Research, University of Copenhagen
Authors: Zanivan, S. (Ekstern), Meves, A. (Ekstern), Behrendt, K. (Ekstern), Schoof, E. (Intern), Neilson, L. J. (Ekstern), Cox, J. (Ekstern), Tang, H. R. (Ekstern), Kalna, G. (Ekstern), van Ree, J. H. (Ekstern), van Deursen, J. M. (Ekstern), Trempus, C. S. (Ekstern), Machesky, L. M. (Ekstern), Linding, R. (Intern), Wickström, S. A. (Ekstern), Fässler, R. (Ekstern), Mann, M. (Forskerdatabase)
Kinetic Model for Signal Binding to the Quorum Sensing Regulator LasR

We propose a kinetic model for the activation of the las regulon in the opportunistic pathogen Pseudomonas aeruginosa. The model is based on in vitro data and accounts for the LasR dimerization and consecutive activation by binding of two OdDHL signal molecules. Experimentally, the production of the active LasR quorum-sensing regulator was studied in an Escherichia coli background as a function of signal molecule concentration. The functional activity of the regulator was monitored via a GFP reporter fusion to lasB expressed from the native lasB promoter. The new data shows that the active form of the LasR dimer binds two signal molecules cooperatively and that the timescale for reaching saturation is independent of the signal molecule concentration. This favors a picture where the dimerized regulator is protected against proteases and remains protected as it is activated through binding of two successive signal molecules. In absence of signal molecules, the dimerized regulator can dissociate and degrade through proteolytic turnover of the monomer. This resolves the apparent contradiction between our data and recent reports that the fully protected dimer is able to “degrade” when the induction of LasR ceases.

General information
State: Published
Organisations: Department of Electrical Engineering, Biomedical Engineering, Department of Systems Biology, Center for Biological Sequence Analysis, University of Cambridge, University of Copenhagen
Authors: Claussen, A. (Intern), Jakobsen, T. H. (Ekstern), Bjarnsholt, T. (Ekstern), Givskov, M. (Ekstern), Welch, M. (Ekstern), Ferkinghoff-Borg, J. (Intern), Sams, T. (Intern)
Pages: 13360-13376
Publication date: 2013
Main Research Area: Technical/natural sciences
LC-MS at core of university-industry link

LC-MS at core of university-industry link Thermo Fisher Scientific (TFS) and the Department of Systems Biology at the Technical University of Denmark, (DTU), have formed a collaboration to pursue breakthroughs in the understanding of how cellular protein networks drive important diseases by exploiting liquid chromatography coupled to mass spectrometry (LC-MS). TFS will provide early access to new technology and designs, and DTU proteomics scientists will provide feedback and collaborate on new applications. The centerpiece of this collaboration is a new proteomics laboratory in Lyngby, Denmark, equipped with the latest LC-MS technology, including the TFS Orbitrap Fusion Tribrid LC-MS system that offers unprecedented depth of analysis of biological samples.

“Studying the dynamic rewiring of cellular signaling networks requires state-of-the-art mass spectrometry,” said DTU’s Professor Rune Linding (Fig. 8). “The Orbitrap Fusion system enables us to push the boundaries and to analyze completely new avenues of cellular decision processes, and to perform genome-scale studies of how the dynamics in
these networks affect cell behavior. This is crucial, as it is now clear that the progression of complex diseases, such as cancer, is due to changes in these molecular networks. "We were extremely excited to see, only a few days after installation, the Orbitrap Fusion system generate the best MS/MS data we have ever seen for the characterization of phosphorylation sites on critical tumor samples." "We are immensely pleased to be working with this talented and motivated team of scientists," said Iain Mylchreest, vice president, research and development, life science mass spectrometry, TFS. "We share with them the objective of pushing the limits of science to make the world a better place, and the Orbitrap Fusion Tribrid system is designed for precisely this type of visionary research." DTU is establishing the state-of-the-art laboratory to develop new experiments to dig deeper into the core machinery of the cell. The new laboratory will use four TFS Q Exactive LC-MS/MS systems, and nano-LC 1000 systems along with one of the first TFS Orbitrap Fusion Tribrid systems to leave the factory since its June 2013 debut.

**General information**
- **State**: Published
- **Organisations**: Department of Systems Biology, Center for Biological Sequence Analysis, Cellular Signal Integration
- **Authors**: Linding, R. (Intern)
- **Pages**: VIII-IX
- **Publication date**: 2013
- **Main Research Area**: Technical/natural sciences

**Publication information**
- **Journal**: Trends in Analytical Chemistry
- **Volume**: 51
- **ISSN (Print)**: 0165-9936
- **Ratings**:
  - BFI (2018): BFI-level 2
  - BFI (2017): BFI-level 2
  - Web of Science (2017): Indexed Yes
  - BFI (2016): BFI-level 2
  - Scopus rating (2016): SJR 2.499 SNIP 2.402 CiteScore 8.09
  - BFI (2015): BFI-level 2
  - Scopus rating (2015): SJR 2.437 SNIP 2.322 CiteScore 7.24
  - BFI (2014): BFI-level 2
  - Scopus rating (2014): SJR 2.194 SNIP 2.253 CiteScore 6.54
  - Web of Science (2014): Indexed yes
  - BFI (2013): BFI-level 2
  - Scopus rating (2013): SJR 2.292 SNIP 2.204 CiteScore 6.47
  - ISI indexed (2013): ISI indexed yes
  - Web of Science (2013): Indexed yes
  - BFI (2012): BFI-level 2
  - Scopus rating (2012): SJR 2.346 SNIP 2.057 CiteScore 5.9
  - ISI indexed (2012): ISI indexed yes
  - Web of Science (2012): Indexed yes
  - BFI (2011): BFI-level 2
  - Scopus rating (2011): SJR 2.715 SNIP 2.084 CiteScore 6.52
  - ISI indexed (2011): ISI indexed yes
  - Web of Science (2011): Indexed yes
  - BFI (2010): BFI-level 2
  - Scopus rating (2010): SJR 2.636 SNIP 1.861
  - BFI (2009): BFI-level 2
  - Scopus rating (2009): SJR 2.791 SNIP 1.851
  - Web of Science (2009): Indexed yes
  - BFI (2008): BFI-level 1
  - Scopus rating (2008): SJR 2.498 SNIP 1.936
  - Web of Science (2008): Indexed yes
  - Scopus rating (2007): SJR 2.124 SNIP 1.952
  - Web of Science (2007): Indexed yes
  - Scopus rating (2006): SJR 2.127 SNIP 1.955
Lipid hydrolysis products affect the composition of microbiota isolated from infant fecal samples after in vitro fermentation

Some lipid hydrolysis products such as medium-chained free fatty acids (FFA) and monoacylglycerols (MAG) have antibacterial activity, while others, including oleic acid, have been reported to be essential for optimal growth of Lactobacillus species. Thus, the FFA and MAG concentration in the distal ileum and in colon can be expected to selectively modulate the growth rate and hereby the composition of the microbiota.

In earlier studies, we have shown that this concentration is dependent on the type of emulsification of the triglycerides, which deviates between breast milk and formula milk.

Here, we have determined effects of selected combinations of FFA and MAG on microbial composition during a 24-hour anaerobic in vitro fermentation in microbiota obtained from infant fecal samples (age 2-5 months). PCR-based quantification of 11 different bacterial taxa revealed that the growth of Firmicutes, Lactobacillus and B. longum is significantly increased in the presence of a mixture of C10-C14 FFAs.
about what the reference might be, transferring a relatively small amount of data. Our system consists of a server with known reference DNA indexed, and a client with raw sequencing reads. The client sends a sample of unidentified reads, and in return receives a list of matching references. Sequences for the references can be retrieved and used for exhaustive computation on the reads, such as alignment. To demonstrate this approach we have implemented a web server, indexing tens of thousands of publicly available genomes and genomic regions from various organisms and returning lists of matching hits from query sequencing reads. We have also implemented two clients: one running in a web browser, and one as a python script. Both are able to handle a large number of sequencing reads and from portable devices (the browser-based running on a tablet), perform its task within seconds, and consume an amount of bandwidth compatible with mobile broadband networks. Such client-server approaches could develop in the future, allowing a fully automated processing of sequencing data and routine instant quality check of sequencing runs from desktop sequencers. A web access is available at http://tapir.cbs.dtu.dk. The source code for a python command-line client, a server, and supplementary data are available at http://bit.ly/1aURxkc.

**General information**

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, DTU Multi Assay Core, Immunological Bioinformatics
Authors: Gautier, L. (Intern), Lund, O. (Intern)
Number of pages: 10
Publication date: 2013
Main Research Area: Technical/natural sciences

**Publication information**

Journal: *P L o S One*
Volume: 8
Issue number: 12
Article number: e83784
ISSN (Print): 1932-6203
Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.11 SJR 1.201 SNIP 1.092
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.414 SNIP 1.131 CiteScore 3.32
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.545 SNIP 1.141 CiteScore 3.54
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.74 SNIP 1.147 CiteScore 3.94
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.945 SNIP 1.142 CiteScore 4.15
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 2.369 SNIP 1.23 CiteScore 4.58
ISI indexed (2011): ISI indexed no
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 2.631 SNIP 1.161
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 2.473 SNIP 0.985
Web of Science (2009): Indexed yes
Mapping Condition-Dependent Regulation of Lipid Metabolism in Saccharomyces cerevisiae.

Lipids play a central role in cellular function as constituents of membranes, as signaling molecules, and as storage materials. Although much is known about the role of lipids in regulating specific steps of metabolism, comprehensive studies integrating genome-wide expression data, metabolite levels, and lipid levels are currently lacking. Here, we map condition-dependent regulation controlling lipid metabolism in Saccharomyces cerevisiae by measuring 5636 mRNAs, 50 metabolites, 97 lipids, and 57 $^{13}$C-reaction fluxes in yeast using a three-factor full-factorial design. Correlation analysis across eight environmental conditions revealed 2279 gene expression level-metabolite/lipid relationships that characterize the extent of transcriptional regulation in lipid metabolism relative to major metabolic hubs within the cell. To query this network, we developed integrative methods for correlation of multi-omics datasets that elucidate global regulatory signatures. Our data highlight many characterized regulators of lipid metabolism and reveal that sterols are regulated more at the transcriptional level than are amino acids. Beyond providing insights into the systems-level organization of lipid metabolism, we anticipate that our dataset and approach can join an emerging number of studies to be widely used for interrogating cellular systems through the combination of mathematical modeling and experimental biology.
9,920 controls. We increased the number of susceptibility loci with genome-wide significant association with allergic sensitization from three to ten, including SNPs in or near TLR6, STAT6, SLC25A46, HLA-DQB1, IL1RL1, LPP, MYC, IL2 and HLA-B. All the top SNPs were associated with allergic symptoms in an independent study. Risk-associated variants at these ten loci were estimated to account for at least 25% of allergic sensitization and allergic rhinitis. Understanding the molecular mechanisms underlying these associations may provide new insights into the etiology of allergic disease.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis

Publication date: 2013
Main Research Area: Technical/natural sciences

Publication information
Journal: Nature Genetics
ISSN (Print): 1061-4036
Ratings:
BFI (2018): BFI-level 3
BFI (2017): BFI-level 2
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): SJR 20.899 SNIP 6.62 CiteScore 20.83
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 23.808 SNIP 6.61 CiteScore 23.17
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 23.792 SNIP 6.306 CiteScore 22.76
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 23.629 SNIP 6.27 CiteScore 24.17
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 25.133 SNIP 7.138 CiteScore 27.17
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 24.838 SNIP 7.198 CiteScore 25.75
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 27.664 SNIP 6.792
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Metagenomic Analysis of the Human Gut Microbiome

Understanding the link between the human gut microbiome and human health is one of the biggest scientific challenges in our decade. Because 90% of our cells are bacteria, and the microbial genome contains 200 times more genes than the human genome, the study of the human microbiome has the potential to impact many areas of our health. This PhD thesis is the first study to generate a large amount of experimental data on the DNA and RNA of the human gut microbiome. This was made possible by our development of a human gut microbiome array capable of profiling any human gut microbiome. Analysis of our results changes the way we link the gut microbiome with diseases. Our results indicate that inflammatory diseases will affect the ecological system of the human gut microbiome, reducing its diversity. Classification analysis of healthy and unhealthy individuals demonstrates that unhealthy individuals have lower diversity microbiomes with incomplete functional capacity. Diversity is an important measurement linking microbiome variance to diseases. Our results suggest that diseases are linked to the microbiome not by the presence of “bad” bacteria, but mostly by the loss of the “good” bacteria. Finally, we show that bacterial adaptations explain the shift observed in the human gut microbiome.
Metagenomic species profiling using universal phylogenetic marker genes

To quantify known and unknown microorganisms at species-level resolution using shotgun sequencing data, we developed a method that establishes metagenomic operational taxonomic units (mOTUs) based on single-copy phylogenetic marker genes. Applied to 252 human fecal samples, the method revealed that on average 43% of the species abundance and 58% of the richness cannot be captured by current reference genome-based methods. An implementation of the method is available at http://www.bork.embl.de/software/mOTU/.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Novo Nordisk Foundation Center for Biosustainability, European Molecular Biology Laboratory, The Exelixis Lab, Scientific Computing Group, Heidelberg Institute for Theoretical Studies, Heidelberg, Hagedorn Research Institute, Novo Nordisk Foundation Center for Biosustainability, University Hospital Vall d’Hebron, Wageningen IMARES, King Abdulaziz University, Beijing Genomics Institute Hong Kong, INRA Institut National de La Recherche Agronomique, MAX DELBRUCK CENTER FOR MOLECULAR MEDICINE
Pages: 1196–1199
Publication date: 2013
Main Research Area: Technical/natural sciences

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Journal: Nature Methods
Volume: 10
Issue number: 12
ISSN (Print): 1548-7091
Ratings:
BFI (2018): BFI-level 2
BFI (2017): BFI-level 2
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 11.58 SJR 19.544 SNIP 5.24
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 20.9 SNIP 6.131 CiteScore 15.62
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 15.179 SNIP 4.815 CiteScore 13.54
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 10.093 SNIP 3.513 CiteScore 12.21
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 8.644 SNIP 2.969 CiteScore 10.1
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 9.535 SNIP 2.862 CiteScore 9.56
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 8.667 SNIP 2.474
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 7.497 SNIP 2.352
MetaRanker 2.0: a web server for prioritization of genetic variation data

MetaRanker 2.0 is a web server for prioritization of common and rare frequency genetic variation data. Based on heterogeneous data sets including genetic association data, protein–protein interactions, large-scale text-mining data, copy number variation data and gene expression experiments, MetaRanker 2.0 prioritizes the protein-coding part of the human genome to shortlist candidate genes for targeted follow-up studies. MetaRanker 2.0 is made freely available at www.cbs.dtu.dk/services/MetaRanker-2.0.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis
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Publication date: 2013
Main Research Area: Technical/natural sciences

Publication information
Journal: Nucleic Acids Research
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ISSN (Print): 0305-1048
Ratings:
BFI (2018): BFI-level 2
BFI (2017): BFI-level 2
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 9.28 SJR 7.397 SNIP 2.657
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 7.239 SNIP 2.639 CiteScore 9.48
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 6.576 SNIP 2.568 CiteScore 8.74
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 6.582 SNIP 2.266 CiteScore 8.46
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 6.13 SNIP 2.392 CiteScore 8.62
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 5.758 SNIP 2.172 CiteScore 7.86
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
Methods for predicting anti-cancer response

The present invention relates to methods for predicting response of a cancer in a subject to anti-cancer therapies based upon a determination and analysis of a chromosomal aberration score, such as the number of allelic imbalance or the number of telomeric allelic imbalance in the chromosomes of the human genome.

General information
State: Published
Organisations: Center for Biological Sequence Analysis
Authors: Szallasi, Z. I. (Intern), Eklund, A. C. (Intern), Birkbak, N. J. (Intern), Richardson, A. L. (Ekstern), Silver, D. P. (Ekstern), Wang, Z. (Ekstern)
Publication date: 2013

Publication information
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Patent number: WO2013130347
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Original language: English
Electronic versions:
WO2013130347A1.pdf
Main Research Area: Technical/natural sciences
Publication: Research - patent - Annual report year: 2012
MHCcluster, a method for functional clustering of MHC molecules

The identification of peptides binding to major histocompatibility complexes (MHC) is a critical step in the understanding of T cell immune responses. The human MHC genomic region (HLA) is extremely polymorphic comprising several thousand alleles, many encoding a distinct molecule. The potentially unique specificities remain experimentally uncharacterized for the vast majority of HLA molecules. Likewise, for nonhuman species, only a minor fraction of the known MHC molecules have been characterized. Here, we describe a tool, MHCcluster, to functionally cluster MHC molecules based on their predicted binding specificity. The method has a flexible web interface that allows the user to include any MHC of interest in the analysis. The output consists of a static heat map and graphical tree-based visualizations of the functional relationship between MHC variants and a dynamic TreeViewer interface where both the functional relationship and the individual binding specificities of MHC molecules are visualized. We demonstrate that conventional sequence-based clustering will fail to identify the functional relationship between molecules, when applied to MHC system, and only through the use of the predicted binding specificity can a correct clustering be found. Clustering of prevalent HLA-A and HLA-B alleles using MHCcluster confirms the presence of 12 major specificity groups (supertypes) some however with highly divergent specificities. Importantly, some HLA molecules are shown not to fit any supertype classification. Also, we use MHCcluster to show that chimpanzee MHC class I molecules have a reduced functional diversity compared to that of HLA class I molecules.
MicroRNA profiling in ocular adnexal lymphoma: a role for MYC and NFκB1 mediated dysregulation of microRNA expression in aggressive disease

Purpose. Ocular adnexal lymphoma (i.e., lymphoma with involvement of the orbit, eyelids, conjunctiva, lacrimal gland, and lacrimal sac), although rare, is common among malignant tumors involving the ocular adnexal region. The main subtypes are low-grade extranodal marginal zone lymphoma (EMZL) and aggressive diffuse large B-cell lymphoma (DLBCL). In rare cases, low-grade EMZL are reported to transform to DLBCL. It is unclear, however, which genetic events distinguish low-grade disease from aggressive, potentially fatal disease.

Methods. Using LNA-based arrays from Exiqon, we performed global microRNA (miRNA) expression profiling of 18 EMZLs and 25 DLBCLs involving ocular adnexal sites to investigate changes in the miRNA expression in low- versus high-grade disease. Findings were confirmed by real-time quantitative PCR (RTq-PCR).

Results. Our analysis revealed 43 miRNAs with altered expression profiles in DLBCL compared to EMZL. Seven of the miRNAs down-regulated in DLBCL relative to EMZL showed enrichment for a direct transcriptional repression by the oncoprotein MYC. We also report a possible loss-of-regulation of NFKB1 and its downstream miRNAs. In addition, our analysis identified a group of DLBCLs whose expression profiles resembled that of EMZL. Although transformation of EMZL to DLBCL in the ocular adnexal region is rare, we hypothesize that the intermediate group potentially may derive from transformation of EMZL that was not recognized by histology.

Conclusions. We conclude that fundamental differences in miRNA expression exist between ocular adnexal EMZL and DLBCL, mainly due to differences in MYC and NF-κB regulatory pathways.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Cancer Systems Biology, Integrative Systems Biology, Regulatory Genomics, Copenhagen University Hospital, University of Copenhagen
Authors: Hother, C. (Forskerdatabase), Rasmussen, P. K. (Ekstern), Joshi, T. (Intern), Reker, D. (Forskerdatabase), Ralfkær, U. (Ekstern), Workman, C. (Intern), Heegaard, S. (Forskerdatabase), Ralfkær, E. (Forskerdatabase), Grønbæk, K. (Forskerdatabase)
Pages: 5169-5175
Publication date: 2013
Main Research Area: Technical/natural sciences
**MISTIC: mutual information server to infer coevolution**

MISTIC (mutual information server to infer coevolution) is a web server for graphical representation of the information contained within a MSA (multiple sequence alignment) and a complete analysis tool for Mutual Information networks in protein families. The server outputs a graphical visualization of several information-related quantities using a circos representation. This provides an integrated view of the MSA in terms of (i) the mutual information (MI) between residue pairs, (ii) sequence conservation and (iii) the residue cumulative and proximity MI scores. Further, an interactive interface to explore and characterize the MI network is provided. Several tools are offered for selecting subsets of nodes from the network for visualization. Node coloring can be set to match different attributes, such as conservation, cumulative MI, proximity MI and secondary structure. Finally, a zip file containing all results can be downloaded. The server is available at [http://mistic.leloir.org.ar](http://mistic.leloir.org.ar). In summary, MISTIC allows for a comprehensive, compact, visually rich view of the information contained within an MSA in a manner unique to any other publicly available web server. In particular, the use of circos representation of MI networks and the visualization of the cumulative MI and proximity MI concepts is novel.

**General information**

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Fundación Instituto Leloir
Authors: Simonetti, F. L. (Ekstern), Teppa, E. (Ekstern), Chernomoretz, A. (Ekstern), Nielsen, M. (Intern), Marino Buslje, C. (Ekstern)
Pages: 20W8-W14
Publication date: 2013
Main Research Area: Technical/natural sciences

**Publication information**

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- BFI (2018): BFI-level 2
- BFI (2017): BFI-level 2
- Web of Science (2017): Indexed yes
- BFI (2016): BFI-level 2
- Scopus rating (2016): CiteScore 9.28 SJR 7.397 SNIP 2.657
- Web of Science (2016): Indexed yes
- BFI (2015): BFI-level 2
- Scopus rating (2015): SJR 7.239 SNIP 2.639 CiteScore 9.48
- Web of Science (2015): Indexed yes
- BFI (2014): BFI-level 2
- Scopus rating (2014): SJR 6.576 SNIP 2.568 CiteScore 8.74
- Web of Science (2014): Indexed yes
- BFI (2013): BFI-level 2
- Scopus rating (2013): SJR 6.582 SNIP 2.266 CiteScore 8.46
- ISI indexed (2013): ISI indexed yes
- Web of Science (2013): Indexed yes
- BFI (2012): BFI-level 2
- Scopus rating (2012): SJR 6.13 SNIP 2.392 CiteScore 8.62
- ISI indexed (2012): ISI indexed yes
- Web of Science (2012): Indexed yes
- BFI (2011): BFI-level 2
- Scopus rating (2011): SJR 5.758 SNIP 2.172 CiteScore 7.86
- ISI indexed (2011): ISI indexed yes
- Web of Science (2011): Indexed yes
- BFI (2010): BFI-level 2
- Scopus rating (2010): SJR 5.24 SNIP 2.034
- Web of Science (2010): Indexed yes
- BFI (2009): BFI-level 2
- Scopus rating (2009): SJR 5.571 SNIP 1.869
- BFI (2008): BFI-level 2
- Scopus rating (2008): SJR 4.641 SNIP 1.557
Molecular signaling networks in regulation of immunity and disease

The gut microbiota, host tissues, and the immune system form a complex network where extensive crosstalk and molecular interactions substantially impact the overall state of the system. Concomitantly, modulation of host immune function is recurrently a result of the interaction of complex and dynamic microbial communities with the immune cell compartment in the gut, and therefore the interaction between components from different gut bacteria can efficiently shape the phenotype of the immune response.

A specialized antigen-presenting cell present at mucosal surfaces, the dendritic cell (DC), plays a crucial role in shaping the nature of the adaptive/memory-based immune response after encountering inflammatory compounds. In the gut, the DC is continuously exposed to microbial and dietary components that are recognized by its innate pattern recognition receptors, and the phenotype developed in the DC during activation is of profound importance for the state of immune response and thereby also affects the inflammatory and metabolic status in tissues.

We have shown that specific fermentation products from gut bacteria have distinct immunoregulatory effects that effectively inhibit the proinflammatory properties of common gut commensals. We are currently looking into the mechanisms behind the antiinflammatory effects of the microbial fermentation products with a specific interest in the complex interactions between enzymes catalyzing posttranslational modifications, transcription factors and other molecules that make up the intracellular signaling networks in DCs and shape specific DC phenotypes of importance for health and disease.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis
Authors: Laursen, J. M. (Intern), Jensen, S. R. (Intern), Sørensen, M. (Ekstern), Pedersen, S. B. (Intern)
Publication date: 2013
Event: Abstract from Copenhagen Bioscience Conference – Genomics in metabolism, Snekkersten, Denmark.
Main Research Area: Technical/natural sciences
Electronic versions:
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Source: dtu
Source-ID: u::9921
Publication: Research - peer-review › Conference abstract for conference – Annual report year: 2013

Monitoring Expansion of T Cell Specificities Against Foot-and-Mouth-Disease Virus (FMDV) in Swine With MHC Class I Tetramers Following a Prime/Boost Vaccination

Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 4.86 SNIP 1.787
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 4.55 SNIP 2.04
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 4.992 SNIP 2.152
Web of Science (2005): Indexed yes
Scopus rating (2004): SJR 4.809 SNIP 1.971
Web of Science (2004): Indexed yes
Scopus rating (2003): SJR 0.108 SNIP 1.862
Web of Science (2003): Indexed yes
Scopus rating (2002): SJR 0.12 SNIP 1.535
Scopus rating (2001): SJR 0.131 SNIP 1.402
Scopus rating (2000): SJR 0.141 SNIP 1.672
Web of Science (2000): Indexed yes
Scopus rating (1999): SJR 0.149 SNIP 1.562
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Source: dtu
Source-ID: n::oai:DTIC-ART:highwire/388317629::29780
Publication: Research - peer-review › Journal article – Annual report year: 2013
Mutations in FGF17, IL17RD, DUSP6, SPRY4, and FLRT3 Are Identified in Individuals with Congenital Hypogonadotropic Hypogonadism

Congenital hypogonadotropic hypogonadism (CHH) and its anosmia-associated form (Kallmann syndrome [KS]) are genetically heterogeneous. Among the >15 genes implicated in these conditions, mutations in FGF8 and FGFR1 account for ~12% of cases; notably, KAL1 and HS6ST1 are also involved in FGFR1 signaling and can be mutated in CHH. We therefore hypothesized that mutations in genes encoding a broader range of modulators of the FGFR1 pathway might contribute to the genetics of CHH as causal or modifier mutations. Thus, we aimed to (1) investigate whether CHH individuals harbor mutations in members of the so-called “FGF8 synexpression” group and (2) validate the ability of a bioinformatics algorithm on the basis of protein-protein interactome data (interactome-based affiliation scoring [IBAS]) to identify high-quality candidate genes. On the basis of sequence homology, expression, and structural and functional data, seven genes were selected and sequenced in 386 unrelated CHH individuals and 155 controls. Except for FGF18 and SPRY2, all other genes were found to be mutated in CHH individuals: FGF17 (n = 3 individuals), IL17RD (n = 8), DUSP6 (n = 5), SPRY4 (n = 14), and FLRT3 (n = 3). Independently, IBAS predicted FGF17 and IL17RD as the two top candidates in the entire proteome on the basis of a statistical test of their protein-protein interaction patterns to proteins known to be altered in CHH. Most of the FGF17 and IL17RD mutations altered protein function in vitro. IL17RD mutations were found only in KS individuals and were strongly linked to hearing loss (6/8 individuals). Mutations in genes encoding components of the FGF pathway are associated with complex modes of CHH inheritance and act primarily as contributors to an oligogenic genetic architecture underlying CHH.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Lausanne, Massachusetts General Hospital, University of Colorado, New York University School of Medicine, University of California, Poznan University of Medical Sciences, Helsinki University Central Hospital, Newcastle University, Sofia Medical University, Service d’Endocrinologie et des Maladies de la Reproduction, Hôpital Bicêtre, Brigham and Women's Hospital, University of Montreal, University of British Columbia
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Main Research Area: Technical/natural sciences

Publication information
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Volume: 92
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BFI (2017): BFI-level 2
Web of Science (2017): Indexed Yes
NetFCM: A Tool for Automated Flow Cytometric Data Analysis

**General information**

**State:** Published

**Organisations:** Department of Systems Biology, Center for Biological Sequence Analysis, Karolinska Institutet
NETMHCSTAB - predicting stability of peptide-MHC-I complexes; impacts for cytotoxic T lymphocyte epitope discovery

Major histocompatibility complex class I (MHC-I) molecules play an essential role in the cellular immune response, presenting peptides to cytotoxic T lymphocytes (CTLs) allowing the immune system to scrutinize ongoing intracellular production of proteins. In the early 1990s, immunogenicity and stability of the peptide-MHC-I (pMHC-I) complex were shown to be correlated. At that time, measuring stability was cumbersome and time consuming and only small data sets were analysed. Here, we investigate this fairly unexplored area on a large scale compared with earlier studies. A recent small-scale study demonstrated that pMHC-I complex stability was a better correlate of CTL immunogenicity than peptide-MHC-I affinity. We here extended this study and analysed a total of 5509 distinct peptide stability measurements covering 10 different HLA class I molecules. Artificial neural networks were used to construct stability predictors capable of predicting the half-life of the pMHC-I complex. These predictors were shown to predict T-cell epitopes and MHC ligands from SYFPEITHI and IEDB to form significantly more stable MHC-I complexes compared with affinity-matched non-epitopes. Combining the stability predictions with a state-of-the-art affinity predictions NetMHCcons significantly improved the performance for identification of T-cell epitopes and ligands. For the HLA alleles included in the study, we could identify distinct sub-motifs that differentiate between stable and unstable peptide binders and demonstrate that anchor positions in the N-terminal of the binding motif (primarily P2 and P3) play a critical role for the formation of stable pMHC-I complexes. A webserver implementing the method is available at www.cbs.dtu.dk/services/NetMHCstab.
Obesity-induced hepatic and placental inflammation are absent in obese gestating mice compared to control fed dams

**General information**

**State:** Published  
**Organisations:** Department of Systems Biology, Center for Biological Sequence Analysis, University of Cambridge  
**Authors:** Ingvorsen, C. (Intern), Thysen, A. H. (Intern), Fernandez-Twinn, D. (Ekstern), Ozanne, S. E. (Ekstern), Pedersen, S. B. (Intern), Hellgren, L. (Intern)

**Number of pages:** 1  
**Publication date:** 2013  
**Event:** Abstract from 15th European Congress of Endocrinology 2013, Copenhagen, Denmark.

**Main Research Area:** Technical/natural sciences  
**Electronic versions:** Abstract_ECE2013_final.pdf

**Source:** dtu  
**Source-ID:** u:9012

**Publication:** Research - peer-review › Conference abstract for conference – Annual report year: 2013

Offspring from rat mothers fed a high-fat/high-sucrose diet during gestation and lactation accumulate free fatty acids in the liver when exposed to high fat diet as adults.

**Introduction:** Maternal diet during gestation and lactation has been implicated as a factor that modifies the risk of developing metabolic diseases later in life. Hepatic lipid accumulation is strongly linked to development of metabolic diseases. Free fatty acids induce ER stress, mitochondrial stress and are the substrate for formation of other lipotoxic species, such as ceramide, diacylglycerol and acyl-CoA. We have therefore investigated if the maternal intake of a high fat diet combined with sucrose-rich beverage alters the offsprings ability to metabolically cope with a high-fat challenge in adult life. In this poster, we report data on hepatic lipid content.

**Methods:** Rat dams were fed a 60 E% fat diet and given 15% sucrose (HFHS) in the drinking water or chow and pure...
water (C) six weeks before mating as well as during gestation and lactation. After birth, male pups was cross-fostered by the dams, so that half of the pups born by HFHS mothers was lactated by C dams and vice versa, generating four groups; CC, CH, HC and HH (first letter maternal diet during pregnancy and the second diet during lactation). At weaning all pups were transferred to chow-diet and kept on this diet until the age of 20 weeks. At 20 weeks of age, all rats, with the exception of one control group, were transferred to a high fat diet (45E% fat). After 6 weeks on this diet, all rats were sacrificed and hepatic lipid content and composition was analyzed using GC-FID.

Results: The high fat intervention caused strongly increased levels of hepatic free fatty acids (FFA) in rats both born and lactated by HFHS-dams. Principal component analysis of the FFA fatty acid composition showed that there were in particular dietary PUFA that accumulated, indicating that it is the ability to metabolize these fatty acids that are hampered in these animals.

Conclusion: Maternal high fat/high sucrose intake during gestation and lactation makes the offspring less able to metabolize dietary PUFA, which cause accumulation of these as FFA. This might make them more prone to develop metabolic diseases when exposed to energy dense diets.

Parallel evolution of tumor subclones mimics diversity between tumors
Intratumor heterogeneity (ITH) may foster tumor adaptation and compromise the efficacy of personalized medicines approaches. The scale of heterogeneity within a tumor (intratumor heterogeneity) relative to genetic differences between tumors (inter-tumor heterogeneity) is unknown. To address this, we obtained 48 biopsies from eight stage III and IV clear cell renal cell carcinomas (ccRCC) and used DNA copy-number analyses to compare biopsies from the same tumor with 440 single-tumor biopsies from The Cancer Genome Atlas (TCGA). Unsupervised hierarchical clustering of TCGA and multi-region ccRCC samples revealed segregation of samples from the same tumor into unrelated clusters. 25% of multi-region samples appeared more similar to unrelated samples than to any other sample originating from the same tumor. We find that the majority of recurrent DNA copy number driver aberrations in single biopsies are not present ubiquitously in late stage ccRCC and are likely to represent subclonal events acquired during tumor progression. Such heterogeneous subclonal genetic alterations within individual tumors may impair the identification of robust ccRCC molecular subtypes classified by distinct copy number alterations and clinical outcomes. The co-existence of distinct subclonal copy number events in different regions of individual tumors reflects the diversification of individual ccRCCs through multiple evolutionary routes and may contribute to tumor sampling bias and impact upon tumor progression and clinical outcome.
PathogenFinder - Distinguishing Friend from Foe Using Bacterial Whole Genome Sequence Data.

Although the majority of bacteria are harmless or even beneficial to their host, others are highly virulent and can cause serious diseases, and even death. Due to the constantly decreasing cost of high-throughput sequencing there are now many completely sequenced genomes available from both human pathogenic and innocuous strains. The data can be used to identify gene families that correlate with pathogenicity and to develop tools to predict the pathogenicity of newly sequenced strains, investigations that previously were mainly done by means of more expensive and time consuming experimental approaches. We describe PathogenFinder (http://cge.cbs.dtu.dk/services/PathogenFinder/), a web-server for the prediction of bacterial pathogenicity by analysing the input proteome, genome, or raw reads provided by the user. The method relies on groups of proteins, created without regard to their annotated function or known involvement in pathogenicity. The method has been built to work with all taxonomic groups of bacteria and using the entire training-set, achieved an accuracy of 88.6% on an independent test-set, by correctly classifying 398 out of 449 completely sequenced bacteria. The approach here proposed is not biased on sets of genes known to be associated with pathogenicity, thus the approach could aid the discovery of novel pathogenicity factors. Furthermore the pathogenicity prediction web-server could be used to isolate the potential pathogenic features of both known and unknown strains.

**General information**

- **State**: Published
- **Organisations**: Department of Systems Biology, Center for Biological Sequence Analysis, Immunological Bioinformatics, Integrative Systems Biology, National Food Institute, Division of Epidemiology and Microbial Genomics
Pathogenic bacteria colonizing the airways in asymptomatic neonates stimulates topical inflammatory mediator release.
Rationale: Bacterial colonization of neonatal airways with the pathogenic bacterial species, Moraxella catarrhalis, Streptococcus pneumoniae, and Haemophilus influenzae, is associated with later development of childhood asthma.

Objectives: To study a possible association between colonization with pathogenic bacterial strains and the immune signature of the upper airways in healthy neonates.

Methods: A total of 20 cytokines and chemokines were quantified in vivo in the airway mucosal lining fluid of 662 neonates from the Copenhagen Prospective Study of Asthma in Childhood 2010 birth cohort. Colonization of the hypopharynx with M. catarrhalis, S. pneumoniae, H. influenzae, and Staphylococcus aureus was assessed simultaneously. The association between immune signatures and bacterial colonization or noncolonized controls was analyzed using conventional statistical methods supplemented by a multivariate approach for pattern identification.

Measurements and Main Results: Colonization with M. catarrhalis and H. influenzae induced a mixed T helper cell (Th) type 1/Th2/Th17 response with high levels of IL-1 beta (M. catarrhalis, P = 2.2 x 10(-12); H. influenzae, P = 7.1 X 10(-10)), TNF-alpha (M. catarrhalis, P = 1.5 x 10(-9); H. influenzae, P = 5.9 x 10(-7)), and macrophage inflammatory protein-1 beta (M. catarrhalis, P = 1.6 X 10(-11); H. influenzae, P = 2.7 x 10(-7)). S. aureus colonization demonstrated a Th17-promoting profile with elevated IL-17 levels (P = 1.6 x 10(-24)). S. pneumoniae colonization was not significantly associated with any of the mediators.

Conclusions: M. catarrhalis and H. influenzae colonization of the airways of asymptomatic neonates is associated with an inflammatory immune response of the airway mucosa, which may result in chronic inflammation.
Patterns of prokaryotic lateral gene transfers affecting parasitic microbial eukaryotes

BACKGROUND: The influence of lateral gene transfer on gene origins and biology in eukaryotes is poorly understood compared with those of prokaryotes. A number of independent investigations focusing on specific genes, individual genomes, or specific functional categories from various eukaryotes have indicated that lateral gene transfer does indeed affect eukaryotic genomes. However, the lack of common methodology and criteria in these studies makes it difficult to assess the general importance and influence of lateral gene transfer on eukaryotic genome evolution.

RESULTS: We used a phylogenomic approach to systematically investigate lateral gene transfer affecting the proteomes of thirteen, mainly parasitic, microbial eukaryotes, representing four of the six eukaryotic super-groups. All of the genomes investigated have been significantly affected by prokaryote-to-eukaryote lateral gene transfers, dramatically affecting the enzymes of core pathways, particularly amino acid and sugar metabolism, but also providing new genes of potential adaptive significance in the life of parasites. A broad range of prokaryotic donors is involved in such transfers, but there is clear and significant enrichment for bacterial groups that share the same habitats, including the human microbiota, as the parasites investigated.

CONCLUSIONS: Our data show that ecology and lifestyle strongly influence gene origins and opportunities for gene transfer and reveal that, although the outlines of the core eukaryotic metabolism are conserved among lineages, the genes making up those pathways can have very different origins in different eukaryotes. Thus, from the perspective of the effects of lateral gene transfer on individual gene ancestries in different lineages, eukaryotic metabolism appears to be chimeric.
Peptide-binding motifs associated with MHC molecules common in Chinese rhesus macaques are analogous to those of human HLA supertypes and include HLA-B27-like alleles.

Chinese rhesus macaques are of particular interest in simian immunodeficiency virus/human immunodeficiency virus (SIV/HIV) research as these animals have prolonged kinetics of disease progression to acquired immunodeficiency syndrome (AIDS), compared to their Indian counterparts, suggesting that they may be a better model for HIV.
Nevertheless, the specific mechanism(s) accounting for these kinetics remains unclear. The study of major histocompatibility complex (MHC) molecules, including their MHC/peptide-binding motifs, provides valuable information for measuring cellular immune responses and deciphering outcomes of infection and vaccine efficacy. In this study, we have provided detailed characterization of six prevalent Chinese rhesus macaque MHC class I alleles, yielding a combined phenotypic frequency of 29%. The peptide-binding specificity of two of these alleles, Mamu-A2*01:02 and Mamu-B*010:01, as well as the previously characterized allele Mamu-B*003:01 (and Indian rhesus Mamu-B*003:01), was found to be analogous to that of alleles in the HLA-B27 supertype family. Specific alleles in the HLA-B27 supertype family, including HLA-B*27:05, have been associated with long-term nonprogression to AIDS in humans. All six alleles characterized in the present study were found to have specificities analogous to HLA supertype alleles. These data contribute to the concept that Chinese rhesus macaque MHC immunogenetics is more similar to HLA than their Indian rhesus macaque counterparts and thereby warrants further studies to decipher the role of these alleles in the context of SIV infection.
Perinatal programming of metabolic dysfunction and obesity-induced inflammation

The number of obese women in the childbearing age is drastically increasing globally. As a consequence, more children are born by obese mothers. Unfortunately, maternal obesity and/or high fat intake during pregnancy increase the risk of developing obesity, type-2 diabetes, cardiovascular disease and non-alcoholic fatty liver disease in the children, which passes obesity and metabolic dysfunction on from generation to generation. Several studies try to elucidate causative effects of maternal metabolic markers on the metabolic imprinting in the children; however diet induced obesity is also associated with chronic low grade inflammation. Nobody have yet investigated the role of this inflammatory phenotype, but here we demonstrate that obesity induced inflammation is reversed during pregnancy in mice, and is therefore less likely to affect the fetal programming of metabolic dysfunction. Instead, we suggest that an early elevated lipid exposure caused by a maternal high fat feeding might be more important for long term metabolic imprinting in the offspring. Therefore, we study the effect of maternal high fat/high sucrose diet during gestation, lactation or both to elucidate if perinatal adaptations to a high fat/high sucrose diet makes the offspring more capable of dealing with a high fat diet later in life. We demonstrate that a dietary mismatch between pre- and post-natal life alters the phenotype in an obese prone rat model at weaning. Thus, exposure to a control diet in utero and a high fat/high sucrose diet during lactation cause more severe phenotypic alteration in the offspring at weaning than pups exposed to the high fat/high sucrose diet both in utero and during lactation. The same pattern is seen in the adult offspring after being challenged with a high fat diet for 6 weeks. However HFHS exposure during fetal life protected against hyperleptinemia in the adult offspring during the challenge. Additionally, offspring exposed to high fat/high sucrose diet during lactation displayed a decrease level of inflammatory genes in the blood, which could indicated that perinatal HFHS exposure protect against the detrimental effects of high fat feeding leading to metabolic disease.
Personalized Network-Based Treatments in Oncology

Network medicine aims at unraveling cell signaling networks to propose personalized treatments for patients suffering from complex diseases. In this short review, we show the relevance of network medicine to cancer treatment by outlining the potential convergence points of the most recent technological and scientific developments in both drug design and signaling network analysis.

General information

State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Cellular Signal Integration
Authors: Robin, X. (Intern), Creixell, P. (Intern), Radetskaya, O. (Intern), Santina, C. C. (Intern), Longden, J. (Intern), Linding, R. (Intern)
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Scopus rating (2013): SJR 2.585 SNIP 1.956 CiteScore 5.38
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ISI indexed (2012): ISI indexed yes
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ISI indexed (2011): ISI indexed yes
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Scopus rating (2010): SJR 2.258 SNIP 1.789
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 2.479 SNIP 1.934
Web of Science (2009): Indexed yes
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Scopus rating (2005): SJR 2.494 SNIP 2.076
Scopus rating (2004): SJR 1.168 SNIP 1.81
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Scopus rating (2002): SJR 0.692 SNIP 1.499
Scopus rating (2001): SJR 1.061 SNIP 1.511
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Scopus rating (1999): SJR 0.838 SNIP 1.658
PHAISTOS: A framework for Markov chain Monte Carlo simulation and inference of protein structure

We present a new software framework for Markov chain Monte Carlo sampling for simulation, prediction, and inference of protein structure. The software package contains implementations of recent advances in Monte Carlo methodology, such as efficient local updates and sampling from probabilistic models of local protein structure. These models form a probabilistic alternative to the widely used fragment and rotamer libraries. Combined with an easily extendible software architecture, this makes PHAISTOS well suited for Bayesian inference of protein structure from sequence and/or experimental data. Currently, two force-fields are available within the framework: PROFASI and OPLS-AA/L, the latter including the generalized Born surface area solvent model. A flexible command-line and configuration-file interface allows users quickly to set up simulations with the desired configuration. PHAISTOS is released under the GNU General Public License v3.0. Source code and documentation are freely available from http://phaistos.sourceforge.net. The software is implemented in C++ and has been tested on Linux and OSX platforms. © 2013 Wiley Periodicals, Inc.

General information

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Scopus rating (2014): SJR 1.489 SNIP 1.451 CiteScore 3.78
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 1.449 SNIP 1.516 CiteScore 4.15
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 1.874 SNIP 1.64 CiteScore 4.43
ISI indexed (2012): ISI indexed yes
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Scopus rating (2011): SJR 1.834 SNIP 1.611 CiteScore 4.47
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Pharmacological profiling of drugs by linking chemoinformatics and bioinformatics data

General information
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Web of Science (2013): Indexed yes
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Scopus rating (2011): SJR 0.101 SNIP 0
Web of Science (2011): Indexed yes
Scopus rating (2010): SJR 0.101 SNIP 0
Scopus rating (2009): SJR 0.101 SNIP 0
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 0.101 SNIP 0
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 0.101 SNIP 0
Scopus rating (2006): SJR 0.101
Web of Science (2006): Indexed yes
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Phytic acid stimulates glucose uptake in a model of skeletal muscles, the primary porcine myotubes

ABSTRACT: BACKGROUND: Phytic acid (PA) is a chlorophyll metabolite with potentials in regulating glucose metabolism, as it is a natural ligand of the peroxisome proliferator-activated receptor (PPAR) that is known to regulate hepatic glucose homeostasis. This study aimed to establish primary porcine myotubes as a model for measuring glucose uptake and glycogen synthesis, and to examine the impact of physiological amounts of PA on glucose uptake and glycogen synthesis either alone or in combination with insulin. METHODS: Porcine satellite cells were cultured into differentiated myotubes and tritiated 2-deoxyglucose (2-DOG) was used to measure glucose uptake, in relation to PA and 2-DOG exposure times and also in relation to PA and insulin concentrations. The MIXED procedure model of SAS was used for statistical analysis of data. RESULTS: PA increased glucose uptake by approximately 35%, and the presence of insulin further increased the uptake, but this further increase in uptake was non- additive and less pronounced at high insulin concentrations. There was no effect of PA alone on glycogen synthesis, while the insulin stimulation of glycogen was increased by 20% in the presence of PA. PA neither stimulated glucose uptake nor glycogen synthesis in insulin-resistant myotubes generated by excess glucose exposure. CONCLUSIONS: Primary porcine myotubes were established as a model of skeletal muscles for measuring glucose uptake and glycogen synthesis, and we showed that PA can play a role in stimulating glucose uptake at no or inadequate insulin concentrations.
Polymorphism in the fatty acid desaturase genes and diet are important determinants of infant n-3 fatty acid status.

**Background and objectives:** Tissue docosahexaenoic acid (DHA) accretion in early infancy has been shown to be supported by the DHA-content of breast-milk and thus may decrease once complementary feeding takes over. Endogenous synthesis of DHA from alpha-linolenic acid has been shown to be very low and polymorphism in the genes that encode the fatty acid desaturases (FADS) has little effect on DHA-status in adults. It is however unclear to what extent endogenous DHA-synthesis contributes to infant DHA-status.

**Aim:** To investigate the role of diet and FADS polymorphism on DHA-status at 9 months and 3 years.

**Methods:** This cross-sectional study with Danish infants use data from two prospective studies (EFiON and the SKOT cohort). We measured erythrocyte (RBC) DHA-status at 9 months (n=409) and 3 years (n=176) and genotyped 4 FADS tagSNPs, rs3834458, rs1535, rs174575 and rs174448 (n=401). Information about breastfeeding was obtained by questionnaires and fish intake was assessed by 7-day pre-coded food diaries.

**Results:** FADS-genotype, breastfeeding, and fish intake were found to explain 25% of the variation in infant RBC DHA-status (mean±SD: 6.6±1.9% of the fatty acids (FA%)). Breastfeeding was the most important contributor and still being breast-fed at 9 months was associated with 0.8 FA% higher DHA vs. no longer breast-fed (p<0.001). Two of the examined FADS-SNPs were highly correlated (rs1535 and rs3834458; r=0.98). Homozygous carriers of the minor allele of rs1535 had an increase in RBC DHA of 1.6 FA% relative to those with wild type, whereas minor allele carriers of rs174448 and rs174575 had a decrease of 0.9 (p=0.017) and 1.9 FA% (p=0.001), respectively. Each 10-gram increment in fish intake was associated with an increase in DHA-status of 0.3 FA%. At 3 years, fish intake was the only significant determinant of DHA-status (0.2 FA%/10g).

**Conclusions:** FADS-genotype and diet are both important determinants of DHA-status in late infancy.

**General information**

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, National Research Center for Working Environment, University of Copenhagen

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Polymorphisms in the fatty acid desaturase genes and diet are important determinants of infant docosahexaenoic acid status

Tissue docosahexaenoic acid (DHA) accretion in early infancy is supported by DHA in breast-milk and may thus decrease once complementary feeding takes over. Endogenous synthesis of DHA from alphalinolenic acid is low and polymorphisms in the genes that encodes the fatty acid desaturases (FADS) has been shown to have little effect on DHA-status in adults. It is unclear to what extent endogenous DHA-synthesis contributes to infant DHA-status at 9 months and 3 years. Methods: This cross-sectional study with Danish infants use data from two prospective studies (EFiON and the SKOTcohort). We measured erythrocyte (RBC) DHA-status at 9 months (n=409) and 3 years (n=176) and genotyped 4 FADS tagSNPs, rs3834458, rs1535, rs174575 and rs174448 (n=401).
Postnatal amniotic fluid intake reduces gut inflammatory responses and necrotizing enterocolitis in preterm neonates

Preterm neonates are susceptible to gastrointestinal disorders such as necrotizing enterocolitis (NEC). Maternal milk and colostrum protects against NEC via growth promoting, immunomodulatory, and antimicrobial factors. The fetal enteral diet amniotic fluid (AF), contains similar components, and we hypothesized that postnatal AF administration reduces inflammatory responses and NEC in preterm neonates. Preterm pigs (92% gestation) were delivered by caesarean section and fed parental nutrition (2 days) followed by enteral (2 days) porcine colostrum (COLOS, n = 7), infant formula (FORM, n = 13), or AF supplied before and after introduction of formula (AF, n = 10) in experiment 1, and supplied only during the enteral feeding period in experiment 2 (FORM, n = 16; AF, n = 14). The NEC score was reduced in both AF and COLOS pigs, relative to FORM, when AF was provided prior to full enteral feeding (9.9 and 7.7 compared with 17.3, P <0.05). There was no effect of AF when provided only during enteral feeding. AF pigs showed decreased bacterial abundance in colon and intestinal inflammation-related genes (e.g., TNF-α, IL-1α, IL-6, NOS) were downregulated, relative to FORM pigs with NEC. Anti-inflammatory properties of AF were supported by delayed maturation and decreased TNF-α production in murine dendritic cells, as well as increased proliferation and migration, and downregulation of IL-6 expression in intestinal cells (IEC-6, IPEC-J2). Like colostrum, AF may reduce NEC development in preterm neonates by suppressing the proinflammatory responses to enteral formula feeding and gut colonization when provided before the onset of NEC.

General information

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Organisations: National Veterinary Institute, Section for Immunology and Vaccinology, Center for Biological Sequence Analysis, Department of Systems Biology, Section for bacteriology, Pathology and Parasitology, Aarhus University, University of Copenhagen
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Pre- and early-postnatal nutrition modify gene and protein expressions of muscle energy metabolism markers and phospholipid fatty acid composition in a muscle type specific manner in sheep.

We previously reported that undernutrition in late fetal life reduced whole-body insulin sensitivity in adult sheep, irrespective of dietary exposure in early postnatal life. Skeletal muscle may play an important role in control of insulin action. We therefore studied a range of putative key muscle determinants of insulin signalling in two types of skeletal muscles (longissimus dorsi (LD) and biceps femoris (BF)) and in the cardiac muscle (ventriculus sinister cordis (VSC)) of sheep from the same experiment. Twin-bearing ewes were fed either 100% (NORM) or 50% (LOW) of their energy and protein requirements during the last trimester of gestation. From day-3 postpartum to 6-months of age (around puberty),
twin offspring received a high-carbohydrate-high-fat (HCHF) or a moderate-conventional (CONV) diet, whereafter all males were slaughtered. Females were subsequently raised on a moderate diet and slaughtered at 2-years of age (young adults). The only long-term consequences of fetal undernutrition observed in adult offspring were lower expressions of the insulin responsive glucose transporter 4 (GLUT4) protein and peroxisome proliferator-activated receptor gamma, coactivator 1a (PGC1a) mRNA in BF, but increased PGC1a expression in VSC. Interestingly, the HCHF diet in early postnatal life was associated with somewhat paradoxically increased expressions in LD of a range of genes (but not proteins) related to glucose uptake, insulin signalling and fatty acid oxidation. Except for fatty acid oxidation genes, these changes persisted into adulthood. No persistent expression changes were observed in BF and VSC. The HCHF diet increased phospholipid ratios of n-6/n-3 polyunsaturated fatty acids in all muscles, even in adults fed identical diets for 1 1/2 years. In conclusion, early postnatal, but not late gestation, nutrition had long-term consequences for a number of determinants of insulin action and metabolism in LD. Tissues other than muscle may account for reduced whole body insulin sensitivity in adult LOW sheep.

General information
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Jiroft, Technical University of Denmark, Copenhagen University Hospital, University of Copenhagen
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Precision mapping of the human O-GalNAc glycoproteome through SimpleCell technology

Glycosylation is the most abundant and diverse posttranslational modification of proteins. While several types of glycosylation can be predicted by the protein sequence context, and substantial knowledge of these glycoproteomes is available, our knowledge of the GalNAc-type O-glycosylation is highly limited. This type of glycosylation is unique in being regulated by 20 polypeptide GalNAc-transferases attaching the initiating GalNAc monosaccharides to Ser and Thr (and likely some Tyr) residues. We have developed a genetic engineering approach using human cell lines to simplify O-glycosylation (SimpleCells) that enables proteome-wide discovery of O-glycan sites using 'bottom-up' ETD-based mass spectrometric analysis. We implemented this on 12 human cell lines from different organs, and present a first map of the human O-glycoproteome with almost 3000 glycosites in over 600 O-glycoproteins as well as an improved NetOGlyc4.0 model for prediction of O-glycosylation. The finding of unique subsets of O-glycoproteins in each cell line provides evidence that the O-glycoproteome is differentially regulated and dynamic. The greatly expanded view of the O-glycoproteome should facilitate the exploration of how site-specific O-glycosylation regulates protein function.

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State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Novo Nordisk Foundation Center for Biosustainability, CFB - Metagenomic Systems Biology, University of Copenhagen
Authors: Steentoft, C. (Forskerdatabase), Vakhrushev, S. (Forskerdatabase), Joshi, H. J. (Forskerdatabase), Kong, Y. (Forskerdatabase), Vester-Christensen, M. B. (Ekstern), Schjoldager, K. T. (Ekstern), Lavrsen, K. (Forskerdatabase), Dabelsteen, S. A. M. (Forskerdatabase), Pedersen, N. B. (Forskerdatabase), Marcos-Silva, L. (Ekstern), Gupta, R. (Intern), Paul Bennett, E. (Ekstern), Mandel, U. (Forskerdatabase), Brunak, S. (Intern), Wandall, H. H. (Forskerdatabase), Levery, S. B. (Forskerdatabase), Clausen, H. (Ekstern)
Pages: 1478-1488
Publication date: 2013
Main Research Area: Technical/natural sciences

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BFI (2017): BFI-level 2
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 7.13 SJR 6.57 SNIP 1.508
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 7.352 SNIP 1.71 CiteScore 7.48
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 8.195 SNIP 1.85 CiteScore 8.28
BFI (2013): BFI-level 2
Prediction of Disease Causing Non-Synonymous SNPs by the Artificial Neural Network Predictor NetDiseaseSNP.

We have developed a sequence conservation-based artificial neural network predictor called NetDiseaseSNP which classifies nsSNPs as disease-causing or neutral. Our method uses the excellent alignment generation algorithm of SIFT to identify related sequences and a combination of 31 features assessing sequence conservation and the predicted surface accessibility to produce a single score which can be used to rank nsSNPs based on their potential to cause disease. NetDiseaseSNP classifies successfully disease-causing and neutral mutations. In addition, we show that NetDiseaseSNP discriminates cancer driver and passenger mutations satisfactorily. Our method outperforms other state-of-the-art methods on several disease/neutral datasets as well as on cancer driver/passenger mutation datasets and can thus be used to pinpoint and prioritize plausible disease candidates among nsSNPs for further investigation. NetDiseaseSNP is publicly available as an online tool as well as a web service: http://www.cbs.dtu.dk/services/NetDiseaseSNP.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Novo Nordisk Foundation Center for Biosustainability, CFB - Metagenomic Systems Biology
Authors: Johansen, M. B. (Intern), Gonzalez-Izarzugaza, J. M. (Intern), Brunak, S. (Intern), Petersen, T. N. (Intern), Gupta, R. (Intern)
Publication date: 2013
Main Research Area: Technical/natural sciences
Predictions of Phase Separation in Three-Component Lipid Membranes by the MARTINI Force Field

The phase behavior of the coarse-grained MARTINI model for three-component lipid bilayers composed of dipalmytoyl-phosphatidylcholine (DPPC), cholesterol (Chol), and an unsaturated phosphatidylcholine (PC) was systematically investigated by molecular dynamics simulations. The aim of this study is to understand which types of unsaturated PC induce the formation of thermodynamically stable coexisting phases when added to mixtures of DPPC and Chol and to unravel the mechanisms that drive phase separation in such three-component mixtures. Our simulations indicate that the currently used MARTINI force field does not induce such phase separation in mixtures of DPPC, Chol, and unsaturated PCs with a low unsaturation level, such as palmitoyl-oleoyl-phosphatidylcholine (POPC) or dioleoyl-phosphatidylcholine (DOPC). Also, we found that phase separation does occur in mixtures of DPPC, Chol, and polyunsaturated PCs, such as dilinoleyl-phosphatidylcholine (DUPC) and diarachidonoyl-phosphatidylcholine (DAPC). Through systematic tweaking of the interactions between the hydrophobic groups of the PC molecules, we show that the appearance of phase separation in three-component lipid bilayers, as modeled through the MARTINI force field, is primarily due to the interactions between the coarse-grained molecules, i.e., the beads, rather than due to the differences between the conformations of saturated and unsaturated lipid acyl chains, namely entropy driven.
Prognostic and Predictive Markers in Metastatic Renal Cell Carcinoma

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Royal Marsden National Health Service Foundation Trust, Cancer Research UK, London Research Institute
Authors: Khattak, M. A. (Ekstern), Bakr, F. (Ekstern), Krzystanek, M. (Intern), Szallasi, Z. I. (Intern), Gerlinger, M. (Ekstern), Santos, C. (Ekstern), Swanton, C. (Ekstern), Pickering, L. M. (Ekstern), Gore, M. E. (Ekstern), Larkin, J. M. (Ekstern)
Pages: 20971-972
Publication date: 2013
Main Research Area: Technical/natural sciences

Publication information
Journal: Journal of Clinical Oncology
Volume: 31
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Ratings:
BFI (2018): BFI-level 2
BFI (2017): BFI-level 2
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): SJR 8.883 SNIP 4.894 CiteScore 10.11
BFI (2015): BFI-level 2
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 8.284 SNIP 4.6 CiteScore 8.89
BFI (2013): BFI-level 2
PROTEINCHALLENGE: Crowd sourcing in proteomics analysis and software development

In large-scale proteomics studies there is a temptation, after months of experimental work, to plug resulting data into a convenient—if poorly implemented—set of tools, which may neither do the data justice nor help answer the scientific question. In this paper we have captured key concerns, including arguments for community-wide open source software development and “big data” compatible solutions for the future. For the meantime, we have laid out ten top tips for data processing. With these at hand, a first large-scale proteomics analysis hopefully becomes less daunting to navigate. However there is clearly a real need for robust tools, standard operating procedures and general acceptance of best practises. Thus we submit to the proteomics community a call for a community-wide open set of proteomics analysis challenges—PROTEINCHALLENGE—that directly target and compare data analysis workflows, with the aim of setting a community-driven gold standard for data handling, reporting and sharing. This article is part of a Special Issue entitled: New Horizons and Applications for Proteomics [EuPA 2012].

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Edinburgh, Heinrich-Heine-University Dusseldorf, Aarhus University, University of Dundee, University of Liverpool
Authors: Martin, S. F. (Ekstern), Falkenberg, H. (Ekstern), Dyrlund, T. F. (Forskerdatabase), Khoudoli, G. A. (Ekstern), Mageean, C. J. (Ekstern), Linding, R. (Intern)
Pages: 41-46
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Journal: Journal of Proteomics
Real-Time WGS-based Typing of VTEC Isolates for Surveillance and Outbreak Detection

Objectives: Fast and accurate typing of foodborne pathogens is essential for effective surveillance and the ability to detect and prevent outbreaks. Current routine typing is based on a variety of different typing techniques, making the complete typing procedure laborious, time-consuming and expensive. With whole-genome sequencing (WGS) becoming continuously cheaper and more available, it has huge potential in both diagnostics and routine surveillance. The aim of this study was to evaluate WGS-based typing, in a real-time setup, for routine typing and surveillance of verocytotoxin-
producing E.coli (VTEC) infections.

Methods: As part of the routine surveillance in Denmark, suspected VTEC isolates are sent to Statens Serum Institut (SSI) for phenotypic and molecular characterisation by a range of methods. During 7 weeks in the fall 2012, the isolates were simultaneously subjected to WGS using the IonTorrent PGM benchtop sequencing technology. WGS-based typing was carried out using web-based tools, developed by the Center for Genomic Epidemiology (www.genomicepidemiology.org), for determination of MLST types, virulence genes and phylogenetic relationship between the isolates. The WGS-based typing was compared to the routine typing and surveillance, with regard to typing results, time consumption and price.

Results: In total, 47 suspected VTEC isolates were typed during the 7 weeks, both by the routine procedures and in parallel by the WGS-approach, and during the period of the study a small outbreak occurred. For all isolates, apart from one resulting in poor sequence output, the WGS-based typing led to detection of the same virulence gene variants as the routine typing, and was also able to detect many other possible virulence features, and in most instances produce a useful typing result faster than routine typing. Also, the WGS-approach was able to correctly detect, according to the routine typing, the isolates belonging to the outbreak.

Conclusion: The real-time WGS-based typing was able to produce typing results comparable to the routine typing, at least as fast as the routine typing. Thus, the benchtop WGS-based typing approach is a reasonable alternative to conventional typing strategies, and could be applicable to typing and surveillance of other pathogens.

**General information**

State: Published
Organisations: National Food Institute, Division of Epidemiology and Microbial Genomics, Department of Systems Biology, Center for Biological Sequence Analysis, Immunological Bioinformatics, Statens Serum Institut
Authors: Joensen, K. G. (Intern), Hasman, H. (Intern), Scheutz, F. (Ekstern), Nielsen, E. M. (Ekstern), Lund, O. (Intern), Aarestrup, F. M. (Intern)
Number of pages: 1
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Publication: Research - peer-review » Conference abstract in proceedings – Annual report year: 2013

Recalibrating Equus evolution using the genome sequence of an early Middle Pleistocene horse.

The rich fossil record of equids has made them a model for evolutionary processes. Here we present a 1.12-times coverage draft genome from a horse bone recovered from permafrost dated to approximately 560-780 thousand years before present (kyr bp). Our data represent the oldest full genome sequence determined so far by almost an order of magnitude. For comparison, we sequenced the genome of a Late Pleistocene horse (43 kyr bp), and modern genomes of five domestic horse breeds (Equus ferus caballus), a Przewalski's horse (E. f. przewalskii) and a donkey (E. asinus). Our analyses suggest that the Equus lineage giving rise to all contemporary horses, zebras and donkeys originated 4.0-4.5 million years before present (Myr bp), twice the conventionally accepted time to the most recent common ancestor of the genus Equus. We also find that horse population size fluctuated multiple times over the past 2 Myr, particularly during periods of severe climatic changes. We estimate that the Przewalski's and domestic horse populations diverged 38-72 kyr bp, and find no evidence of recent admixture between the domestic horse breeds and the Przewalski's horse investigated. This supports the contention that Przewalski's horses represent the last surviving wild horse population. We find similar levels of genetic variation among Przewalski's and domestic populations, indicating that the former are genetically viable and worthy of conservation efforts. We also find evidence for continuous selection on the immune system and olfaction throughout horse evolution. Finally, we identify 29 genomic regions among horse breeds that deviate from neutrality and show low levels of genetic variation compared to the Przewalski's horse. Such regions could correspond to loci selected early during domestication.

**General information**

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Novo Nordisk Foundation Center for Biosustainability, CFB - Metagenomic Systems Biology, BGI-Shenzhen, University of Alberta, University of Copenhagen, Emory University, University of Texas, Government of Yukon, NABsys Inc, University of Southampton, Norwegian School of Veterinary Science, Uppsala University, Cornell University, Copenhagen Zoo, King Saud University, San Diego Zoo's Institute for Conservation Research, University of York, King Abdulaziz University, Centre National de la Recherche Scientifique
Authors: Orlando, L. A. A. (Forskerdatabase), Ginolhac, A. (Forskerdatabase), Zhang, G. (Forskerdatabase), Froese, D. (Ekstern), Albrechtsen, A. (Forskerdatabase), Stiller, M. (Ekstern), Schubert, M. (Forskerdatabase), Cappellini, E. (Forskerdatabase), Petersen, B. (Intern), Moltke, I. (Forskerdatabase), Johnson, P. L. F. (Ekstern), Fumagalli, M. (Ekstern), Vilstrup, J. T. (Ekstern), Raghavan, M. (Forskerdatabase), Korneliussen, T. S. (Forskerdatabase), Malaspinas, A. S. (Forskerdatabase), Vogt, J. K. (Intern), Szklarczyk, D. (Ekstern), Kelstrup, C. (Forskerdatabase), Vinther, J. (Ekstern), Dolocan, A. (Ekstern), Stenderup, J. (Forskerdatabase), Velazquez, A. M. V. (Ekstern), Cahill, J. (Ekstern), Rasmussen, M. (Ekstern), Wang, X. (Ekstern), Min, J. (Ekstern), Zazula, G. D. (Ekstern), Seguin-Orlando, A. (Forskerdatabase),
Reconstructing the highly virulent Classical Swine Fever Virus strain Koslov

Classical swine fever virus (CSFV) may be highly virulent in pigs with a mortality rate close to 100%. The CSFV “Koslov strain” is known to be one of the most virulent CSFV, but so far a functional cloned cDNA of this strain has not been described. We suggest that this may be due to the error-prone nature of the RNA-dependent RNA polymerase resulting in the majority of circulating forms being non-functional. However, since any infectious virus particle should necessarily be the offspring of a functional virus, we hypothesized that it should be possible to synthesize a highly virulent form by reconstructing ancestral sequences. To test this hypothesis, we inferred sequences that correspond to ancestral nodes in a phylogenetic tree built from full-length nucleotide sequences of non-functional Koslov cDNAs and then proceeded to test the reconstructions. Specifically, we altered a non-functional cDNA by site directed mutagenesis, removing non-synonymous mutations step by step. In vitro testing of modified constructs did indeed lead to fully functional viruses with similar growth kinetics as the wild-type strain. Moreover, viruses rescued from the construct had the ancestral amino acid sequence and, when tested in pigs, were at least as virulent as the Koslov strain. The ancestral reconstruction therefore proved to give rise to a functional cDNA of the highly virulent Koslov strain. In vivo studies confirmed our methods and enabled us to identify nucleotide positions within the viral genome important for virulence.
Reply to 'Mining electronic health records: an additional perspective'

General information
State: Published
Organisations: Department of Energy Conversion and Storage, Atomic scale modelling and materials, Department of Physics, Department of Systems Biology, Center for Biological Sequence Analysis, University of Copenhagen
Authors: Jensen, P. B. (Ekstern), Jensen, L. J. (Ekstern), Brunak, S. (Intern)
Pages: -
Publication date: 2013
Main Research Area: Technical/natural sciences

Publication information
Journal: Nature Reviews. Genetics
Volume: 14
Issue number: 1
ISSN (Print): 1471-0056
Ratings:
- BFI (2018): BFI-level 2
- BFI (2017): BFI-level 2
- Web of Science (2017): Indexed Yes
- BFI (2016): BFI-level 2
- Scopus rating (2016): SJR 33.238 SNIP 7.846 CiteScore 15.15
- BFI (2015): BFI-level 2
- Scopus rating (2015): SJR 32.343 SNIP 8.669 CiteScore 17.4
- BFI (2014): BFI-level 2
- Scopus rating (2014): SJR 29.06 SNIP 8.633 CiteScore 16.59
- BFI (2013): BFI-level 2
- Scopus rating (2013): SJR 23.707 SNIP 6.677 CiteScore 18.31
- ISI indexed (2013): ISI indexed yes
- Web of Science (2013): Indexed yes
- BFI (2012): BFI-level 2
- Scopus rating (2012): SJR 17.601 SNIP 5.115 CiteScore 16.91
- ISI indexed (2012): ISI indexed yes
- Web of Science (2012): Indexed yes
- BFI (2011): BFI-level 2
- ISI indexed (2011): ISI indexed yes
- BFI (2010): BFI-level 2
- Scopus rating (2010): SJR 12.802 SNIP 3.319
- BFI (2009): BFI-level 2
- BFI (2008): BFI-level 2
- Scopus rating (2008): SJR 10.816 SNIP 3.169
- Scopus rating (2007): SJR 8.458 SNIP 2.999
- Scopus rating (2006): SJR 7.151 SNIP 2.64
- Scopus rating (2005): SJR 6.842 SNIP 2.396
- Scopus rating (2004): SJR 7.596 SNIP 2.974
- Scopus rating (2002): SJR 8.205 SNIP 2.875
- Scopus rating (2001): SJR 3.645 SNIP 1.23
Original language: English
GENETICS
Richness of human gut microbiome correlates with metabolic markers.

We are facing a global metabolic health crisis provoked by an obesity epidemic. Here we report the human gut microbial composition in a population sample of 123 non-obese and 169 obese Danish individuals. We find two groups of individuals that differ by the number of gut microbial genes and thus gut bacterial richness. They contain known and previously unknown bacterial species at different proportions; individuals with a low bacterial richness (23% of the population) are characterized by more marked overall adiposity, insulin resistance and dyslipidaemia and a more pronounced inflammatory phenotype when compared with high bacterial richness individuals. The obese individuals among the lower bacterial richness group also gain more weight over time. Only a few bacterial species are sufficient to distinguish between individuals with high and low bacterial richness, and even between lean and obese participants. Our classifications based on variation in the gut microbiome identify subsets of individuals in the general white adult population who may be at increased risk of progressing to adiposity-associated co-morbidities.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Behavioral Phenomics, Metagenomics, Novo Nordisk Foundation Center for Biosustainability, Integrative Systems Biology, CFB - Metagenomic Systems Biology, Functional Human Variation, INRA Institut National de La Recherche Agronomique, BGI-Shenzhen, Vrije Universiteit Brussel, European Molecular Biology Laboratory, South China University of Technology, University of Southern Denmark, Wageningen IMARES, INSERM, University of Helsinki, Institut de Recherche pour le Développement, University of Copenhagen, Copenhagen University Hospital
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Main Research Area: Technical/natural sciences

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Journal: Nature
Volume: 500
Issue number: 7464
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Ratings:
BFI (2018): BFI-level 3
BFI (2017): BFI-level 2
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 13.33
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): CiteScore 14.38
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): CiteScore 14.22
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): CiteScore 14.96
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
Scientific competency questions as the basis for semantically enriched open pharmacological space development

Molecular information systems play an important part in modern data-driven drug discovery. They do not only support decision making but also enable new discoveries via association and inference. In this review, we outline the scientific requirements identified by the Innovative Medicines Initiative (IMI) Open PHACTS consortium for the design of an open pharmacological space (OPS) information system. The focus of this work is the integration of compound–target–pathway–disease/phenotype data for public and industrial drug discovery research. Typical scientific competency questions provided by the consortium members will be analyzed based on the underlying data concepts and associations needed to answer the questions. Publicly available data sources used to target these questions as well as the need for and potential of semantic web-based technology will be presented.
Sigma factors in a thousand E. coli genomes

Everyone working with bacterial genomics is familiar with the phrase 'too much data'. In this Genome Update, we discuss two methods for helping to deal with this explosion of genomic information. First, we introduce the concept of calculating a quality score for each sequenced genome, and second, we describe a method to quickly sort through genomes for a particular set of protein families. We apply these two methods to all of the current Escherichia coli genomes available in the The National Center for Biotechnology Information database. Out of the 2074 E. coli/Shigella genomes listed (June, 2013), only less than half (983) are of sufficient quality to use in comparative genomic work. Unfortunately, even some of the ‘complete’ E. coli genomes are in pieces, and a few ‘draft’ genomes are good quality. Six of the seven known sigma factors in E. coli strain K-12 are extremely well conserved; the iron-regulating sigma factor FecI (σ19) is missing in most genomes. Surprisingly, the E. coli strain CFT073 genome does not encode a functional RpoD (σ70), which is obviously essential, and this is likely due to poor genome assembly/annotation. We find a possible novel sigma factor present in more than a hundred E. coli genomes.
General information
State: Published
Organisations: Comparative Microbial Genomics, Department of Systems Biology, Center for Biological Sequence Analysis
Authors: Cook, H. V. (Intern), Ussery, D. (Intern)
Pages: 3121-3129
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Main Research Area: Technical/natural sciences

Publication information
Journal: Environmental Microbiology
Volume: 15
Issue number: 12
ISSN (Print): 1462-2912
Ratings:
BFI (2018): BFI-level 2
BFI (2017): BFI-level 2
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 5.02 SJR 2.221 SNIP 1.406
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 2.999 SNIP 1.584 CiteScore 5.61
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 2.85 SNIP 1.616 CiteScore 5.6
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 3.246 SNIP 1.843 CiteScore 6.37
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 3.128 SNIP 1.646 CiteScore 5.94
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 3.33 SNIP 1.708 CiteScore 6.1
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 2.738 SNIP 1.544
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 2.463 SNIP 1.373
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 2.446 SNIP 1.322
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 2.312 SNIP 1.502
Scopus rating (2006): SJR 2.414 SNIP 1.511
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 2.387 SNIP 1.521
Web of Science (2005): Indexed yes
Scopus rating (2004): SJR 2.05 SNIP 1.232
Web of Science (2004): Indexed yes
Scopus rating (2003): SJR 1.773 SNIP 1.24
SigniSite: Identification of residue-level genotype-phenotype correlations in protein multiple sequence alignments

Identifying which mutation(s) within a given genotype is responsible for an observable phenotype is important in many aspects of molecular biology. Here, we present SigniSite, an online application for subgroup-free residue-level genotype–phenotype correlation. In contrast to similar methods, SigniSite does not require any pre-definition of subgroups or binary classification. Input is a set of protein sequences where each sequence has an associated real number, quantifying a given phenotype. SigniSite will then identify which amino acid residues are significantly associated with the data set phenotype. As output, SigniSite displays a sequence logo, depicting the strength of the phenotype association of each residue and a heat-map identifying ‘hot’ or ‘cold’ regions. SigniSite was benchmarked against SPEER, a state-of-the-art method for the prediction of specificity determining positions (SDP) using a set of human immunodeficiency virus protease-inhibitor genotype–phenotype data and corresponding resistance mutation scores from the Stanford University HIV Drug Resistance Database, and a data set of protein families with experimentally annotated SDPs. For both data sets, SigniSite was found to outperform SPEER. SigniSite is available at: http://www.cbs.dtu.dk/services/SigniSite/.

General information
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Copenhagen
Authors: Jessen, L. I. (Intern), Hoof, I. (Ekstern), Lund, O. (Intern), Nielsen, M. (Intern)
Pages: 20W286-W291
Publication date: 2013
Main Research Area: Technical/natural sciences

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Volume: 41
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BFI (2018): BFI-level 2
BFI (2017): BFI-level 2
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 9.28 SJR 7.397 SNIP 2.657
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 7.239 SNIP 2.639 CiteScore 9.48
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 6.576 SNIP 2.568 CiteScore 8.74
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 6.582 SNIP 2.266 CiteScore 8.46
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 6.13 SNIP 2.392 CiteScore 8.62
ISI indexed (2012): ISI indexed yes
Simultaneous alignment and clustering of peptide data using a Gibbs sampling approach

Motivation: Proteins recognizing short peptide fragments play a central role in cellular signaling. As a result of high-throughput technologies, peptide-binding protein specificities can be studied using large peptide libraries at dramatically lower cost and time. Interpretation of such large peptide datasets, however, is a complex task, especially when the data contain multiple receptor binding motifs, and/or the motifs are found at different locations within distinct peptides.

Results: The algorithm presented in this article, based on Gibbs sampling, identifies multiple specificities in peptide data by performing two essential tasks simultaneously: alignment and clustering of peptide data. We apply the method to deconvolute binding motifs in a panel of peptide datasets with different degrees of complexity spanning from the simplest case of pre-aligned fixed-length peptides to cases of unaligned peptide datasets of variable length. Example applications described in this article include mixtures of binders to different MHC class I and class II alleles, distinct classes of ligands for SH3 domains and sub-specificities of the HLA-A*02:01 molecule.

Availability: The Gibbs clustering method is available online as a web server at http://www.cbs.dtu.dk/services/GibbsCluster. Contact: massimo@cbs.dtu.dk

Supplementary information: Supplementary data are available at Bioinformatics online.
The binding of antigens to antibodies is one of the key events in an immune response against foreign molecules and is a critical element of several biomedical applications including vaccines and immunotherapeutics. For development of such applications, the identification of antibody binding sites (B-cell epitopes) is essential. However experimental epitope mapping is highly cost-intensive and computer-aided methods do in general have moderate performance. One major reason for this moderate performance is an incomplete understanding of what characterizes an epitope. To fill this gap, we
here developed a novel framework for comparing and superimposing B-cell epitopes and applied it on a dataset of 107 non-similar antigen:antibody structures extracted from the PDB database. With the presented framework, we were able to describe the general B-cell epitope as a flat, oblong, oval shaped volume consisting of predominantly hydrophobic amino acids in the center flanked by charged residues. The average epitope was found to be made up of ~15 residues with one linear stretch of 5 or more residues constituting more than half of the epitope size. Furthermore, the epitope area is predominantly constrained to a plane above the antibody tip, in which the epitope is orientated in a −30° to 60° angle relative to the light to heavy chain antibody direction. Contrary to previously findings, we did not find a significant deviation between the amino acid composition in epitopes and the composition of equally exposed parts of the antigen surface. Our results, in combination with previously findings, give a detailed picture of the B-cell epitope that may be used in development of improved B-cell prediction methods.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Novo Nordisk A/S
Authors: Kringelum, J. V. (Intern), Nielsen, M. (Intern), Padkjær, S. B. (Ekstern), Lund, O. (Intern)
Pages: 24-34
Publication date: 2013
Main Research Area: Technical/natural sciences

Publication information
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Volume: 53
Issue number: 1-2
ISSN (Print): 0161-5890
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BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): SJR 1.523 SNIP 0.961 CiteScore 3.2
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.572 SNIP 0.928 CiteScore 3.16
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.474 SNIP 0.916 CiteScore 2.89
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.46 SNIP 0.94 CiteScore 2.89
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.406 SNIP 0.862 CiteScore 2.94
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.403 SNIP 0.874 CiteScore 3.01
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.39 SNIP 0.861
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.482 SNIP 0.905
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 1.556 SNIP 0.929
Scopus rating (2007): SJR 1.944 SNIP 1.075
Web of Science (2007): Indexed yes
Targeted Metabolic Engineering Guided by Computational Analysis of Single-Nucleotide Polymorphisms (SNPs)

The non-synonymous SNPs, the so-called non-silent SNPs, which are single-nucleotide variations in the coding regions that give "birth" to amino acid mutations, are often involved in the modulation of protein function. Understanding the effect of individual amino acid mutations on a protein/enzyme function or stability is useful for altering its properties for a wide variety of engineering studies. Since measuring the effects of amino acid mutations experimentally is a laborious process, a variety of computational methods have been discussed here that aid to extract direct genotype to phenotype information.

General information
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Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Novo Nordisk Foundation Center for Biosustainability, CFB - Metagenomic Systems Biology, Chalmers University of Technology, University of Hong Kong
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Host publication information
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Source: dtu
Source-ID: n:oai:DTIC-ART:pubmed/380229179::26971
Publication: Research - peer-review › Book chapter – Annual report year: 2013

Targeting of conserved gag-epitopes in early HIV infection is associated with lower plasma viral load and slower CD4+ T cell depletion.
We aimed to investigate whether the character of the immunodominant HIV-Gag peptide (variable or conserved) targeted by CD8+ T cells in early HIV infection would influence the quality and quantity of T cell responses, and whether this would affect the rate of disease progression. Treatment-naive HIV-infected study subjects within the OPTIONS cohort at the University of California, San Francisco, were monitored from an estimated 44 days postinfection for up to 6 years. CD8+ T cells responses targeting HLA-matched HIV-Gag-epitopes were identified and characterized by multicolor flow cytometry. The autologous HIV gag sequences were obtained. We demonstrate that patients targeting a conserved HIV-Gag-epitope in early infection maintained their epitope-specific CD8+ T cell response throughout the study period. Patients targeting a variable epitope showed decreased immune responses over time, although there was no limitation of the functional profile, and they were likely to target additional variable epitopes. Maintained immune responses to conserved epitopes were associated with no or limited sequence evolution within the targeted epitope. Patients with immune responses targeting conserved epitopes had a significantly lower median viral load over time compared to patients with responses targeting a variable epitope (0.63 log10 difference). Furthermore, the rate of CD4+ T cell decline was slower for subjects targeting a conserved epitope (0.85% per month) compared to subjects targeting a variable epitope (1.85% per month). Previous
studies have shown that targeting of antigens based on specific HLA types is associated with a better disease course. In this study we show that categorizing epitopes based on their variability is associated with clinical outcome.

**General information**

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Swedish Institute for Communicable Disease Control, University of California, Karolinska Institutet
Authors: Perez, C. L. (Ekstern), Milush, J. M. (Ekstern), Buggert, M. (Ekstern), Eriksson, E. M. (Ekstern), Larsen, M. V. (Intern), Liegler, T. (Ekstern), Hartogensis, W. (Ekstern), Bacchetti, P. (Ekstern), Lund, O. (Intern), Hecht, F. M. (Ekstern), Nixon, D. F. (Ekstern), Karlsson, A. C. (Ekstern)
Pages: 602-612
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Main Research Area: Technical/natural sciences

**Publication information**

Journal: AIDS Research and Human Retroviruses
Volume: 29
Issue number: 3
ISSN (Print): 0889-2229
Ratings:
- BFI (2018): BFI-level 1
- BFI (2017): BFI-level 1
- Web of Science (2017): Indexed Yes
- BFI (2016): BFI-level 1
- Scopus rating (2016): SJR 1.039 SNIP 0.572 CiteScore 1.66
- BFI (2015): BFI-level 1
- Scopus rating (2015): SJR 1.037 SNIP 0.583 CiteScore 1.67
- BFI (2014): BFI-level 1
- Scopus rating (2014): SJR 1.147 SNIP 0.648 CiteScore 2.01
- BFI (2013): BFI-level 1
- Scopus rating (2013): SJR 1.124 SNIP 0.715 CiteScore 2.15
- ISI indexed (2013): ISI indexed yes
- Web of Science (2013): Indexed yes
- BFI (2012): BFI-level 1
- Scopus rating (2012): SJR 1.147 SNIP 0.783 CiteScore 2.34
- ISI indexed (2012): ISI indexed yes
- BFI (2011): BFI-level 1
- Scopus rating (2011): SJR 1.174 SNIP 0.671 CiteScore 2.22
- ISI indexed (2011): ISI indexed yes
- Web of Science (2011): Indexed yes
- BFI (2010): BFI-level 1
- Scopus rating (2010): SJR 1.183 SNIP 0.684
- BFI (2009): BFI-level 1
- Scopus rating (2009): SJR 1.041 SNIP 0.655
- BFI (2008): BFI-level 1
- Scopus rating (2008): SJR 1.124 SNIP 0.721
- Scopus rating (2007): SJR 1.137 SNIP 0.701
- Web of Science (2007): Indexed yes
- Scopus rating (2006): SJR 1.205 SNIP 0.648
- Scopus rating (2005): SJR 1.285 SNIP 0.771
- Scopus rating (2004): SJR 1.106 SNIP 0.743
- Scopus rating (2003): SJR 1.055 SNIP 0.62
- Scopus rating (2002): SJR 1.14 SNIP 0.626
- Web of Science (2002): Indexed yes
- Scopus rating (2001): SJR 1.361 SNIP 0.706
- Scopus rating (2000): SJR 1.299 SNIP 0.662
- Scopus rating (1999): SJR 1.21 SNIP 0.748
Temporal variability in urinary phthalate metabolite excretion based on spot, morning, and 24-h urine samples: Considerations for epidemiological studies

Urinary phthalate excretion is used as a marker of phthalate exposure in epidemiological studies. Here we examine the reliability of urinary phthalate levels in exposure classification by comparing the inter- and intrasubject variation of urinary phthalate metabolite levels. Thirty-three young healthy men each collected two spot, three first-morning, and three 24-h urine samples during a 3-month period. Samples were analyzed for the content of 12 urinary metabolites of 7 different phthalates. Variability was assessed as intraclass correlation coefficients (ICC). For the metabolites of diethyl-, dibutyl-, and butylbenzyl-phthalates moderate ICCs were observed in all three sample types, albeit highest in 24-h urine (0.51-0.59). For the metabolites of di(2-ethylhexyl) phthalate and di-iso-nonyl phthalates lower ICCs (0.06-0.29) were found. These low ICCs indicate a high risk of misclassification of exposures for these two phthalates in population studies and hence an attenuation of the power to detect possible exposure-outcome associations. The only slightly higher ICCs for 24-h pools compared to first-morning and spot urine samples do not seem to justify the extra effort needed to collect 24-h pools. © 2012 American Chemical Society.
The chemical interactome space between the human host and the genetically defined gut metabotypes

The bacteria that colonize the gastrointestinal tracts of mammals represent a highly selected microbiome that has a profound influence on human physiology by shaping the host's metabolic and immune system activity. Despite the recent advances on the biological principles that underlie microbial symbiosis in the gut of mammals, mechanistic understanding of the contributions of the gut microbiome and how variations in the metabotypes are linked to the host health are obscure. Here, we mapped the entire metabolic potential of the gut microiome based solely on metagenomics sequencing data derived from fecal samples of 124 Europeans (healthy, obese and with inflammatory bowel disease). Interestingly, three distinct clusters of individuals with high, medium and low metabolic potential were observed. By illustrating these results in the context of bacterial population, we concluded that the abundance of the Prevotella genera is a key factor indicating a low metabolic potential. These metagenome-based metabolic signatures were used to study the interaction networks between bacteria-specific metabolites and human proteins. We found that thirty-three such metabolites interact with disease-relevant protein complexes several of which are highly expressed in cells and tissues involved in the signaling and shaping of the adaptive immune system and associated with squamous cell carcinoma and bladder cancer. From this set of metabolites, eighteen are present in DrugBank providing evidence that we carry a natural pharmacy in our guts. Furthermore, we established connections between the systemic effects of non-antibiotic drugs and the gut microbiome of relevance to drug side effects and health-care solutions.
The CIN4 chromosomal instability qPCR classifier defines tumor aneuploidy and stratifies outcome in grade 2 breast cancer.

Purpose: Quantifying chromosomal instability (CIN) has both prognostic and predictive clinical utility in breast cancer. In order to establish a robust and clinically applicable gene expression-based measure of CIN, we assessed the ability of
four qPCR quantified genes selected from the 70-gene Chromosomal Instability (CIN70) expression signature to stratify outcome in patients with grade 2 breast cancer.

Methods: AURKA, FOXM1, TOP2A and TPX2 (CIN4), were selected from the CIN70 signature due to their high level of correlation with histological grade and mean CIN70 signature expression in silico. We assessed the ability of CIN4 to stratify outcome in an independent cohort of patients diagnosed between 1999 and 2002. 185 formalin-fixed, paraffin-embedded (FFPE) samples were included in the qPCR measurement of CIN4 expression. In parallel, ploidy status of tumors was assessed by flow cytometry. We investigated whether the categorical CIN4 score derived from the CIN4 signature was correlated with recurrence-free survival (RFS) and ploidy status in this cohort.

Results: We observed a significant association of tumor proliferation, defined by Ki67 and mitotic index (MI), with both CIN4 expression and aneuploidy. The CIN4 score stratified grade 2 carcinomas into good and poor prognostic cohorts (mean RFS: 83.86 ± 4.9 and 69.46 ± 8.2 months, respectively, \( p = 0.016 \)) and its predictive power was confirmed by multivariate analysis outperforming MI and Ki67 expression.

Conclusions: The first clinically applicable qPCR derived measure of tumor aneuploidy from FFPE tissue, stratifies grade 2 tumors into good and poor prognosis groups.
The effect of network biology on drug toxicology.

Introduction: The high failure rate of drug candidates due to toxicity, during clinical trials, is a critical issue in drug discovery. Network biology has become a promising approach, in this regard, using the increasingly large amount of biological and chemical data available and combining it with bioinformatics. With this approach, the assessment of chemical safety can be done across multiple scales of complexity from molecular to cellular and system levels in human health. Network biology can be used at several levels of complexity. Areas covered: This review describes the strengths and limitations of network biology. The authors specifically assess this approach across different biological scales when it is applied to toxicity. Expert opinion: There has been much progress made with the amount of data that is generated by various omics technologies. With this large amount of useful data, network biology has the opportunity to contribute to a better understanding of a drug’s safety profile. The authors believe that considering a drug action and protein’s function in a global physiological environment may benefit our understanding of the impact some chemicals have on human health and toxicity. The next step for network biology will be to better integrate differential and quantitative data.
The piRNAs forge an immune system for the genome

Genome integrity of germline is essential for the survival of any species. A dedicated defence mechanism based on small RNA called piRNA (PIWI-interacting RNA) has evolved to protect the germline from the deleterious effects of transposon mobility in genomes such as mutations, deletions or chromosomal rearrangements. The piRNA machinery ensures genomic integrity to germ cells by setting a response similar to the immune system. The recognition of the threat is mediated by sequence complementarity between a vast repertoire of piRNAs and the intruders, and initiates a rapid and efficient degradation of the targets. Akin to acquired immunity, the response is memorized throughout generations thanks to epigenetic modifications. Investigations are progressing to unravel the mysterious mechanisms of this exciting class of non coding RNAs. This review summarizes some of the recent advances on this exceptional immunity that protects transmission of genetic information.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis
Authors: Muller, S. (Intern), Pandey, R. (Ekstern), Pillai, R. (Ekstern)
Pages: 487-494
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Main Research Area: Technical/natural sciences

Publication information
Journal: Medecine Sciences
Volume: 29
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ISSN (Print): 0767-0974
Ratings:
Web of Science (2017): Indexed Yes
Scopus rating (2016): SJR 0.203 SNIP 0.204 CiteScore 0.38
Scopus rating (2015): SJR 0.186 SNIP 0.19 CiteScore 0.39
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.2 SNIP 0.173 CiteScore 0.37
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 0.197 SNIP 0.182 CiteScore 0.39
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 0.188 SNIP 0.209 CiteScore 0.38
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 0.18 SNIP 0.28 CiteScore 0.32
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 0.185 SNIP 0.207
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 0.183 SNIP 0.179
The SH2 Domain Interaction Landscape

Cells respond to growth factors and additional external and internal molecular cues by changing their tyrosine phosphorylation profile. This in turn triggers the modulation of complexes that read and process the information. Cesareni and colleagues now help to define the code that permits recognition of phosphotyrosine residues by SH2 domains, the most abundant class of phosphotyrosine binding domains.

General information

State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, University of Roma 'Tor Vergata', University of Connecticut, JPT Peptide Technologies GmbH, University of Copenhagen
Authors: Tinti, M. (Ekstern), Kiemer, L. (Ekstern), Costa, S. (Ekstern), Miller, M. L. (Intern), Sacco, F. (Ekstern), Olsen, J. (Forskerdatabase), Carducci, M. (Ekstern), Paoluzi, S. (Ekstern), Langone, F. (Ekstern), Workman, C. (Intern), Blom, N. (Intern), Machida, K. (Ekstern), Thompson, C. M. (Ekstern), Schuttowski, M. (Ekstern), Brunak, S. (Intern), Mann, M. (Forskerdatabase), Mayer, B. J. (Ekstern), Castagnoli, L. (Ekstern), Cesareni, G. (Ekstern)
Pages: 1293-1305
Publication date: 2013
Main Research Area: Technical/natural sciences

Publication information

Journal: Cell Reports
Volume: 3
Issue number: 4
Ratings:
BFI (2018): BFI-level 2
BFI (2017): BFI-level 2
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 8.4 SJR 8.012 SNIP 1.749
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 8.507 SNIP 1.754 CiteScore 8.15
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 8.334 SNIP 1.883 CiteScore 7.88
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 8.046 SNIP 1.677 CiteScore 7.22
ISI indexed (2013): ISI indexed no
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
ISI indexed (2012): ISI indexed no
Original language: English
Electronic versions:
The objective of the project was to investigate the time-dependent batch growth effects of oxidative environmental conditions on protein kinase (PK) and phosphatase (PP) deletion mutants and relevant wild type strains of Saccharomyces cerevisiae. To achieve this goal, 44 different PK and PP mutants were selected for their known activities in various stress response pathways, including oxidative stress, and were investigated for their response to oxidative stress. Hydrogen peroxide was used as the oxidizing agent at a number of different concentrations ranging from mild to moderate stress (0.25, 0.50 and 1.0 mM). Understanding the growth physiology of S. cerevisiae allows us to estimate the link between genotype and stress-response phenotype. Growth physiology parameters, such as growth rate, diauxic shift times, stress-induced stasis times, were measured in fermentative batch cultures as important indicators of cellular fitness. We used a high-throughput microfermentation system (BioLector, m2p-labs) to retrieve these indicators of cellular fitness and perform our batch fermentations.
TIMP-1 increases expression and phosphorylation of proteins associated with drug resistance in breast cancer cells

Tissue inhibitor of metalloproteinase 1 (TIMP-1) is a protein with a potential biological role in drug resistance. To elucidate the unknown molecular mechanisms underlying the association between high TIMP-1 levels and increased chemotherapy resistance, we employed SILAC-based quantitative mass spectrometry to analyze global proteome and phosphoproteome differences of MCF-7 breast cancer cells expressing high or low levels of TIMP-1. In TIMP-1 high expressing cells, 312 proteins and 452 phosphorylation sites were up-regulated. Among these were the cancer drug targets topoisomerase 1, 2A and 2B, which may explain the resistance phenotype to topoisomerase inhibitors that was observed in cells with high TIMP-1 levels. Pathway analysis showed an enrichment of proteins from functional categories such as apoptosis, cell cycle, DNA repair, transcription factors, drug targets and proteins associated with drug resistance or sensitivity and drug transportation. The NetworKIN algorithm predicted the protein kinases CK2a, CDK1, PLK1 and ATM as likely candidates involved in the hyper-phosphorylation of the topoisomerases. Up-regulation of protein and/or phosphorylation levels of topoisomerases in TIMP-1 high expressing cells may be part of the mechanisms by which TIMP-1 confers resistance to treatment with the widely-used topoisomerase inhibitors in breast- and colorectal cancer.

General information

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Danish Cancer Society, University of Copenhagen
Authors: Hekmat, O. (Ekstern), Munk, S. (Ekstern), Fogh, L. (Ekstern), Yadav, R. (Intern), Francavilla, C. (Ekstern), Horn, H. (Ekstern), Wurtz, S. O. (Ekstern), Schrohl, A. (Ekstern), Damsgaard, B. (Ekstern), Romer, M. U. (Ekstern), Belling, K. C. (Intern), Jensen, N. F. (Ekstern), Gromova, I. (Ekstern), Bekker-Jensen, D. B. (Ekstern), Moreira, J. M. M.
TIMP1 overexpression mediates resistance of MCF-7 human breast cancer cells to fulvestrant and down-regulates progesterone receptor expression

Abstract High levels of Tissue Inhibitor of Metalloproteinases-1 (TIMP1) are associated with poor prognosis, reduced response to chemotherapy, and, potentially, also poor response to endocrine therapy in breast cancer patients. Our objective was to further investigate the hypothesis that TIMP1 is associated with endocrine sensitivity. We established a panel of 11 MCF-7 subclones with a wide range of TIMP1 mRNA and protein expression levels. Cells with high expression of TIMP1 versus low TIMP1 displayed significantly reduced sensitivity to the antiestrogen fulvestrant (ICI 182,780, Faslodex®), while TIMP1 levels did not influence the sensitivity to 4-hydroxytamoxifen. An inverse correlation between expression of the progesterone receptor and TIMP1 was found, but TIMP1 levels did not correlate with estrogen receptor levels or growth-promoting effects of estrogen (estradiol, E2). Additionally, the effects of fulvestrant, 4-hydroxytamoxifen, or estrogen on estrogen receptor expression were not associated with TIMP1 levels. Gene expression analyses revealed associations between expression of TIMP1 and genes involved in metabolic pathways, epidermal growth factor receptor 1/cancer signaling pathways, and cell cycle. Gene and protein expression analyses showed no general defects in estrogen receptor signaling except from lack of progesterone receptor expression and estrogen inducibility in clones with high TIMP1. The present study suggests a relation between high expression level of TIMP1 and loss of progesterone receptor expression combined with fulvestrant resistance. Our findings in vitro may have clinical implications as the data suggest that high tumor levels of TIMP1 may be a predictive biomarker for reduced response to fulvestrant.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Integrative Systems Biology, Functional Human Variation, DTU Multi Assay Core, Behavioral Phenomics, Metagenomics, University of Southern Denmark, Danish Cancer Society, Sino-Danish Breast Cancer Research Centre, University of Copenhagen
Authors: Bjerre, C. (Ekstern), Vinther, L. (Ekstern), Belling, K. C. (Intern), Würtz, S. Ø. (Ekstern), Yadav, R. (Intern), Lademan, U. (Ekstern), Rigna, O. (Intern), Nguyen Do, K. (Intern), Ditzel, H. J. (Forskerdatabase), Lykkesfeldt, A. E. (Forskerdatabase), Wang, J. (Forskerdatabase), Nielsen, H. B. (Intern), Brünner, N. (Ekstern), Gupta, R. (Intern), Schrol, A. (Ekstern), Stenvang, J. (Ekstern)
Pages: 3839-3851
Publication date: 2013
Main Research Area: Technical/natural sciences

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Journal: Tumor Biology
Volume: 34
ISSN (Print): 1010-4283
Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): SJR 1.026 SNIP 0.837 CiteScore 3.15
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.002 SNIP 0.803 CiteScore 2.79
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.03 SNIP 1.012 CiteScore 3.12
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 0.982 SNIP 1.077 CiteScore 2.61
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 0.922 SNIP 0.839 CiteScore 2.24
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 0.892 SNIP 0.833 CiteScore 2.02
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 0.856 SNIP 0.816
Transcriptome profiling of mice testes following low dose irradiation

ABSTRACT: BACKGROUND: Radiotherapy is used routinely to treat testicular cancer. Testicular cells vary in radio-sensitivity and the aim of this study was to investigate cellular and molecular changes caused by low dose irradiation of mice testis and to identify transcripts from different cell types in the adult testis. METHODS: Transcriptome profiling was performed on total RNA from testes sampled at various time points (n = 17) after 1 Gy of irradiation. Transcripts displaying large overall expression changes during the time series, but small expression changes between neighbouring time points were selected for further analysis. These transcripts were separated into clusters and their cellular origin was determined. Immunohistochemistry and in silico quantification was further used to study cellular changes post-irradiation (pi).

RESULTS: We identified a subset of transcripts (n = 988) where changes in expression pi can be explained by changes in cellularity. We separated the transcripts into five unique clusters that we associated with spermatogonia, spermatocytes, early spermatids, late spermatids and somatic cells, respectively. Transcripts in the somatic cell cluster showed large changes in expression pi, mainly caused by changes in cellularity. Further investigations revealed that the low dose irradiation seemed to cause Leydig cell hyperplasia, which contributed to the detected expression changes in the somatic cell cluster. CONCLUSIONS: The five clusters represent gene expression in distinct cell types of the adult testis. We observed large expression changes in the somatic cell profile, which mainly could be attributed to changes in cellularity, but hyperplasia of Leydig cells may also play a role. We speculate that the possible hyperplasia may be caused by lower testosterone production and inadequate inhibin signalling due to missing germ cells.
Transcriptome Responses to Combinations of Stresses in Arabidopsis

In Arabidopsis, the response of the majority of the genes cannot be predicted from single stress experiments and only a small fraction of the genes have potential antagonistic responses, indicating that plants have evolved to cope with combinations of stresses and therefore may be bred to endure them.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Norwegian University of Science and Technology, Sapienza University of Rome, University of Copenhagen
Authors: Rasmussen, S. (Intern), Barah, P. (Ekstern), Suarez-Rodriguez, M. C. (Ekstern), Bressendorff, S. (Forskerdatabase), Friis, P. (Intern), Costantino, P. (Ekstern), Bones, A. M. (Ekstern), Nielsen, H. B. (Intern), Mundy, J. (Forskerdatabase)
Pages: 1783-1794
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Main Research Area: Technical/natural sciences

Publication information
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Volume: 161
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ISSN (Print): 0032-0889
Ratings:
BFI (2018): BFI-level 2
BFI (2017): BFI-level 2
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 6.58 SJR 3.735 SNIP 1.75
BFI (2015): BFI-level 2
Tumor Mutation Burden Forecasts Outcome in Ovarian Cancer with BRCA1 or BRCA2 Mutations

Background: Increased number of single nucleotide substitutions is seen in breast and ovarian cancer genomes carrying disease-associated mutations in BRCA1 or BRCA2. The significance of these genome-wide mutations is unknown. We hypothesize genome-wide mutation burden mirrors deficiencies in DNA repair and is associated with treatment outcome in ovarian cancer. Methods and Results: The total number of synonymous and non-synonymous exome mutations (Nmut), and the presence of germline or somatic mutation in BRCA1 or BRCA2 (mBRCA) were extracted from whole-exome sequences of high-grade serous ovarian cancers from The Cancer Genome Atlas (TCGA).
Cox regression and Kaplan-Meier methods were used to correlate Nmut with chemotherapy response and outcome. Higher Nmut correlated with a better response to chemotherapy after surgery. In patients with mBRCA-associated cancer, low Nmut was associated with shorter progression-free survival (PFS) and overall survival (OS), independent of other prognostic factors in multivariate analysis. Patients with mBRCA-associated cancers and a high Nmut had remarkably favorable PFS and OS. The association with survival was similar in cancers with either BRCA1 or BRCA2 mutations. In cancers with wild-type BRCA, tumor Nmut was associated with treatment response in patients with no residual disease after surgery.

Conclusions: Tumor Nmut was associated with treatment response and with both PFS and OS in patients with high-grade serous ovarian cancer carrying BRCA1 or BRCA2 mutations. In the TCGA cohort, low Nmut predicted resistance to chemotherapy, and for shorter PFS and OS, while high Nmut forecasts a remarkably favorable outcome in mBRCA-associated ovarian cancer. Our observations suggest that the total mutation burden coupled with BRCA1 or BRCA2 mutations in ovarian cancer is a genomic marker of prognosis and predictor of treatment response. This marker may reflect the degree of deficiency in BRCA-mediated pathways, or the extent of compensation for the deficiency by alternative mechanisms.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Cancer Systems Biology, Functional Human Variation, Integrative Systems Biology, Behavioral Phenomics, Dana-Farber Cancer Institute, Brigham and Women's Hospital
Authors: Birkbak, N. J. (Intern), Kochupurakkal, B. (Ekstern), Gonzalez-Izarzugaza, J. M. (Intern), Eklund, A. C. (Intern), Li, Y. (Ekstern), Liu, J. (Ekstern), Szallasi, Z. I. (Intern), Matulonis, U. A. (Ekstern), Richardson, A. L. (Ekstern), Iglehart, J. D. (Ekstern), Wang, Z. C. (Ekstern)
Publication date: 2013
Main Research Area: Technical/natural sciences

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Volume: 8
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ISSN (Print): 1932-6203
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BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.11 SJR 1.201 SNIP 1.092
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.414 SNIP 1.131 CiteScore 3.32
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.545 SNIP 1.141 CiteScore 3.54
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.74 SNIP 1.147 CiteScore 3.94
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.945 SNIP 1.142 CiteScore 4.15
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 2.369 SNIP 1.23 CiteScore 4.58
ISI indexed (2011): ISI indexed no
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 2.631 SNIP 1.161
VAR2CSA Epitope Identification - Finding All the Needles in All the Haystacks

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Immunological Bioinformatics, Technical University of Denmark, Copenhagen University Hospital, University of Copenhagen, Schafer-N
Authors: Jessen, L. E. (Ekstern), Ditlev, S. B. (Ekstern), Schafer-Nielsen, C. (Ekstern), Buus, S. (Ekstern), Salanti, A. (Ekstern), Lund, O. (Intern)
Pages: 318-319
Publication date: 2013
Conference: 41st Meeting and Summer School of the Scandinavian-Society-for-Immunology, Copenhagen, Denmark, 14/04/2013 - 14/04/2013
Main Research Area: Technical/natural sciences

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Journal: Scandinavian Journal of Immunology
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BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.03 SJR 0.951 SNIP 0.646
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.93 SNIP 0.684 CiteScore 1.97
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.898 SNIP 0.666 CiteScore 1.91
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 0.86 SNIP 0.712 CiteScore 2.05
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 0.88 SNIP 0.749 CiteScore 2.16
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Veillonella, Firmicutes: Microbes disguised as Gram negatives

The Firmicutes represent a major component of the intestinal microflora. The intestinal Firmicutes are a large, diverse group of organisms, many of which are poorly characterized due to their anaerobic growth requirements. Although most Firmicutes are Gram positive, members of the class Negativicutes, including the genus Veillonella, stain Gram negative. Veillonella are among the most abundant organisms of the oral and intestinal microflora of animals and humans, in spite of being strict anaerobes. In this work, the genomes of 24 Negativicutes, including eight Veillonella spp., are compared to 20 other Firmicutes genomes; a further 101 prokaryotic genomes were included, covering 26 phyla. Thus a total of 145 prokaryotic genomes were analyzed by various methods to investigate the apparent conflict of the Veillonella Gram stain and their taxonomic position within the Firmicutes. Comparison of the genome sequences confirms that the Negativicutes are distantly related to Clostridium spp., based on 16S rRNA, complete genomic DNA sequences, and a consensus tree based on conserved proteins. The genus Veillonella is relatively homogeneous: inter-genus pairwise comparison identifies at least 1,350 shared proteins, although less than half of these are found in any given Clostridium genome. Only 27 proteins are found conserved in all analyzed prokaryote genomes. Veillonella has distinct metabolic properties, and significant similarities to genomes of Proteobacteria are not detected, with the exception of a shared LPS biosynthesis pathway. The clade within the class Negativicutes to which the genus Veillonella belongs exhibits unique properties, most of which are in common with Gram-positives and some with Gram negatives. They are only distantly related to Clostridia, but are even less closely related to Gram-negative species. Though the Negativicutes stain Gram-negative and possess two membranes, the genome and proteome analysis presented here confirm their place within the (mainly) Gram positive phylum of the Firmicutes. Further studies are required to unveil the evolutionary history of the Veillonella and other Negativicutes.

General information

State: Published
Organisations: Center for Biological Sequence Analysis, Comparative Microbial Genomics, Department of Systems Biology, National Food Institute, Division of Food Microbiology, Division of Epidemiology and Microbial Genomics
Authors: Vesth, T. C. (Intern), Ozen, A. (Ekstern), Andersen, S. C. (Intern), Kaas, R. S. (Intern), Lukjancenko, O. (Intern), Bohlin, J. (Ekstern), Nookaew, I. (Ekstern), Wassenaar, T. M. (Ekstern), Ussery, D. (Intern)
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Main Research Area: Technical/natural sciences
Whey protein reduces early life weight gain in mice fed a high-fat diet.

An increasing number of studies indicate that dairy products, including whey protein, alleviate several disorders of the metabolic syndrome. Here, we investigated the effects of whey protein isolate (whey) in mice fed a high-fat diet hypothesizing that the metabolic effects of whey would be associated with changes in the gut microbiota composition. Five-week-old male C57BL/6 mice were fed a high-fat diet ad libitum for 14 weeks with the protein source being either whey or casein. Faeces were collected at week 0, 7, and 13 and the fecal microbiota was analysed by denaturing gradient gel electrophoresis analyses of PCR-derived 16S rRNA gene (V3-region) amplicons. At the end of the study, plasma samples were collected and assayed for glucose, insulin and lipids. Whey significantly reduced body weight gain during the first four weeks of the study compared with casein (P<0.001–0.05). Hereafter weight gain was similar resulting in a 15% lower final body weight in the whey group relative to casein (34.0±1.0 g vs. 40.2±1.3 g, P<0.001). Food intake was unaffected by protein source throughout the study period. Fasting insulin was lower in the whey group (P<0.01) and glucose clearance was improved after an oral glucose challenge (P<0.05). Plasma cholesterol was lowered by whey compared to casein (P<0.001). The composition of the fecal microbiota differed between high- and low-fat groups at 13 weeks (P<0.05) whereas no difference was seen between whey and casein. In conclusion, whey initially reduced weight gain in young C57BL/6 mice fed a high-fat diet compared to casein. Although the effect on weight gain ceased, whey alleviated glucose intolerance, improved insulin sensitivity and reduced plasma cholesterol. These findings could not be explained by changes in food intake or gut microbiota composition. Further studies are needed to clarify the mechanisms behind the metabolic effects of whey.
Whole-Exome Sequencing of 2,000 Danish Individuals and the Role of Rare Coding Variants in Type 2 Diabetes

It has been hypothesized that, in aggregate, rare variants in coding regions of genes explain a substantial fraction of the heritability of common diseases. We sequenced the exomes of 1,000 Danish cases with common forms of type 2 diabetes (including body mass index $> 27.5 \text{ kg/m}^2$ and hypertension) and 1,000 healthy controls to an average depth of 56×. Our simulations suggest that our study had the statistical power to detect at least one causal gene (a gene containing causal mutations) if the heritability of these common diseases was explained by rare variants in the coding regions of a limited number of genes. We applied a series of gene-based tests to detect such susceptibility genes. However, no gene showed a significant association with disease risk after we corrected for the number of genes analyzed. Thus, we could reject a model for the genetic architecture of type 2 diabetes where rare nonsynonymous variants clustered in a modest number of genes (fewer than 20) are responsible for the majority of disease risk.

General information

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of California, BGI-Shenzhen, Aarhus University, University of Southern Denmark, University of Copenhagen
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Main Research Area: Technical/natural sciences

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BFI (2015): BFI-level 2
Scopus rating (2015): SJR 8.808 SNIP 3.037 CiteScore 9.71
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 8.792 SNIP 3.133 CiteScore 9.66
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 7.803 SNIP 3.036 CiteScore 9.58
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 7.718 SNIP 3.07 CiteScore 9.86
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 8.373 SNIP 3.092 CiteScore 10.01
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
BFI (2009): BFI-level 2
wKinMut: An integrated tool for the analysis and interpretation of mutations in human protein kinases

Background
Protein kinases are involved in relevant physiological functions and a broad number of mutations in this superfamily have been reported in the literature to affect protein function and stability. Unfortunately, the exploration of the consequences on the phenotypes of each individual mutation remains a considerable challenge.

Results
The wKinMut web-server offers direct prediction of the potential pathogenicity of the mutations from a number of methods, including our recently developed prediction method based on the combination of information from a range of diverse sources, including physicochemical properties and functional annotations from FireDB and Swissprot and kinase-specific characteristics such as the membership to specific kinase groups, the annotation with disease-associated GO terms or the occurrence of the mutation in PFAM domains, and the relevance of the residues in determining kinase subfamily specificity from S3Det. This predictor yields interesting results that compare favourably with other methods in the field when applied to protein kinases.
Absorption difference between diacylglycerol oil and butter blend containing diacylglycerol oil

This study aims at investigating whether the intake of butter blends containing diacylglycerol (DAG) oil may result in reduced fat accumulation, in similarity to DAG oil, and the potential metabolic differences between butter blends and DAG oil. Four experimental diets containing either 10 wt% DAG butter blend (BDAG), triacylglycerol (TAG) butter blend (BTAG), DAG oil (ODAG) or TAG oil (OTAG) were prepared, and each was fed to a group of 8 male Wistar rats. The design of the experiment was a combined balance and feeding experiment. The rats fed the BTAG and ODAG-diets had a significantly higher protein content than rats fed the BDAG and OTAG-diets, and the fat content was significantly lower in rats fed the ODAG-diet as compared to rats fed the OTAG and BDAG-diets. A significantly higher content of ash was observed in rats fed the two TAG diets. The ratio of abdominal fat weight/body weight was significantly higher for rats fed the BDAG-diet than for rats fed the BTAG and ODAG-diets. To conclude, the beneficial effects of DAG oil in reducing body fat...
accumulation cannot be observed in DAG oil containing butter blends, and the effect of DAG on bone health requires further investigation.

**General information**

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Aarhus University
Authors: Kristensen, J. B. (Intern), Jørgensen, H. (Forskerdatabase), Mu, H. (Intern)
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Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.06 SJR 0.71 SNIP 1.024
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.642 SNIP 0.881 CiteScore 1.85
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.737 SNIP 1.051 CiteScore 1.98
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 0.852 SNIP 1.124 CiteScore 2.16
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 0.873 SNIP 1.207 CiteScore 2.06
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 0.732 SNIP 0.945 CiteScore 1.75
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 0.791 SNIP 1.049
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 0.838 SNIP 1.077
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 0.606 SNIP 0.815
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 0.598 SNIP 0.801
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 0.704 SNIP 0.9
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 0.674 SNIP 0.98
Web of Science (2005): Indexed yes
Scopus rating (2004): SJR 0.585 SNIP 0.946
A comparative analysis of the intestinal metagenomes present in guinea pigs (Cavia porcellus) and humans (Homo sapiens)

Background: Guinea pig (Cavia porcellus) is an important model for human intestinal research. We have characterized the faecal microbiota of 60 guinea pigs using Illumina shotgun metagenomics, and used this data to compile a gene catalogue of its prevalent microbiota. Subsequently, we compared the guinea pig microbiome to existing human gut metagenome data from the MetaHIT project.

Results: We found that the bacterial richness obtained for human samples was lower than for guinea pig samples. The intestinal microbiotas of both species were dominated by the two phyla Bacteroidetes and Firmicutes, but at genus level, the majority of identified genera (320 of 376) were differently abundant in the two hosts. For example, the guinea pig contained considerably more of the mucin-degrading Akkermansia, as well as of the methanogenic archaea Methanobrevibacter than found in humans. Most microbiome functional categories were less abundant in guinea pigs than in humans. Exceptions included functional categories possibly reflecting dehydration/rehydration stress in the guinea pig intestine. Finally, we showed that microbiological databases have serious anthropocentric biases, which impacts model organism research.

Conclusions: The results lay the foundation for future gastrointestinal research applying guinea pigs as models for humans.
A genome-wide association study of men with symptoms of testicular dysgenesis syndrome and its network biology interpretation.

Background Testicular dysgenesis syndrome (TDS) is a common disease that links testicular germ cell cancer, cryptorchidism and some cases of hypospadias and male infertility with impaired development of the testis. The incidence of these disorders has increased over the last few decades, and testicular cancer now affects 1% of the Danish and Norwegian male population. Methods To identify genetic variants that span the four TDS phenotypes, the authors performed a genome-wide association study (GWAS) using Affymetrix Human SNP Array 6.0 to screen 488 patients with symptoms of TDS and 439 selected controls with excellent reproductive health. Furthermore, they developed a novel integrative method that combines GWAS data with other TDS-relevant data types and identified additional TDS markers. The most significant findings were replicated in an independent cohort of 671 Nordic men. Results Markers located in the...
region of TGFBR3 and BMP7 showed association with all TDS phenotypes in both the discovery and replication cohorts. An immunohistochemistry investigation confirmed the presence of transforming growth factor β receptor type III (TGFBR3) in peritubular and Leydig cells, in both fetal and adult testis. Single-nucleotide polymorphisms in the KITLG gene showed significant associations, but only with testicular cancer. Conclusions The association of single-nucleotide polymorphisms in the TGFBR3 and BMP7 genes, which belong to the transforming growth factor β signalling pathway, suggests a role for this pathway in the pathogenesis of TDS. Integrating data from multiple layers can highlight findings in GWAS that are biologically relevant despite having border significance at currently accepted statistical levels.

**General information**

**State:** Published

**Organisations:** Center for Biological Sequence Analysis, Department of Systems Biology, Lund University, Karolinska Institute and University Hospital, University of Turku, Copenhagen University Hospital, University of Copenhagen


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- BFI (2017): BFI-level 2
- Web of Science (2017): Indexed Yes
- BFI (2016): BFI-level 2
- Scopus rating (2016): SJR 3.085 SNIP 1.737 CiteScore 5.05
- BFI (2015): BFI-level 2
- Scopus rating (2015): SJR 3.696 SNIP 1.883 CiteScore 5.79
- BFI (2014): BFI-level 2
- Scopus rating (2014): SJR 3.449 SNIP 2.265 CiteScore 5.87
- BFI (2013): BFI-level 2
- Scopus rating (2013): SJR 3.018 SNIP 2.183 CiteScore 5.72
- ISI indexed (2013): ISI indexed yes
- BFI (2012): BFI-level 2
- Scopus rating (2012): SJR 3.318 SNIP 2.034 CiteScore 6.03
- ISI indexed (2012): ISI indexed yes
- Web of Science (2012): Indexed yes
- BFI (2011): BFI-level 2
- Scopus rating (2011): SJR 2.979 SNIP 2.046 CiteScore 5.75
- ISI indexed (2011): ISI indexed yes
- BFI (2010): BFI-level 2
- Scopus rating (2010): SJR 3.288 SNIP 2.084
- BFI (2009): BFI-level 2
- Scopus rating (2009): SJR 2.794 SNIP 2.132
- BFI (2008): BFI-level 2
- Scopus rating (2008): SJR 2.893 SNIP 2.242
- Scopus rating (2007): SJR 2.885 SNIP 2.016
- Scopus rating (2006): SJR 2.556 SNIP 1.866
- Scopus rating (2005): SJR 2.27 SNIP 1.869
- Scopus rating (2004): SJR 1.81 SNIP 1.799
- Scopus rating (2003): SJR 1.845 SNIP 1.798
- Scopus rating (2002): SJR 2.136 SNIP 1.716
Analysis of cytotoxic T cell epitopes in relation to cancer

The human immune system is a highly adaptable system, defending our bodies against pathogens and tumor cells. Cytotoxic T cells (CTLs) are cells of the adaptive immune system, capable of inducing a programmed cell death and thus able to eliminate infected or tumor cells. CTLs discriminate between healthy and infected cells based on peptide fragments presented on the cells surface. All nucleated cells present these peptide fragments in complex with Major Histocompatibility Complex (MHC) class I molecules. Peptides that are recognized by CTLs are called epitopes and induce the CTLs to subsequently kill the infected cells.

The focus of my PhD project has been on improving a method for CTL epitope pathway prediction, on analyzing the epitope density in the alternative cancer exome, and on a study investigating minor histocompatibility antigens (mHags) associated with leukemia.

Part I is an introduction to the fields covered in the thesis. Part II describes a pan-specific, integrative approach for the prediction of CTL epitopes. The presented method, NetCTLpan, an improved and extended version of NetCTL, performs predictions for all MHC class I molecules with known protein sequence and allows predictions for 8, 9, 10 and 11-mer epitopes. One of the major benefits of the method is its optimization to achieve high specificity. Its low false positive rate is especially useful in rational reverse immunogenetic epitope discovery approaches. When this method is compared to the NetMHCpan and NetCTL methods, the experimental effort to identify 90% of new epitopes can be reduced by 15% and 40%, respectively.

Part III reports the results of an analysis investigating how the alternatively spliced cancer exome differs from the exome of normal tissue in terms of containing predicted MHC class I binding epitopes. We show that peptides unique to cancer splice variants comprise significantly fewer predicted HLA class I epitopes than peptides unique to spliced transcripts in normal tissue. We furthermore find that hydrophilic amino acids are significantly enriched in the unique carcinoma sequences, which contribute to the lower likelihood of carcinoma-specific peptides to be predicted epitopes. Carcinoma is known to have developed mechanisms for evading the host’s immune system. Here, we show for the first time that carcinoma has a bias towards fewer possible epitopes already at the step of mRNA splicing.

Part IV of the thesis deals with the analysis of 93 patient-donor pairs that underwent hematopoietic stem cell transplantation (HCT). HCT is a standard treatment for a variety of hematological diseases. Graft-versus-host disease is a possible complication after an HCT, where the recipient’s cells are perceived as foreign and the target of an immune response mediated by the donor’s transplanted immune cells. The immune response is provoked by epitopes unique to the patient, so-called mHags. Here, a gene-specific association between the number of SNPs or predicted mHags and the possible clinical outcome following an HCT is presented.

General information

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Functional Human Variation, Integrative Systems Biology, Novo Nordisk Foundation Center for Biosustainability, CFB - Metagenomic Systems Biology, Immunological Bioinformatics
Authors: Stranzl, T. (Intern), Brunak, S. (Intern), Larsen, M. V. (Intern)
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Analyzing the genomic variation of microbial cell factories in the era of "New Biotechnology"

The application of genome-scale technologies, both experimental and in silico, to industrial biotechnology has allowed improving the conversion of biomass-derived feedstocks to chemicals, materials and fuels through microbial fermentation.
In particular, due to rapidly decreasing costs and its suitability for identifying the genetic determinants of a phenotypic trait of interest, whole genome sequencing is expected to be one of the major driving forces in industrial biotechnology in the coming years. We present some of the recent studies that have successfully applied high-throughput sequencing technologies for finding the underlying molecular mechanisms for (a) improved carbon source utilization, (b) increased product formation, and (c) stress tolerance. We also discuss the strengths and weaknesses of different strategies for mapping industrially relevant genotype-to-phenotype links including exploiting natural diversity in natural isolates or crosses between isolates, classical mutagenesis and evolutionary engineering.

Androgen receptor signalling in peritubular myoid cells is essential for normal differentiation and function of adult Leydig cells
Testosterone synthesis depends on normal Leydig cell (LC) development, but the mechanisms controlling this development remain unclear. We recently demonstrated that androgen receptor (AR) ablation from a proportion of testicular peritubular myoid cells (PTM-ARKO) did not affect LC number, but resulted in compensated LC failure. The current study extends these investigations, demonstrating that PTM AR signalling is important for normal development, ultrastructure and function of adult LCs. Notably, mRNAs for LC markers [e.g. steroidogenic factor 1 (Nr5a1), insulin-like growth factor (Igf-1) and insulin-like factor 3 (Insl3)] were significantly reduced in adult PTM-ARKOs, but not all LCs were similarly affected. Two LC sub-populations were identified, one apparently 'normal' sub-population that expressed adult LC markers and steroidogenic enzymes as in controls, and another 'abnormal' subpopulation that had arrested development and only weakly expressed INSL3, luteinizing hormone receptor, and several steroidogenic enzymes. Furthermore, unlike 'normal' LCs in PTM-ARKOs, the 'abnormal' LCs did not involute as expected in response to exogenous testosterone. Differential function of these LC sub-populations is likely to mean that the 'normal' LCs work harder to compensate for the 'abnormal' LCs to maintain normal serum testosterone. These findings reveal new paracrine mechanisms underlying adult LC development, which can be further investigated using PTM-ARKOs.
Association between chemical pattern in breast milk and congenital cryptorchidism: modelling of complex human exposures

During the past four decades, there has been an increase in the incidence rate of male reproductive disorders in some, but not all, Western countries. The observed increase in the prevalence of male reproductive disorders is suspected to be ascribable to environmental factors as the increase has been too rapid to be explained by genetics alone. To study the association between complex chemical exposures of humans and congenital cryptorchidism, the most common...
malformation of the male genitalia, we measured 121 environmental chemicals with suspected or known endocrine
disrupting properties in 130 breast milk samples from Danish and Finnish mothers. Half the newborns were healthy
controls, whereas the other half was boys with congenital cryptorchidism. The measured chemicals included
polychlorinated biphenyls (PCBs), polybrominated diphenyl-ethers, dioxins (OCDD/PCDFs), phthalates, polybrominated
biphenyls and organochlorine pesticides. Computational analysis of the data was performed using logistic regression and
three multivariate machine learning classifiers. Furthermore, we performed systems biology analysis to explore the
chemical influence on a molecular level. After correction for multiple testing, exposure to nine chemicals was significantly
different between the cases and controls in the Danish cohort, but not in the Finnish cohort. The multivariate analysis
indicated that Danish samples exhibited a stronger correlation between chemical exposure patterns in breast milk and
cryptorchidism than Finnish samples. Moreover, PCBs were indicated as having a protective effect within the Danish
cohort, which was supported by molecular data recovered through systems biology. Our results lend further support to the
hypothesis that the mixture of environmental chemicals may contribute to observed adverse trends in male reproductive
health.
A Steered Molecular Dynamics Study of Binding and Translocation Processes in the GABA Transporter

The entire substrate translocation pathway in the human GABA transporter (GAT-1) was explored for the endogenous substrate GABA and the anti-convulsive drug tiagabine. Following a steered molecular dynamics (SMD) approach, in which a harmonic restraining potential is applied to the ligand, dissociation and re-association of ligands were simulated revealing events leading to substrate (GABA) translocation and inhibitor (tiagabine) mechanism of action. We succeeded in turning the transporter from the outward facing occluded to the open-to-out conformation, and also to reorient the transporter to the open-to-in conformation. The simulations are validated by literature data and provide a substrate pathway fingerprint in terms of which, how, and in which sequence specific residues are interacted with. They reveal the essential functional roles of specific residues, e.g. the role of charged residues in the extracellular vestibule including two lysines (K76 (TM1) and K448 (TM10)) and a TM6-triad (D281, E283, and D287) in attracting and relocating substrates towards the secondary/interim substrate-binding site (S2). Likewise, E101 is highlighted as essential for the relocation of the substrate from the primary substrate-binding site (S1) towards the cytoplasm.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, H. Lundbeck A/S, University of Copenhagen
Authors: Skovstrup, S. (Ekstern), David, L. (Ekstern), Taboureau, O. (Intern), Jorgensen, F. S. (Ekstern)
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BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.414 SNIP 1.131 CiteScore 3.32
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.545 SNIP 1.141 CiteScore 3.54
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Scopus rating (2013): SJR 1.74 SNIP 1.147 CiteScore 3.94
Bacterial adaptive response to changing herbicide discharge rates in the streambed sediments impacted by a landfill

General information
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Organisations: Department of Environmental Engineering, Department of Systems Biology, Center for Biological Sequence Analysis, Novo Nordisk Foundation Center for Biosustainability, CFB - Metagenomic Systems Biology, Helmholtz Zentrum München, Geological Survey of Denmark and Greenland, University of Copenhagen
Authors: Pazarbasi, M. B. (Intern), Bælum, J. (Intern), Pilloni, G. (Ekstern), Larentis, M. (Ekstern), Jacobsen, C. S. (Ekstern), Lueders, T. (Ekstern), Hansen, L. H. (Ekstern), Aamand, J. (Ekstern)
Number of pages: 1
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Bayesian prediction of bacterial growth temperature range based on genome sequences

Background: The preferred habitat of a given bacterium can provide a hint of which types of enzymes of potential industrial interest it might produce. These might include enzymes that are stable and active at very high or very low temperatures. Being able to accurately predict this based on a genomic sequence, would thus allow for an efficient and targeted search for production organisms, reducing the need for culturing experiments. Results: This study found a total of 40 protein
families useful for distinction between three thermophilicity classes (thermophiles, mesophiles and psychrophiles). The predictive performance of these protein families were compared to those of 87 basic sequence features (relative use of amino acids and codons, genomic and 16S rDNA AT content and genome size). When using naive Bayesian inference, it was possible to correctly predict the optimal temperature range with a Matthews correlation coefficient of up to 0.68. The best predictive performance was always achieved by including protein families as well as structural features, compared to either of these alone. A dedicated computer program was created to perform these predictions. Conclusions: This study shows that protein families associated with specific thermophilicity classes can provide effective input data for thermophilicity prediction, and that the naive Bayesian approach is effective for such a task. The program created for this study is able to efficiently distinguish between thermophilic, mesophilic and psychrophilic adapted bacterial genomes.

General information
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Novozymes A/S
Authors: Jensen, D. B. (Intern), Vesth, T. C. (Intern), Hallin, P. F. (Ekstern), Pedersen, A. G. (Intern), Ussery, D. (Intern)
Publication date: 2012
Conference: Asia Pacific Bioin11th International Conference on Bioinformatics (InCoB), Bangkok, Thailand, 03/10/2012 - 03/10/2012
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Scopus rating (2016): CiteScore 4.05 SJR 2.065 SNIP 1.122
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.287 SNIP 1.172 CiteScore 4.3
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.297 SNIP 1.205 CiteScore 4.18
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 2.141 SNIP 1.174 CiteScore 4.39
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 2.181 SNIP 1.225 CiteScore 4.61
ISI indexed (2012): ISI indexed yes
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BFI (2011): BFI-level 1
Scopus rating (2011): SJR 2.271 SNIP 1.197 CiteScore 4.38
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 2.109 SNIP 1.038
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 2.181 SNIP 1.015
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 2.067 SNIP 1.005
Web of Science (2008): Indexed yes
BDDCS Class Prediction for New Molecular Entities

The Biopharmaceutics Drug Disposition Classification System (BDDCS) was successfully employed for predicting drug–drug interactions (DDIs) with respect to drug metabolizing enzymes (DMEs), drug transporters and their interplay. The major assumption of BDDCS is that the extent of metabolism (EoM) predicts high versus low intestinal permeability rate, and vice versa, at least when uptake transporters or paracellular transport is not involved. We recently published a collection of over 900 marketed drugs classified for BDDCS. We suggest that a reliable model for predicting BDDCS class, integrated with in vitro assays, could anticipate disposition and potential DDIs of new molecular entities (NMEs). Here we describe a computational procedure for predicting BDDCS class from molecular structures. The model was trained on a set of 300 oral drugs, and validated on an external set of 379 oral drugs, using 17 descriptors calculated or derived from the VolSurf+ software. For each molecule, a probability of BDDCS class membership was given, based on predicted EoM, FDA solubility (FDAS) and their confidence scores. The accuracy in predicting FDAS was 78% in training and 77% in validation, while for EoM prediction the accuracy was 82% in training and 79% in external validation. The actual BDDCS class corresponded to the highest ranked calculated class for 55% of the validation molecules, and it was within the top two ranked more than 92% of the time. The unbalanced stratification of the data set did not affect the prediction, which showed highest accuracy in predicting classes 2 and 3 with respect to the most populated class 1. For class 4 drugs a general lack of predictability was observed. A linear discriminant analysis (LDA) confirming the degree of accuracy for the prediction of the different BDDCS classes is tied to the structure of the data set. This model could routinely be used in early drug discovery to prioritize in vitro tests for NMEs (e.g., affinity to transporters, intestinal metabolism, intestinal absorption and plasma protein binding). We further applied the BDDCS prediction model on a large set of medicinal chemistry compounds (over 30,000 chemicals). Based on this application, we suggest that solubility, and not permeability, is the major difference between NMEs and drugs. We anticipate that the forecast of BDDCS categories in early drug discovery may lead to a significant R&D cost reduction.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, University of Perugia, University of California, San Francisco
Authors: Broccatelli, F. (Ekstern), Cruciani, G. (Ekstern), Benet, L. Z. (Ekstern), Oprea, T. (Intern)
Pages: 570-580
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Main Research Area: Technical/natural sciences

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BFI (2017): BFI-level 1
Bioinformatics Training Network (BTN): a community resource for bioinformatics trainers

Funding bodies are increasingly recognizing the need to provide graduates and researchers with access to short intensive courses in a variety of disciplines, in order both to improve the general skills base and to provide solid foundations on which researchers may build their careers. In response to the development of 'high-throughput biology', the need for training in the field of bioinformatics, in particular, is seeing a resurgence: it has been defined as a key priority by many Institutions and research programmes and is now an important component of many grant proposals. Nevertheless, when it comes to planning and preparing to meet such training needs, tension arises between the reward structures that predominate in the scientific community which compel individuals to publish or perish, and the time that must be devoted to the design, delivery and maintenance of high-quality training materials. Conversely, there is much relevant teaching material and training expertise available worldwide that, were it properly organized, could be exploited by anyone who needs to provide training or needs to set up a new course. To do this, however, the materials would have to be centralized in a database and clearly tagged in relation to target audiences, learning objectives, etc. Ideally, they would also be peer reviewed, and easily and efficiently accessible for downloading. Here, we present the Bioinformatics Training Network (BTN), a new enterprise that has been initiated to address these needs and review it, respectively, to similar initiatives and collections.

General information
Campylobacter fetus subspecies: Comparative genomics and prediction of potential virulence targets

The genus Campylobacter contains pathogens causing a wide range of diseases, targeting both humans and animals. Among them, the Campylobacter fetus subspecies fetus and venerealis deserve special attention, as they are the etiological agents of human bacterial gastroenteritis and bovine genital campylobacteriosis, respectively. We compare the whole genomes of both subspecies to get insights into genomic architecture, phylogenetic relationships, genome conservation and core virulence factors. Pan-genomic approach was applied to identify the core- and pan-genome for both C. fetus subspecies and members of the genus. The C. fetus subspecies conserved (76%) proteome were then analyzed for their subcellular localization and protein functions in biological processes. Furthermore, with pathogenomic strategies, unique candidate regions in the genomes and several potential core-virulence factors were identified. The potential candidate factors identified for attenuation and/or subunit vaccine development against C. fetus subspecies contain: nucleoside diphosphate kinase (Ndk), type IV secretion systems (T4SS), outer membrane proteins (OMP), substrate binding proteins CjaA and CjaC, surface array proteins, sap gene, and cytolethal distending toxin (CDT). Significantly, many of those genes were found in genomic regions with signals of horizontal gene transfer and, therefore, predicted as putative pathogenicity islands. We found CRISPR loci and dam genes in an island specific for C. fetus subsp. fetus, and T4SS and sap genes in an island specific for C. fetus subsp. venerealis. The genomic variations and potential core and unique virulence factors characterized in this study would lead to better insight into the species virulence and to more efficient use of the candidates for antibiotic, drug and vaccine development.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Federal University of Minas Gerais, Federal University of Pará, ESR Christchurch Science Centre, Universidade Federal de Minas Gerais
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BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): SJR 0.987 SNIP 0.892 CiteScore 2.42
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.05 SNIP 0.862 CiteScore 2.35
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.006 SNIP 0.8 CiteScore 2.18
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 0.971 SNIP 0.726 CiteScore 2.2
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.085 SNIP 0.846 CiteScore 2.45
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Cells, shared memory and breaking the PTM code.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis
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Publication date: 2012
Main Research Area: Technical/natural sciences

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Journal: Molecular Systems Biology
Volume: 8
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BFI (2018): BFI-level 2
BFI (2017): BFI-level 2
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 8.23 SJR 8.366 SNIP 2.15
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 8.731 SNIP 2.395 CiteScore 9.76
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Ceramide profile in hypohidrotic ectodermal dysplasia

Background. Hypohidrotic ectodermal dysplasia (HED) is a rare genetic disease. The clinical presentation includes lack of sweating ability, and an often widely spread dermatitis resembling atopic dermatitis (AD). In AD, the skin-barrier defect is partly ascribed to the altered lipid profile in the stratum corneum and partly to mutations of the filaggrin genes. To our knowledge, no data are available about the epidermal lipid profile of HED. Aim. To compare the ceramide profile for patients with HED and AD. Methods. The ceramide profile and ceramide/cholesterol ratio were compared between patients with HED (n = 7) and patients with AD (n = 21), using cyanoacrylate to take biopsy samples from the stratum corneum. Lipids were extracted from the biopsies and analysed using high-performance thin-layer chromatography. Results. The lipid profiles of HED and AD were similar in distribution, apart from ceramide 1, which was significantly higher in HED (P = 0.04). Conclusions. The increased ceramide 1 level found in HED compared with AD is known to play a role in the structure of the lipid bilayers. However, further studies are needed to identify the functional significance of these observations and thereby elucidate differences in the skin barrier between HED and AD.
CERT depletion predicts chemotherapy benefit and mediates cytotoxic and polyploid-specific cancer cell death through autophagy induction

Chromosomal instability (CIN) has been implicated in multidrug resistance and the silencing of the ceramide transporter, CERT, promotes sensitization to diverse cytotoxics. An improved understanding of mechanisms governing multidrug sensitization might provide insight into pathways contributing to the death of CIN cancer cells. Using an integrative functional genomics approach, we find that CERT-specific multidrug sensitization is associated with enhanced autophagosome–lysosome flux, resulting from the expression of LAMP2 following CERT silencing in colorectal and HER2+ breast cancer cell lines. Live cell microscopy analysis revealed that CERT depletion induces LAMP2-dependent death of polyploid cells following exit from mitosis in the presence of paclitaxel. We find that CERT is relatively over-expressed in HER2+ breast cancer and CERT protein expression acts as an independent prognostic variable and predictor of outcome in adjuvant chemotherapy-treated patients with primary breast cancer. These data suggest that the induction of LAMP2-dependent autophagic flux through CERT targeting may provide a rational approach to enhance...
multidrug sensitization and potentiate the death of polyploid cells following paclitaxel exposure to limit the acquisition of CIN and intra-tumour heterogeneity. Copyright © 2011 Pathological Society of Great Britain and Ireland. Published by John Wiley & Sons, Ltd.
Characterization of HIV-Specific CD4+T Cell Responses against Peptides Selected with Broad Population and Pathogen Coverage

CD4+ T cells orchestrate immunity against viral infections, but their importance in HIV infection remains controversial. Nevertheless, comprehensive studies have associated increase in breadth and functional characteristics of HIV-specific CD4+ T cells with decreased viral load. A major challenge for the identification of HIV-specific CD4+ T cells targeting broadly reactive epitopes in populations with diverse ethnic background stems from the vast genomic variation of HIV and the diversity of the host cellular immune system. Here, we describe a novel epitope selection strategy, PopCover, that aims to resolve this challenge, and identify a set of potential HLA class II-restricted HIV epitopes that in concert will provide optimal viral and host coverage. Using this selection strategy, we identified 64 putative epitopes (peptides) located in the Gag, Nef, Env, Pol and Tat protein regions of HIV. In total, 73% of the predicted peptides were found to induce HIV-specific CD4+ T cell responses. The Gag and Nef peptides induced most responses. The vast majority of the peptides (93%) had predicted restriction to the patient's HLA alleles. Interestingly, the viral load in viremic patients was inversely correlated to the number of targeted Gag peptides. In addition, the predicted Gag peptides were found to induce broader polyfunctional CD4+ T cell responses compared to the commonly used Gag-p55 peptide pool. These results demonstrate the power of the PopCover method for the identification of broadly recognized HLA class II-restricted epitopes. All together, selection strategies, such as PopCover, might with success be used for the evaluation of antigen-specific CD4+ T cell responses and design of future vaccines.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Karolinska Institutet, Public Health Agency of Canada, Swedish Institute for Infectious Disease Control, Stockholm South General Hospital
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Publication information
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BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed yes
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Scopus rating (2016): CiteScore 3.11 SJR 1.201 SNIP 1.092
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.414 SNIP 1.131 CiteScore 3.32
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.545 SNIP 1.141 CiteScore 3.54
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.74 SNIP 1.147 CiteScore 3.94
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Characterizing the binding motifs of 11 common human HLA-DP and HLA-DQ molecules using NNAliGn

Compared with HLA-DR molecules, the specificities of HLA-DP and HLA-DQ molecules have only been studied to a limited extent. The description of the binding motifs has been mostly anecdotal and does not provide a quantitative measure of the importance of each position in the binding core and the relative weight of different amino acids at a given position. The recent publication of larger data sets of peptide-binding to DP and DQ molecules opens the possibility of using data-driven bioinformatics methods to accurately define the binding motifs of these molecules. Using the neural network-based method NNAliGn, we characterized the binding specificities of five HLA-DP and six HLA-DQ among the most frequent in the human population. The identified binding motifs showed an overall concurrence with earlier studies but revealed subtle differences. The DP molecules revealed a large overlap in the pattern of amino acid preferences at core positions, with conserved hydrophobic/aromatic anchors at P1 and P6, and an additional hydrophobic anchor at P9 in some variants. These results confirm the existence of a previously hypothesized supertype encompassing the most common DP alleles. Conversely, the binding motifs for DQ molecules appear more divergent, displaying unconventional anchor positions and in some cases rather unspecific amino acid preferences.
Cometin is a novel neurotrophic factor that promotes neurite outgrowth and neuroblast migration in vitro and supports survival of spiral ganglion neurons in vivo.

Neurotrophic factors are secreted proteins responsible for migration, growth and survival of neurons during development, and for maintenance and plasticity of adult neurons. Here we present a novel secreted protein named Cometin which together with Meteorin defines a new evolutionary conserved protein family. During early mouse development, Cometin is found exclusively in the floor plate and from E13.5 also in dorsal root ganglions and inner ear but apparently not in the adult nervous system. In vitro, Cometin promotes neurite outgrowth from dorsal root ganglion cells which can be blocked...
by inhibition of the Janus or MEK kinases. In this assay, additive effects of Cometin and Meteorin are observed indicating separate receptors. Furthermore, Cometin supports migration of neuroblasts from subventricular zone explants to the same extent as stromal cell derived factor 1a. Given the neurotrophic properties in vitro, combined with the restricted inner ear expression during development, we further investigated Cometin in relation to deafness. In neomycin deafened guinea pigs, two weeks intracochlear infusion of recombinant Cometin supports spiral ganglion neuron survival and function. In contrast to the control group receiving artificial perilymph, Cometin treated animals retain normal electrically-evoked brainstem response which is maintained several weeks after treatment cessation. Neuroprotection is also evident from stereological analysis of the spiral ganglion. Altogether, these studies show that Cometin is a potent new neurotrophic factor with therapeutic potential.
Common and Distant Structural Characteristics of Feruloyl Esterase Families from Aspergillus oryzae

Background: Feruloyl esterases (FAEs) are important biomass degrading accessory enzymes due to their capability of cleaving the ester links between hemicellulose and pectin to aromatic compounds of lignin, thus enhancing the accessibility of plant tissues to cellulolytic and hemicellulolytic enzymes. FAEs have gained increased attention in the area of biocatalytic transformations for the synthesis of value added compounds with medicinal and nutritional applications. Following the increasing attention on these enzymes, a novel descriptor based classification system has been proposed for FAEs resulting into 12 distinct families and pharmacophore models for three FAE sub-families have been developed. Methodology/Principal Findings: The feruloylome of Aspergillus oryzae contains 13 predicted FAEs belonging to six subfamilies based on our recently developed descriptor-based classification system. The three-dimensional structures of the 13 FAEs were modeled for structural analysis of the feruloylome. The three genes coding for three enzymes, viz., A.O.2, A.O.8 and A.O.10 from the feruloylome of A. oryzae, representing sub-families with unknown functional features, were heterologously expressed in Pichia pastoris, characterized for substrate specificity and structural characterization through CD spectroscopy. Common feature-based pharmacophore models were developed according to substrate specificity characteristics of the three enzymes. The active site residues were identified for the three expressed FAEs by determining the titration curves of amino acid residues as a function of the pH by applying molecular simulations. Conclusions/Significance: Our findings on the structure-function relationships and substrate specificity of the FAEs of A. oryzae will be instrumental for further understanding of the FAE families in the novel classification system. The developed pharmacophore models could be applied for virtual screening of compound databases for short listing the putative substrates prior to docking studies or for post-processing docking results to remove false positives. Our study exemplifies how computational predictions can complement to the information obtained through experimental methods.
Comparative genomics of bifidobacterium, lactobacillus and related probiotic genera.
Six bacterial genera containing species commonly used as probiotics for human consumption or starter cultures for food fermentation were compared and contrasted, based on publicly available complete genome sequences. The analysis included 19 Bifidobacterium genomes, 21 Lactobacillus genomes, 4 Lactococcus and 3 Leuconostoc genomes, as well as a selection of Enterococcus (11) and Streptococcus (23) genomes. The latter two genera included genomes from probiotic or commensal as well as pathogenic organisms to investigate if their non-pathogenic members shared more genes with the other probiotic genomes than their pathogenic members. The pan- and core genome of each genus was defined. Pairwise BLASTP genome comparison was performed within and between genera. It turned out that pathogenic Streptococcus and Enterococcus shared more gene families than did the non-pathogenic genomes. In silico multilocus sequence typing was carried out for all genomes per genus, and the variable gene content of genomes was compared within the genera. Informative BLAST Atlases were constructed to visualize genomic variation within genera. The clusters of orthologous groups (COG) classes of all genes in the pan- and core genome of each genus were compared. In addition, it was investigated whether pathogenic genomes contain different COG classes compared to the probiotic or fermentative organisms, again comparing their pan- and core genomes. The obtained results were compared with published data from the literature. This study illustrates how over 80 genomes can be broadly compared using simple bioinformatic tools, leading to both confirmation of known information as well as novel observations.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Molecular Microbiology and Genomics Consultants
Authors: Lukjancenko, O. (Intern), Ussery, D. (Intern), Wassenaar, T. M. (Ekstern)
Pages: 651-673
Condition-dependent transcriptome reveals high-level regulatory architecture in Bacillus subtilis.

Bacteria adapt to environmental stimuli by adjusting their transcriptomes in a complex manner, the full potential of which has yet to be established for any individual bacterial species. Here, we report the transcriptomes of Bacillus subtilis exposed to a wide range of environmental and nutritional conditions that the organism might encounter in nature. We comprehensively mapped transcription units (TUs) and grouped 2935 promoters into regulons controlled by various RNA polymerase sigma factors, accounting for ~66% of the observed variance in transcriptional activity. This global classification of promoters and detailed description of TUs revealed that a large proportion of the detected antisense RNAs arose from potentially spurious transcription initiation by alternative sigma factors and from imperfect control of transcription termination.
Congenital diaphragmatic hernia candidate genes derived from embryonic transcriptomes.

Congenital diaphragmatic hernia (CDH) is a common (1 in 3,000 live births) major congenital malformation that results in significant morbidity and mortality. The discovery of CDH loci using standard genetic approaches has been hindered by its
genetic heterogeneity. We hypothesized that gene expression profiling of developing embryonic diaphragms would help identify genes likely to be associated with diaphragm defects. We generated a time series of whole-transcriptome expression profiles from laser captured embryonic mouse diaphragms at embryonic day (E)11.5 and E12.5 when experimental perturbations lead to CDH phenotypes, and E16.5 when the diaphragm is fully formed. Gene sets defining biologically relevant pathways and temporal expression trends were identified by using a series of bioinformatic algorithms. These developmental sets were then compared with a manually curated list of genes previously shown to cause diaphragm defects in humans and in mouse models. Our integrative filtering strategy identified 27 candidates for CDH. We examined the diaphragms of knockout mice for one of the candidate genes, pre-B-cell leukemia transcription factor 1 (Pbx1), and identified a range of previously undetected diaphragmatic defects. Our study demonstrates the utility of genetic characterization of normal development as an integral part of a disease gene identification and prioritization strategy for CDH, an approach that can be extended to other diseases and developmental anomalies.

**General information**

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Massachusetts General Hospital, The Jackson Laboratory, University of Rochester
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Pages: 2978-2983
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Main Research Area: Technical/natural sciences

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- BFI (2017): BFI-level 2
- Web of Science (2017): Indexed yes
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- Scopus rating (2016): CiteScore 8.56 SJR 6.321 SNIP 2.629
- Web of Science (2016): Indexed yes
- BFI (2015): BFI-level 2
- Scopus rating (2015): SJR 6.767 SNIP 2.682 CiteScore 8.84
- Web of Science (2015): Indexed yes
- BFI (2014): BFI-level 2
- Scopus rating (2014): SJR 6.853 SNIP 2.725 CiteScore 8.86
- Web of Science (2014): Indexed yes
- BFI (2013): BFI-level 2
- Scopus rating (2013): SJR 6.989 SNIP 2.73 CiteScore 9.5
- ISI indexed (2013): ISI indexed yes
- Web of Science (2013): Indexed yes
- BFI (2012): BFI-level 2
- Scopus rating (2012): SJR 6.792 SNIP 2.682 CiteScore 9.49
- ISI indexed (2012): ISI indexed yes
- Web of Science (2012): Indexed yes
- BFI (2011): BFI-level 2
- Scopus rating (2011): SJR 6.771 SNIP 2.636 CiteScore 9.31
- ISI indexed (2011): ISI indexed yes
- Web of Science (2011): Indexed yes
- BFI (2010): BFI-level 2
- Scopus rating (2010): SJR 6.769 SNIP 2.529
- Web of Science (2010): Indexed yes
- BFI (2009): BFI-level 2
- Scopus rating (2009): SJR 6.913 SNIP 2.544
- Web of Science (2009): Indexed yes
Congenital diaphragmatic hernia interval on chromosome 8p23.1 characterized by genetics and protein interaction networks

Chromosome 8p23.1 is a common hotspot associated with major congenital malformations, including congenital diaphragmatic hernia (CDH) and cardiac defects. We present findings from high-resolution arrays in patients who carry a loss (n = 18) or a gain (n = 1) of sub-band 8p23.1. We confirm a region involved in both diaphragmatic and heart malformations. Results from a novel CNVConnect algorithm, prioritizing protein–protein interactions between products of genes in the 8p23.1 hotspot and products of previously known CDH causing genes, implicated GATA4, NEIL2, and SOX7 in diaphragmatic defects. Sequence analysis of these genes in 226 chromosomally normal CDH patients, as well as in a small number of deletion 8p23.1 patients, showed rare unreported variants in the coding region; these may be contributing to the diaphragmatic phenotype. We also demonstrated that two of these three genes were expressed in the E11.5–12.5 trimordial mouse diaphragm, the developmental stage at which CDH is thought to occur. This combination of bioinformatics and expression studies can be applied to other chromosomal hotspots, as well as private microdeletions or microduplications, to identify causative genes and their interaction networks. © 2012 Wiley Periodicals, Inc.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Massachusetts General Hospital, Kaiser Permanente, University of Mississippi, King Edward Memorial Hospital, University of Utah, University Hospital Louven, Mackay Memorial Hospital, Universität zu Lübeck, Mitsubishi Chemical Corporation, Mercy Children's Hospital, Universitätsklinikum Essen, The Children's Hospital of Philadelphia, Harvard Medical School
Pages: 3148-3158
Publication date: 2012
Main Research Area: Technical/natural sciences

Publication information
Journal: American Journal of Medical Genetics. Part A
Volume: 158A
Defining the Pseudomonas Genus: Where Do We Draw the Line with Azotobacter?

The genus Pseudomonas has gone through many taxonomic revisions over the past 100 years, going from a very large and diverse group of bacteria to a smaller, more refined and ordered list having specific properties. The relationship of the Pseudomonas genus to Azotobacter vinelandii is examined using three genomic sequence-based methods. First, using 16S rRNA trees, it is shown that A. vinelandii groups within the Pseudomonas close to Pseudomonas aeruginosa. Genomes from other related organisms (Acinetobacter, Psychrobacter, and Cellvibrio) are outside the Pseudomonas cluster. Second, pan genome family trees based on conserved gene families also show A. vinelandii to be more closely related to Pseudomonas than other related organisms. Third, exhaustive BLAST comparisons demonstrate that the fraction of shared genes between A. vinelandii and Pseudomonas genomes is similar to that of Pseudomonas species with each other. The results of these different methods point to a high similarity between A. vinelandii and the Pseudomonas genus, suggesting that Azotobacter might actually be a Pseudomonas.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology
Authors: Özen, A. I. (Intern), Ussery, D. (Intern)
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Publication information
Journal: Microbial Ecology in Health & Disease
Volume: 63
Issue number: 2
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Ratings:
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BFI (2017): BFI-level 1
BFI (2016): BFI-level 1
Describing the Peptide Binding Specificity of HLA-C

Human leukocyte antigen (HLA) presents peptides to T-cells for immune scrutiny. Whereas HLA-A and -B have been described in great detail, HLA-C has received much less attention. Here, to increase the coverage of HLA-C and the accuracy of the corresponding tools, we have generated HLA-C molecules; peptide-binding assays, data and predictors; and tetramers; representing the most prevalent HLA-C molecules. We have combined positional scanning combinatorial peptide library (PSCPL) with a homogenous high-throughput dissociation assay and generated specificity matrices for 11 different HLA-C molecules. We find preference for hydrophobic residues at the peptide C-terminus for all HLA-C molecules. Most molecules were found to have an additional strong anchor at P2 or P3, with auxiliary anchor observed at P1, P2, P3, and P7. The binding affinity is measured for peptides fitting the specificity matrix for 5 HLA-C molecules and for all, but one, molecule we find a high frequency of binders, >70%, among these peptides. To extend the examined peptide space, we use bioinformatic prediction tools to search for additional binders. Finally, we update our prediction tool, NetMHCpan, with the HLA-C affinity data and show that the predictive performance for HLA-C molecules now is increased to a level comparable with that of HLA-A and -B. These novel HLA-C molecules and predictors are successfully used to generate HLA-C tetramers and validate HLA-C-restricted T cell responses.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Copenhagen
Authors: Rasmussen, M. (Ekstern), Harndahl, M. N. (Forskerdatabase), Nielsen, M. (Intern), Buus, S. (Ekstern), Stryhn, A. (Ekstern)
Designing bovine T cell vaccines via reverse immunology

T cell responses contribute to immunity against many intracellular infections. There is, for example, strong evidence that major histocompatibility complex (MHC) class I-restricted cytotoxic T lymphocytes (CTLs) play an essential role in mediating immunity to East Coast fever (ECF), a fatal lymphoproliferative disease of cattle prevalent in sub-Saharan Africa and caused by Thelileria parva. To complement the more traditional approaches to CTL antigen identification and vaccine development that we have previously undertaken we propose a use of immunoinformatics to predict CTL peptide epitopes followed by experimental verification of T cell specificity to candidate epitopes using peptide–MHC (pMHC) tetramers. This system, adapted from human and rodent studies, is in the process of being developed for cattle. Briefly, we have used an artificial neural network called NetMHCpan, which has been trained mainly on existing human, mouse, and non-human primate MHC–peptide binding data in an attempt to predict the peptide-binding specificity of bovine MHC class I molecules. Our data indicate that this algorithm needs to be further optimized by incorporation of bovine MHC–peptide binding data. When retrained, NetMHCpan may be used to predict parasite peptide epitopes by scanning the predicted T. parva proteome and known parasite CTL antigens. A range of pMHC tetramers, made “on-demand”, will then be used to assay cattle that are immune to ECF or in vaccine trials to determine if CTLs of the predicted epitope specificity are present or not. Thus, pMHC tetramers can be used in one step to identify candidate CTL antigens and to map CTL epitopes. Our current research focuses on 9 different BoLA class I molecules. By expanding this repertoire to include the most common bovine MHCs, these methods could be used as generic assays to predict and measure bovine T cell immune responses to any pathogen.
Differential Protein Pathways in 1,25-Dihydroxyvitamin D-3 and Dexamethasone Modulated Tolerogenic Human Dendritic Cells

Tolerogenic dendritic cells (DC) that are maturation-resistant and locked in a semimature state are promising tools in clinical applications for tolerance induction. Different immunomodulatory agents have been shown to induce a tolerogenic DC phenotype, such as the biologically active form of vitamin D (1,25(OH)(2)D-3), glucocorticoids, and a synergistic combination of both. In this study, we aimed to characterize the protein profile, function and phenotype of DCs obtained in vitro in the presence of 1,25(OH)(2)D-3, dexamethasone (DEX), and a combination of both compounds (combi). Human CD14(+) monocytes were differentiated toward mature DCs, in the presence or absence of 1,25(OH)(2)D-3 and/or DEX.

Cells were prefractionated into cytoplasmic and microsomal fractions and protein samples were separated in two different pH ranges (pH 3-7NL and 6-9), analyzed by 2D-DIGE and differentially expressed spots (p <0.05) were identified after MALDI-TOF/TOF analysis. In parallel, morphological and phenotypical analyses were performed, revealing that 1,25(OH)(2)D-3- and combi-mDCs are closer related to each other than DEX-mDCs. This was translated in their protein profile, indicating that 1,25(OH)(2)D-3 is more potent than DEX in inducing a tolerogenic profile on human DCs. Moreover, we demonstrate that combining 1,25(OH)(2)D-3 with DEX induces a unique protein expression pattern with major imprinting of the 1,25(OH)(2)D-3 effect. Finally, protein interaction networks and pathway analysis suggest that 1,25(OH)(2)D-3, rather than DEX treatment, has a severe impact on metabolic pathways involving lipids, glucose, and oxidative phosphorylation, which may affect the production of or the response to ROS generation. These findings provide new insights on the molecular basis of DC tolerogenicity induced by 1,25(OH)(2)D-3 and/or DEX, which may lead to the discovery of new pathways involved in DC immunomodulation.

General information
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Catholic University of Leuven, Leiden University
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Publication information
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BFI (2018): BFI-level 2
BFI (2017): BFI-level 2
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 4.34 SJR 1.705 SNIP 1.002
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 1.934 SNIP 1.092 CiteScore 4.45
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 1.945 SNIP 1.185 CiteScore 4.64
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 2.002 SNIP 1.256 CiteScore 5.16
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 2.027 SNIP 1.328 CiteScore 5.12
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 2.119 SNIP 1.267 CiteScore 5.12
ISI indexed (2011): ISI indexed yes
Disentangling evolutionary signals: conservation, specificity determining positions and coevolution. Implication for catalytic residue prediction

Background: A large panel of methods exists that aim to identify residues with critical impact on protein function based on evolutionary signals, sequence and structure information. However, it is not clear to what extent these different methods overlap, and if any of the methods have higher predictive potential compared to others when it comes to, in particular, the identification of catalytic residues (CR) in proteins. Using a large set of enzymatic protein families and measures based on different evolutionary signals, we sought to break up the different components of the information content within a multiple sequence alignment to investigate their predictive potential and degree of overlap. Results: Our results demonstrate that the different methods included in the benchmark in general can be divided into three groups with a limited mutual overlap. One group containing real-value Evolutionary Trace (rvET) methods and conservation, another containing mutual information (MI) methods, and the last containing methods designed explicitly for the identification of specificity determining positions (SDPs): integer-value Evolutionary Trace (ivET), SDPfox, and XDET. In terms of prediction of CR, we find using a proximity score integrating structural information (as the sum of the scores of residues located within a given distance of the residue in question) that only the methods from the first two groups displayed a reliable performance. Next, we investigated to what degree proximity scores for conservation, rvET and cumulative MI (cMI) provide complementary information capable of improving the performance for CR identification. We found that integrating conservation with proximity scores for rvET and cMI achieved the highest performance. The proximity conservation score contained no complementary information when integrated with proximity rvET. Moreover, the signal from rvET provided only a limited gain in predictive performance when integrated with mutual information and conservation proximity scores. Combined, these observations demonstrate that the rvET and cMI scores add complementary information to the prediction system. Conclusions: This work contributes to the understanding of the different signals of evolution and also shows that it is possible to improve the detection of catalytic residues by integrating structural and higher order sequence evolutionary information with sequence conservation.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Fundación Instituto Leloir, Baylor College of Medicine
Authors: Teppa, E. (Ekstern), Wilkins, A. D. (Ekstern), Nielsen, M. (Intern), Marino Buslje, C. (Ekstern)
Pages: -
Divergent pro-inflammatory profile of human dendritic cells in response to commensal and pathogenic bacteria associated with the airway microbiota.

Recent studies using culture-independent methods have characterized the human airway microbiota and report microbial communities distinct from other body sites. Changes in these airway bacterial communities appear to be associated with inflammatory lung disease, yet the pro-inflammatory properties of individual bacterial species are unknown. In this study, we compared the immune stimulatory capacity on human monocyte-derived dendritic cells (DCs) of selected airway commensal and pathogenic bacteria predominantly associated with lungs of asthma or COPD patients (pathogenic *Haemophilus* spp. and *Moraxella* spp.), healthy lungs (commensal *Prevotella* spp.) or both (commensal *Veillonella* spp. and *Actinomyces* spp.). All bacteria were found to induce activation of DCs as demonstrated by similar induction of CD83, CD40 and CD86 surface expression. However, asthma and COPD-associated pathogenic bacteria provoked a 3-5 fold higher production of IL-23, IL-12p70 and IL-10 cytokines compared to the commensal bacteria. Based on the differential cytokine production profiles, the studied airway bacteria could be segregated into three groups (*Haemophilus* spp. and *Moraxella* spp. vs. *Prevotella* spp. and *Veillonella* spp. vs. *Actinomyces* spp.) reflecting their pro-inflammatory effects on DCs. Co-culture experiments found that *Prevotella* spp. were able to reduce *Haemophillus influenzae*-induced IL-12p70 in DCs, whereas no effect was observed on IL-23 and IL-10 production. This study demonstrates intrinsic differences in DC stimulating properties of bacteria associated with the airway microbiota.
Drug Repurposing: Far Beyond New Targets for Old Drugs

Repurposing drugs requires finding novel therapeutic indications compared to the ones for which they were already approved. This is an increasingly utilized strategy for finding novel medicines, one that capitalizes on previous investments while derisking clinical activities. This approach is of interest primarily because we continue to face significant gaps in the drug–target interactions matrix and to accumulate safety and efficacy data during clinical studies. Collecting and making publicly available as much data as possible on the target profile of drugs offer opportunities for drug repurposing, but may limit the commercial applications by patent applications. Certain clinical applications may be more feasible for repurposing than others because of marked differences in side effect tolerance. Other factors that ought to be considered when assessing drug repurposing opportunities include relevance to the disease in question and the intellectual property landscape. These activities go far beyond the identification of new targets for old drugs.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Pompeu Fabra University
Authors: Oprea, T. (Intern), Mestres, J. (Ekstern)
Pages: 759-763
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BFI (2015): BFI-level 2
Scopus rating (2015): SJR 1.267 SNIP 1.336 CiteScore 4.13
Effects of Butter and Phytanic acid intake on metabolic parameters and T-cell polarization

The still growing obesity epidemic is a major risk for our society, as it is associated with the development of the so called metabolic syndrome, which is a clinical diagnosis correlated to development of metabolic disorders. Lack of physical activity, excess energy intake, and nutritional factors e.g. fatty acid composition of the diet, are important factors with regard to development of metabolic syndrome. There is a controversy between the fact that several studies has shown that intake of saturated fatty acids are strongly correlated to the development of metabolic related diseases, such as cardiovascular diseases and type 2 diabetes, and against the fact that other studies has shown that intake of dairy fat, which has high saturated fatty acid content, correlates negatively with risk factors. Hence, it has even been suggested that dairy fat might have beneficial impacts in relation to metabolic disorders. Dairy fat is the most complex type of fat occurring in the nature, with more than 400 identified fatty acids. Several of these fatty acids that occur in low amounts have been suggested to have beneficial properties with regard to metabolic disorders. The concentrations of certain of these minor fatty acids are raised in dairy fat along with the amount of green plant material intake of the cattle. Phytanic acid is one of these minor fatty acids, due to agonist activities for nuclear receptors with central roles in among others the lipid and glucose metabolism.

To determine the effects of both dairy fat in general and phytanic acid on metabolic parameters, we performed several studies. First, we investigated effects on hepatic lipid metabolism, glucose homeostasis, and circulating metabolic markers, of high fat diets based on butter from high- or low-yield production, a diet based on high oleic acid sunflower oil, and a diet based on grape-seed oil with high amount of linoleic acid, in diet induced obese mice. Second, we investigated phytanic acid effects on similar parameters in obese mice, both as dose response in butter based diets, and in grape-seed oil based diets with and without addition of phytanic acid. Third, we investigated butter and phytanic acid effects on human T-cell polarization, both by in vitro incubation with phytanic acid, and by a 12 weeks intervention with intake of butter. Finally, we performed two human interventions, first one with intake of butter and cheese, and the second with intake of butter. In these studies we investigated whether it is possible to alter the human plasma concentration of phytanic acid due to dairy fat intake, and if butter from different feeding regimes, and production forms has different effects on metabolic parameters upon intake.
Fat type intervention in mice
Obesity was induced in mice, by addition of sucrose to the drinking water, and giving high fat diets, based on butter from either grazing or conventional fed cattle, high oleic acid (monounsaturated fatty acid) sunflower oil, or finally from grape-seed oil with high content of the n-6 poly unsaturated fatty acid linoleic acid, along with having a lean reference group. Oral glucose tolerance test was performed after 10 weeks intervention, and animals sacrificed two days later. Parameters relevant to glucose metabolism, and hepatic lipid metabolism e.g. lipid deposition, were measured, just as RT-qPCR were used to measure expression of genes relevant for lipid metabolism in the liver. Plasma lipids, adipokines, and a marker of inflammation were also measured. We found that the hyper caloric diet based on oleic acid had the most detrimental effects on metabolic parameters, of the tested fats, as it led to increased hepatic lipid deposition, and reduced glucose tolerance. The butter based diets had more unfavorable effects on concentration of blood lipids, observed as raised triacylglycerol and total cholesterol. Compared to the literature the results with regard to oleic acid are controversial, as the common advice is to substitute SFA by MUFA in the diet.

Phytanic acid effects in mice
Production of phytanic acid by organic synthesis, allowed us to investigate isolated effects of phytanic acid intake. Obesity were induced in similar manner as in the fat type intervention described above, with different amounts of phytanic acid ethyl-esters added to either butter or grape-seed oil based diets, to investigate the effects from phytanic acid intake, on parameters similar to those in the fat type intervention. We saw that PA intake have aggravating effect on glucose homeostasis in dosages of 1.0 % of total fat. We did se limited up regulation of PPARalpha and ACOX1 due to 1.0 % phytanic acid in butter. As we are the first to perform interventions with physiological realistic amounts of phytanic acid, which have been proposed to have protective effects due to its agonist activities for central nuclear receptors, our results most definitely, add to the knowledge of the field.

Butter and phytanic acid effects in humans, and on T-cell polarization
Two human dairy fat interventions was conducted, with healthy subjects divided into groups and given dairy fat (as butter and cheese) from cattle under different feeding regimes, resulting in among others difference in phytanic acid content. From the first intervention, we found that it is possible to alter the human plasma phytanic acid concentration due to four weeks dairy fat intervention. From the second intervention we found that butter from grazing cattle, which among others have increased phytanic acid content, increase plasma LDL cholesterol and insulin, compared to conventional butter. From a subpopulation of the second intervention, T-cells were isolated from blood before and after the intervention, to analyze the effect on T-cell polarization. Furthermore we performed an in vitro incubation of T-cells, from eight donors, with phytanic- and palmitic acid, to investigate if phytanic acid affects T-cell polarization as hypothesized. Phytanic acid was not found to change the T-cell polarization, neither in the incubation study nor due to the difference in concentrations in the butter intervention. We saw up regulation in mRNA expression of both IL-4 and IFN-gamma due to the butter intervention, when the groups were regarded as one. This was more pronounced for IL-4 than IFN-gamma, and we observed increase in the ratio IL-4: IFN-gamma due to the intervention. This is pointing towards a general effect towards Th2 polarization of human T-cells due to increased intake of butter. These results add to the understanding of potential phytanic acid and butter effects, on the immune system as similar studies have not been performed on T-cells before.

General information
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis
Authors: Drachmann, T. (Intern), Hellgren, L. (Intern), Pedersen, S. B. (Intern)
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Enantioselective determination of methylphenidate and ritalinic acid in whole blood from forensic cases using automated solid-phase extraction and liquid chromatography-tandem mass spectrometry.
A chiral liquid chromatography tandem mass spectrometry (LC–MS-MS) method was developed and validated for quantifying methylphenidate and its major metabolite ritalinic acid in blood from forensic cases. Blood samples were prepared in a fully automated system by protein precipitation followed by solid-phase extraction. The LC–MS-MS method was linear in the range of 0.5 to 500 ng/g for the enantiomers of both analytes. For concentrations above the limit of quantification, coefficients of variation were 15% or less, and the accuracy was 89 to 94%. For 12 postmortem samples in which methylphenidate was not determined to be related to the cause of death, the femoral blood concentration of d- methylphenidate ranged from 5 to 58 ng/g, and from undetected to 48 ng/g for l-methylphenidate (median d/l-ratio 5.9). Ritalinic acid was present at concentrations 10–20 times higher with roughly equal amounts of the d- and l-forms. In blood from 10 living subjects that were not suspected of being intoxicated by methylphenidate, the concentration ranges and patterns were similar to those of the
postmortem cases. Thus, methylphenidate does not appear to undergo significant postmortem redistribution.

**General information**

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, The INDICES Consortium, Copenhagen University Hospital, University of Copenhagen
Authors: Thomsen, R. (Ekstern), B. Rasmussen, H. (Ekstern), Linnet, K. (Ekstern), Brunak, S. (Intern), Taboureau, O. (Intern)
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Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): SJR 1.188 SNIP 1.067 CiteScore 2.52
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.007 SNIP 0.997 CiteScore 2.18
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.298 SNIP 1.048 CiteScore 2.66
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.166 SNIP 1.117 CiteScore 2.48
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 0.884 SNIP 1.047 CiteScore 1.9
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.063 SNIP 1.214 CiteScore 2.13
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 0.756 SNIP 0.868
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.055 SNIP 1.03
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 0.779 SNIP 0.831
Scopus rating (2007): SJR 1.235 SNIP 0.927
Scopus rating (2006): SJR 0.826 SNIP 1.073
Scopus rating (2005): SJR 1.382 SNIP 1.263
Scopus rating (2004): SJR 1.242 SNIP 1.431
Scopus rating (2003): SJR 1.086 SNIP 1.133
Scopus rating (2002): SJR 1.023 SNIP 1.035
Scopus rating (2001): SJR 1.114 SNIP 1.391
Scopus rating (2000): SJR 1.111 SNIP 1.133
Scopus rating (1999): SJR 2.043 SNIP 1.321
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Established and Emerging Trends in Computational Drug Discovery in the Structural Genomics Era

Bioinformatics and chemoinformatics approaches contribute to hit discovery, hit-to-lead optimization, safety profiling, and target identification and enhance our overall understanding of the health and disease states. A vast repertoire of computational methods has been reported and increasingly combined in order to address more and more challenging targets or complex molecular mechanisms in the context of large-scale integration of structure and bioactivity data produced by private and public drug research. This review explores some key computational methods directly linked to drug discovery and chemical biology with a special emphasis on compound collection preparation, virtual screening, protein docking, and systems pharmacology. A list of generally freely available software packages and online resources is provided, and examples of successful applications are briefly commented upon.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, University of Melbourne, Barcelona Supercomputing Center, University Paris Diderot - Paris 7
Authors: Taboureau, O. (Intern), Baell, J. B. (Ekstern), Fernández-Recio, J. (Ekstern), Villoutreix, B. O. (Ekstern)
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BFI (2017): BFI-level 2
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 5.43 SJR 3.201 SNIP 1.301
Scopus rating (2015): SJR 3.192 SNIP 1.416
Scopus rating (2014): SJR 3 SNIP 1.385
Web of Science (2014): Indexed yes
Scopus rating (2013): SJR 2.988 SNIP 1.359
ISI indexed (2013): ISI indexed yes
Scopus rating (2012): SJR 2.787 SNIP 1.302
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
Scopus rating (2011): SJR 2.861 SNIP 1.394
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
Scopus rating (2010): SJR 2.786 SNIP 1.319
Web of Science (2010): Indexed yes
Scopus rating (2009): SJR 2.885 SNIP 1.464
Scopus rating (2008): SJR 2.483 SNIP 1.273
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 2.761 SNIP 1.355
Scopus rating (2006): SJR 2.57 SNIP 1.364
Scopus rating (2005): SJR 2.644 SNIP 1.421
Scopus rating (2004): SJR 2.758 SNIP 1.424
Scopus rating (2003): SJR 3.046 SNIP 1.558
Scopus rating (2002): SJR 3.015 SNIP 1.59
Scopus rating (2001): SJR 3.081 SNIP 1.475
Scopus rating (2000): SJR 4.008 SNIP 1.553
Scopus rating (1999): SJR 4.622 SNIP 1.668
Establishment of tolerance to commensal bacteria requires a complex microbiota and is accompanied by decreased intestinal chemokine expression

Intricate regulation of tolerance to the intestinal commensal microbiota acquired at birth is critical. We hypothesized that epithelial cell tolerance toward early gram-positive and gram-negative colonizing bacteria is established immediately after birth, as has previously been shown for endotoxin. Gene expression in the intestine of mouse pups born to dams that were either colonized with a conventional microbiota or monocolonized (Lactobacillus acidophilus or Eschericia coli) or germ free was examined on day 1 and day 6 after birth. Intestinal epithelial cells from all groups of pups were stimulated ex vivo with L. acidophilus and E. coli to assess tolerance establishment. Intestine from pups exposed to a conventional microbiota displayed lower expression of Ccl2, Ccl3, Cxcl1, Cxcl2, and Tslp than germ-free mice, whereas genes encoding proteins in Toll-like receptor signaling pathways and cytokines were upregulated. When comparing pups on day 1 and day 6 after birth, a specific change in gene expression pattern was evident in all groups of mice. Tolerance to ex vivo stimulation with E. coli was only established in conventional animals. Colonization of the intestine was reflected in the spleen displaying downregulation of Cxcl2 compared with germ-free animals on day 1 after birth. Colonization reduced the expression of genes involved in antigen presentation in the intestine-draining mesenteric lymph nodes, but not in the popliteal lymph nodes, as evidenced by gene expression on day 23 after birth. We propose that microbial detection systems in the intestine are upregulated by colonization with a diverse microbiota, whereas expression of proinflammatory chemokines is reduced to avoid excess recruitment of immune cells to the maturing intestine.

General information

State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Division of Toxicology and Risk Assessment, National Food Institute, Division of Microbiology and Risk Assessment, University of Copenhagen
Authors: Fink, L. N. (Intern), Metzdorff, S. B. (Ekstern), Zeuthen, L. (Intern), Nellemann, C. L. (Intern), Kristensen, M. B. (Intern), Licht, T. R. (Intern), Frøkiær, H. (Ekstern)
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Publication information

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BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.62 SJR 1.81 SNIP 1.033
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.01 SNIP 1.011 CiteScore 3.59
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.17 SNIP 1.182 CiteScore 4.06
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 2.182 SNIP 1.226 CiteScore 4.14
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.674 SNIP 1.157 CiteScore 3.85
ISI indexed (2012): ISI indexed yes
Estimating variation within the genes and inferring the phylogeny of 186 sequenced diverse Escherichia coli genomes

Background

Escherichia coli exists in commensal and pathogenic forms. By measuring the variation of individual genes across more than a hundred sequenced genomes, gene variation can be studied in detail, including the number of mutations found for any given gene. This knowledge will be useful for creating better phylogenies, for determination of molecular clocks and for improved typing techniques.

Results

We find 3,051 gene clusters/families present in at least 95% of the genomes and 1,702 gene clusters present in 100% of the genomes. The former ‘soft core’ of about 3,000 gene families is perhaps more biologically relevant, especially considering that many of these genome sequences are draft quality. The E. coli pan-genome for this set of isolates contains 16,373 gene clusters.

A core-gene tree, based on alignment and a pan-genome tree based on gene presence/absence, maps the relatedness of the 186 sequenced E. coli genomes. The core-gene tree displays high confidence and divides the E. coli strains into the observed MLST type clades and also separates defined phylotypes.

Conclusion

The results of comparing a large and diverse E. coli dataset support the theory that reliable and good resolution phylogenies can be inferred from the core-genome. The results further suggest that the resolution at the isolate level may, subsequently be improved by targeting more variable genes. The use of whole genome sequencing will make it possible to eliminate, or at least reduce, the need for several typing steps used in traditional epidemiology.

General information

State: Published
Organisations: Center for Systems Microbiology, National Food Institute, Division of Epidemiology and Microbial Genomics, Division of Microbiology and Risk Assessment, Department of Systems Biology, Center for Biological Sequence Analysis
Authors: Kaas, R. S. (Intern), Rundsten, C. F. (Intern), Ussery, D. (Intern), Aarestrup, F. M. (Intern)
Number of pages: 29
Evolution and diversification of Pseudomonas aeruginosa in the paranasal sinuses of cystic fibrosis children have implications for chronic lung infection

The opportunistic pathogen Pseudomonas aeruginosa is a frequent colonizer of the airways of patients suffering from cystic fibrosis (CF). Depending on early treatment regimens, the colonization will, with high probability, develop into chronic infections sooner or later, and it is important to establish under which conditions the switch to chronic infection takes place. In association with a recently established sinus surgery treatment program for CF patients at the Copenhagen CF Center, colonization of the paranasal sinuses with P. aeruginosa has been investigated, paralleled by sampling of sputum from the same patients. On the basis of genotyping and phenotypic characterization including transcription profiling, the diversity of the P. aeruginosa populations in the sinuses and the lower airways was investigated and compared. The observations made from several children show that the paranasal sinuses constitute an important niche for the colonizing bacteria in many patients. The paranasal sinuses often harbor distinct bacterial subpopulations, and in the early colonization phases there seems to be a migration from the sinuses to the lower airways, suggesting that independent adaptation and evolution take place in the sinuses. Importantly, before the onset of chronic lung infection, lineages with mutations conferring a large fitness benefit in CF airways such as mucA and lasR as well as small colony variants and antibiotic-resistant clones are part of the sinus populations. Thus, the paranasal sinuses potentially constitute a protected niche of adapted clones of P. aeruginosa, which can intermittently seed the lungs and pave the way for subsequent chronic lung infections.
Fish intake, erythrocyte n-3 fatty acid status and metabolic health in Danish adolescent girls and boys

Marine n-3 long-chain PUFA (n-3 LCPUFA) may have a beneficial effect on several aspects of the metabolic syndrome (dyslipidaemia, insulin resistance, hypertension and abdominal obesity). The metabolic syndrome is increasing in prevalence during adolescence, but only few studies have investigated the effects of n-3 LCPUFA in adolescence. The present study examines associations between fish intake (assessed by a 7 d pre-coded food diary), erythrocyte (RBC) DHA status (analysed by GC) and metabolic syndrome measures (anthropometry, blood pressure and plasma lipids, insulin and glucose) in 109 17-year-old children from the Copenhagen Birth Cohort Study. Of the children, 8% were overweight or obese and few showed signs of the metabolic syndrome, but all the metabolic syndrome variables were correlated. Median fish intake was 10·7 (interquartile range 3·6–21·2) g/d. Boys tended to have a higher fish intake (P¼0·052), but girls had significantly higher RBC levels of DHA (P¼0·001). Sex and fish intake explained 37% of the variance in RBC-DHA (P¼0·001). After adjusting for confounders, high DHA status was found to be significantly correlated with higher systolic blood pressure (P¼0·014) and increased fasting insulin (P¼0·018), but no adverse association was observed with the mean metabolic syndrome z-score. Overall, the present study showed the expected association between fish intake and RBC-DHA, which in contrast to our expectations tended to be associated with a poorer metabolic profile. Whether these results reflect the physiological function of n-3 LCPUFA, lifestyle factors associated with fish intake in Denmark, or mere chance remains to be investigated.

General information

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Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, University of Copenhagen
Authors: Lauritzen, L. (Ekstern), Harsløf, L. B. S. (Ekstern), Hellgren, L. (Intern), Pedersen, M. H. (Intern), Mølgaard, C. (Ekstern), Michaelsen, K. F. (Ekstern)
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Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Fitting the complexity of GPCRs modulation into simple hypotheses of ligand design

G-protein coupled receptors (GPCRs) are a large family of membrane-bound receptors that mediate a wide range of physiologic responses to hormones, neurotransmitters and dietary lipids, which represent an important class of drug targets. Significant chemical space regions have been explored both in the academia and by pharmaceutical companies, in the quest for new GPCR modulators as potential therapeutic agents. This accumulated body of evidence provides new opportunities to evaluate potential features of GPCR agonists and antagonists, and how to distinguish them. In this study, the chemical space covered within the WOMBAT database by GPCRs modulators was investigated with the aim of identifying specific molecular determinants that distinguish GPCR agonists from antagonists. While instrumental to get insights into the design strategies of GPCRs modulators, the results of this study provide novel clues on the molecular mechanisms that underlie the complexity of GPCR modulation.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, University of Perugia
Authors: Custodi, C. (Ekstern), Nuti, R. (Ekstern), Oprea, T. (Intern), Macchiarulo, A. (Ekstern)
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Main Research Area: Technical/natural sciences

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Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): SJR 0.517 SNIP 0.735 CiteScore 1.77
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.474 SNIP 0.673 CiteScore 1.87
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.599 SNIP 0.702 CiteScore 1.9
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 0.574 SNIP 0.783 CiteScore 2.23
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 0.746 SNIP 0.869 CiteScore 2.28
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 0.637 SNIP 0.843 CiteScore 2.21
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 0.681 SNIP 0.891
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 0.642 SNIP 0.889
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 0.815 SNIP 0.829
Scopus rating (2007): SJR 0.804 SNIP 0.762
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Flip-Flop of Steroids in Phospholipid Bilayers: Effects of the Chemical Structure on Transbilayer Diffusion

The transverse motion of molecules from one leaflet to the other of a lipid bilayer, or flip-flop, represents a putative mechanism for their transmembrane transport and may contribute to the asymmetric distribution of components in biomembranes. However, a clear understanding of this process is still missing. The scarce knowledge derives from the difficulty of experimental determination. Because of its slow rate on the molecular time scale, flip-flop is challenging also for computational techniques. Here, we report a study of the passive transbilayer diffusion of steroids, based on a kinetic model derived from the analysis of their free energy surface, as a function of their position and orientation in the bilayer. An implicit membrane description is used, where the anisotropy and the nonuniformity of the bilayer environment are taken into account in terms of the gradients of density, dielectric permittivity, acyl chain order parameters, and lateral pressure. The flip-flop rates are determined by solving the Master Equation that governs the time evolution of the system, with transition rates between free energy minima evaluated according to the Kramers theory. Considering various steroids (cholesterol, lanosterol, ketosterone, 5-cholestene, 25-hydroxycholesterol, and testosterone), we can discuss how differences in molecular shape and polarity affect the pathway and the rate of flip-flop in a liquid crystalline 1,2-dipalmitoyl-sn-glycero-3-phosphatidylcholine (DPPC) bilayer, at low steroid concentration. We predict time scales ranging from microseconds to milliseconds, strongly affected by the presence of polar substituents and by their position in the molecular skeleton.
The relative ease of sequencing bacterial genomes has resulted in thousands of sequenced bacterial genomes available in the public databases. This same technology now allows for using the entire genome sequence as an identifier for an organism. There are many methods available which attempt to use genome sequences to classify bacteria, and the method of choice, as always, depends on the question asked and the particular need. For example, 16S rRNA can define a bacterial species, and relate species, genera, and higher orders into groups consistent with their known biological properties. However, distinguishing between strains of the same species requires additional information. The advantage of having the whole-genome sequence is that roughly a 1,000 times as much information is available, and this information can be used for rapid classification of strains, based on DNA sequence. This chapter reviews many commonly used methods and also describes potential pitfalls if used inappropriately, as well as which questions are best addressed by particular methods. After a brief introduction to the classical methods of taxonomy, a description of the bacterial genomes currently available is given, and then whole-genome-based methods are explored using three different data sets.
From genomic variation to personalized medicine

Genomic variation is the basis of interindividual differences in observable traits and disease susceptibility. Genetic studies are the driving force of personalized medicine, as many of the differences in treatment efficacy can be attributed to our genomic background. The rapid development of next-generation sequencing technologies accelerates the discovery of the complete landscape of human variation. The main limitation is not anymore the available genotyping technology or cost, but rather the lack of understanding of the functionality of individual variations. Single polymorphisms rarely explain a considerable amount of the phenotype variability, hence the major difficulty of interpretation lies in the complexity of molecular interactions. This PhD thesis describes the state-of-art of the functional human variation research (Chapter 1) and introduces childhood acute lymphoblastic leukaemia (ALL) as a model disease for studying pharmacogenomic effects (Chapter 2 and 3). Chapter 4 describes the current interpretations of variations' effect and deleteriousness, accompanied by investigations of amino acid mutability compared to their deleteriousness presented in Paper I. Chapter 5 describes a pipeline used for calling variants from next-generation sequencing data and describes the common challenges encountered during analysis. Chapter 6 provides the motivation for a hypothesis-driven SNP selection and describes the publicly available resources used for this task. Following a review of the available large-scale genotyping techniques, Paper II introduces a novel cost-effective method for genotyping of a large custom SNP panel by means of multiplexed targeted sequencing and includes recommendations for efficient capture bait design. In Chapter 7 various methods of integrative analyses of genomic variations are presented, including testing of overrepresentation of rare variants, effects of multiple SNPs acting in the same biological pathway, contribution of coding variation to individual's disease risk, as well as identifying groups of patients differing in disease mechanisms defined by aberrations in protein-protein complexes. Chapters 8, 9 and 10 contain three papers applying the methods presented in Chapters 5 - 7 to investigate the heterogeneity of treatment response (Paper III), risk of infections (Paper IV) and disease aetiology (Paper V) in childhood ALL patients. Chapter 11 summarizes the thesis and includes some final remarks on the perspectives of genomic variation research and personalized medicine. In summary, this thesis demonstrates the feasibility of integrative analyses of genomic variations and introduces large-scale hypothesis-driven SNP exploration studies as an emerging alternative to data-driven genome-wide association studies. Finally, the findings of the presented studies set new directions for future pharmacogenetic investigations and provide a framework for future implementation of personalized medicine.

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From Viral genome to specific peptide epitopes - Methods for identifying porcine T cell epitopes based on in silico predictions, in vitro identification and ex vivo verification

The affinity for and stability of peptides bound by major histocompatibility complex (MHC) class I molecules are instrumental factors in presentation of viral epitopes to cytotoxic T lymphocytes (CTLs). In swine, such peptide presentations by swine leukocyte antigens (SLA) are crucial for swine immunity during viral infections and disease. Here we combine the ability of complete nonamer peptide based binding matrices for three different SLA proteins to predict good candidates for peptide-SLA (pSLA) binding with that of an online available algorithm, NetMHCpan. Further, we analyze the correlation between high affinity and high stability peptides bound by the highly expressed SLA molecules, SLA-1*0401, SLA-2*0401, and SLA-3*0401, using a luminescence oxygen channeling (LOCI) and a scintillation proximity assay, respectively. With this procedure, high affinity and highly stable SLA peptide epitopes can be identified within a given viral genome, along with the elimination of hundreds, or even thousands, of peptide sequences, which are not likely to be bound. Applying these methods can save enormous amounts of time and costs of epitope discovery studies and MHC binding analysis not only in swine but in almost any species of interest. Finally, peptide candidates of interest were verified as actual T cell epitopes using peptide-SLA complexes assembled into fluorescent tetramers to stain influenza-specific CTLs derived from vaccinated animals. From 20 such animals 16 had the correct SLA allele match and 7 of these qualified as potential candidates for tetramer staining. From the 7 animals 3 responded with a positive tetramer staining of 1% or higher.

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Functional and phenotypic profiling of innate immunity during Salmonella infection
Salmonellae are food borne pathogens, typically acquired by the oral ingestion of contaminated food or water, causing disease in both healthy and immunocompromised individuals. To gain insight into early immune regulation events caused by Salmonella as well as inflammatory signatures induced by Salmonella and other bacteria in human monocyte-derived dendritic cells (DC), we examined these properties using in vivo and in vitro experimental settings.

The outcome of infection with Salmonella depends on the host as well as the infecting serovar. Understanding the relative risks associated with and within different serovars is of major importance for public health. Using an established mouse model, we compared the pathogenicity of two S. Typhimurium strains (SL1344 and DT120) and found that the passage through and the ability to proliferate within the host gastrointestinal system determined the pathogenicity of these strains. Salmonella is a mucosal pathogen, gaining access to host systemic circulation by crossing the gut epithelial barrier and residing intracellularly in DC and Mφ. Until recently focus has been centred on the involvement of Mφ and the conventional antigen-presenting DC (mDC) in bacterial infections, whereas the other major dendritic cell subset, plasmacytoid DC (pDC), plays an important part in antiviral responses, and is less well characterised in regard to antibacterial immunity. Using multi-parametric flow cytometry, we were able to show for the first time that pDC accumulated in Peyer’s patches 24 hours after murine oral Salmonella challenge and while Mφ and mDC exhibited dose-related cellular atrophy, pDC were less susceptible to bacteria-induced cell death, suggesting a role for pDC in early stage Salmonella containment. Furthermore, we identified a number of both DC and Mφ subsets, two of which following infection, accumulated in Peyer’s patches and lamina propria, respectively.

Generally, we tend to set apart pathogenic bacteria from opportunistic pathogens and commensal bacteria based on their abilities to induce disease in different hosts, however, the nature of the inflammatory response they induce in DC that set them apart from commensal bacteria remains largely unclear. In the present study, we developed a system by which we were able to compare the bacteria-induced imprint of important regulatory proteins in DC to bacterial-encoded ligands. We observed that DC responded to six different bacteria in a phyla-specific manner giving rise to similar inflammatory signatures within the groups of proteobacteria, firmicutes and actinobacteria, hence being independent on pathogenic versus non-pathogenic properties, and also on the bacteria-to-cell ratio for most bacteria.

The results presented in this thesis add to the current knowledge about innate immunity to Salmonella, suggest new host immune cell subsets important for bacterial containment and provide a basic understanding of bacteria-induced DC inflammatory programs. The two latter could prove important in regard to treatment regimes, as targeted modulation of DC
profiles for instance by probiotics, could lead to improved therapy for a number of gut related diseases.

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**Gene expression dynamics in the oxidative stress response of fission yeast**
Changes in the environment continuously challenge living organisms during their lifetime. A cell’s survival depends on its ability to coordinate a rapid and successful stress response when exposed to acute doses of damaging agents. Oxidative stress caused by an excess of reactive oxygen species, is known to damage cellular components. In humans, redox imbalance is associated with aging, cancer, atherosclerosis, Alzheimer’s and Parkinson’s disease among others. Therefore, studies investigating the cellular mechanisms employed in response to oxidative stress have markedly increased in recent years, especially using model organisms.

The fission yeast Schizosaccharomyces pombe is a unicellular eukaryotic organism that possesses genome features and molecular pathways that are highly conserved in humans. Moreover, the limited redundancy of its genome makes S. pombe well suited for phenotypic studies and the investigation of stress responses in particular. Notably, the fission yeast stress-activated protein kinase pathway is activated in multiple stress conditions including oxidative stress, and it activates transcription factors that are conserved in humans (Chapter 4). Several gene expression studies have uncovered the transcriptional program of fission yeast cells in response to oxidative stimuli. Thus, a solid basis of stress response data is available for this yeast and constitutes a valuable framework for further studies on gene expression in stress.

Post-transcriptional control of gene expression is, however, less well understood. Only few reports describing the correlation between mRNA and protein levels in different species exist. Also, the vast majority of these studies were conducted at low time-resolution and primarily in normal growth conditions. We were interested in investigating the correlation between mRNA and protein expression and define their time dynamics in the oxidative stress response. Towards this goal, we measured the mRNA and protein levels in samples collected from exponentially growing fission yeast cultures at multiple points after cellular treatment with hydrogen peroxide (HP, 0.5 mM). The applied experimental design allowed us to measure both the activation and recovery phases of the response at a sufficiently high time resolution to model transcription and translation dynamics.

Absolute expression levels (copies per cell) and time-resolved expression profiles for 4,972 mRNAs and 2,310 proteins were determined, and a web application for profile visualization was developed. We found a high correlation between mRNA and protein levels both at the steady state and the time of the maximum expression response. In most cases increase in protein abundance was concomitant with transcript induction, while the mRNA and protein levels of repressed genes were not correlated. Changes only at the level of mRNA (futile transcription) or protein (translational regulation) were common. For coherently induced proteins the time of maximum production rate was reached when mRNA levels peaked. Accordingly, for coherently repressed proteins the maximum degradation rate was often observed at the time of the minimum mRNA response (Chapter 5).

To date, gene expression in the stress response of fission yeast cells to HP has been studied in batch cultures of different starting cell densities, while HP decay profiles in these populations have not been described. Also, contrary to the budding yeast, high-throughput growth profiling studies in normal and stress conditions are missing for fission yeast.

Using time-resolved mRNA profiles of low and high cell density populations in stress, we found a close relationship between cell density and HP depletion rate, and thus, the exposure time and mRNA response dynamics. Based on the dependence of response times (or other time dynamics features) of mRNA profiles on cell density, we defined different transcriptional responses. We observed that most mRNAs of commonly regulated genes in stress reached the time of the maximum (or minimum) response earlier in cultures of higher densities (negative cell concentration-dependent response, CCDRn). Similar response dynamics in high and low cell populations (cell concentration-independent response, CCIR) were often observed. Finally, core oxidative stress genes showed a positive correlation between the response time and cell density (positive cell concentration-dependent response, CCDRp). We also determined the rapid response of fission yeast cells to oxidative stress by assessing the maximum response times of all significant mRNA responses. We found gene functions associated with cellular redox homeostasis and the fate of the cell to become rapidly regulated in response to HP (Chapter 6).

Moreover, we characterized the growth physiology of yeast cells in multiple conditions of HP stress and resolved individual growth variables with high precision for hundreds of segregants in a high-throughput setting. The extent of the dosage dependent, negative-effects on growth of segregant strains was observed to be non-trivially related to the stress phenotypes of the parental strains. Accordingly, segregants could be grouped by the extent of stress effects exerted on
each growth variable. These findings are currently under investigation in a larger quantitative trait loci (QTL) study.

**Gene prioritization for livestock diseases by data integration**

Identifying causal genes that underlie complex traits such as susceptibility to disease is a primary aim of genetic and biomedical studies. Genetic mapping of quantitative trait loci (QTL) and gene expression profiling based on high-throughput technologies are common first approaches toward identifying associations between genes and traits; however, it is often difficult to assess whether the biological function of a putative candidate gene is consistent with a particular phenotype. Here, we have implemented a network-based disease gene prioritization approach for ranking genes associated with quantitative traits and diseases in livestock species. The approach uses ortholog mapping and integrates information on disease or trait phenotypes, gene-associated phenotypes, and protein-protein interactions. It was used for ranking all known genes present in the cattle genome for their potential roles in bovine mastitis. Gene-associated phenotype profile and transcriptome profile in response to *Escherichia coli* infection in the mammary gland were integrated to make a global inference of bovine genes involved in mastitis. The top ranked genes were highly enriched for pathways and biological processes underlying inflammation and immune responses, which supports the validity of our approach for identifying genes that are relevant to animal health and disease. These gene-associated phenotypes were used for a local prioritization of candidate genes located in a QTL affecting the susceptibility to mastitis. Our study provides a general framework for prioritizing genes associated with various complex traits in different species. To our knowledge this is the first time that gene expression, ortholog mapping, protein interactions, and biomedical text data have been integrated systematically for ranking candidate genes in any livestock species.
Genetic and environmental risk factors in congenital heart disease functionally converge in protein networks driving heart development

Congenital heart disease (CHD) occurs in ~1% of newborns. CHD arises from many distinct etiologies, ranging from genetic or genomic variation to exposure to teratogens, which elicit diverse cell and molecular responses during cardiac development. To systematically explore the relationships between CHD risk factors and responses, we compiled and integrated comprehensive datasets from studies of CHD in humans and model organisms. We examined two alternative models of potential functional relationships between genes in these datasets: direct convergence, in which CHD risk factors significantly and directly impact the same genes and molecules and functional convergence, in which risk factors significantly impact different molecules that participate in a discrete heart development network. We observed no evidence for direct convergence. In contrast, we show that CHD risk factors functionally converge in protein networks driving the development of specific anatomical structures (e.g., outflow tract, ventricular septum, and atrial septum) that are malformed by CHD. This integrative analysis of CHD risk factors and responses suggests a complex pattern of functional interactions between genomic variation and environmental exposures that modulate critical biological systems during heart development.

General information
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Genome-wide analysis of cytogenetic aberrations in ETV6/RUNX1-positive childhood acute lymphoblastic leukaemia

The chromosomal translocation t(12;21) resulting in the ETV6/RUNX1 fusion gene is the most frequent structural cytogenetic abnormality among patients with childhood acute lymphoblastic leukaemia (ALL). We investigated 62 ETV6/RUNX1-positive childhood ALL patients by single nucleotide polymorphism array to explore acquired copy number alterations (CNAs) at diagnosis. The mean number of CNAs was 2.82 (range 0–14). Concordance with available G-band karyotyping and comparative genomic hybridization was 93%. Based on three major protein–protein complexes disrupted by these CNAs, patients could be categorized into four distinct subgroups, defined by different underlying biological mechanisms relevant to the aetiology of childhood ALL. When recurrent CNAs were evaluated by an oncogenetic tree analysis classifying their sequential order, the most common genetic aberrations (deletions of 6q, 9p, 13q and X, and gains of 10 and 21) seemed independent of each other. Finally, we identified the most common regions with recurrent gains and losses, which comprise microRNA clusters with known oncogenic or tumour-suppressive roles. The present study sheds further light on the genetic diversity of ETV6/RUNX1-positive childhood ALL, which may be important for understanding poor responses among this otherwise highly curable subset of ALL and lead to novel targeted treatment strategies.
Genomic variation in Salmonella enterica core genes for epidemiological typing

Background: Technological advances in high throughput genome sequencing are making whole genome sequencing (WGS) available as a routine tool for bacterial typing. Standardized procedures for identification of relevant genes and of variation are needed to enable comparison between studies and over time. The core genes-the genes that are conserved in all (or most) members of a genus or species-are potentially good candidates for investigating genomic variation in phylogeny and epidemiology. Results: We identify a set of 2,882 core genes clusters based on 73 publicly available Salmonella enterica genomes and evaluate their value as typing targets, comparing whole genome typing and traditional methods such as 16S and MLST. A consensus tree based on variation of core genes gives much better resolution than 16S and MLST; the pan-genome family tree is similar to the consensus tree, but with higher confidence. The core genes can be divided into two categories: a few highly variable genes and a larger set of conserved core genes, with low variance. For the most variable core genes, the variance in amino acid sequences is higher than for the corresponding nucleotide sequences, suggesting that there is a positive selection towards mutations leading to amino acid changes. Conclusions: Genomic variation within the core genome is useful for investigating molecular evolution and providing candidate genes for bacterial genome typing. Identification of genes with different degrees of variation is important especially in trend analysis.

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Global network reorganization during dynamic adaptations of Bacillus subtilis metabolism.

Adaptation of cells to environmental changes requires dynamic interactions between metabolic and regulatory networks, but studies typically address only one or a few layers of regulation. For nutritional shifts between two preferred carbon sources of Bacillus subtilis, we combined statistical and model-based data analyses of dynamic transcript, protein, and metabolite abundances and promoter activities. Adaptation to malate was rapid and primarily controlled posttranscriptionally compared with the slow, mainly transcriptionally controlled adaptation to glucose that entailed nearly half of the known transcription regulation network. Interactions across multiple levels of regulation were involved in adaptive changes that could also be achieved by controlling single genes. Our analysis suggests that global trade-offs and evolutionary constraints provide incentives to favor complex control programs.

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Group a Pfemp1 functional domains bind icam1 and induce cross-reactive and adhesion inhibitory antibodies during malaria infections

The Plasmodium falciparum erythrocyte membrane protein 1 (PfEMP1) plays an important role in antigenic variation and pathogenesis of malaria. PfEMP1 proteins encoded by group A var genes appear to be involved in the pathogenesis of severe disease and have been suggested as attractive candidates for a vaccine against life-threatening P. falciparum malaria. In this study, we identified group A pfd1235w-like genes in Ghanaian isolates and found these to encode a three-domain cassette structure 64-80% identical to the equivalent region of P. falciparum clone 3D7 PFD1235w. Parasites expressing PFD1235w-like proteins on the surface of infected erythrocytes were found to mediate binding to ICAM1, a phenotype linked to cerebral malaria. ICAM1 binding was mediated by a particular sub-domain which induces cross-reactive and ICAM1 adhesion inhibitory antibodies during P. falciparum infections. These results have implications for our understanding of how PfEMP1 interacts with host receptors and for the development of therapeutic interventions targeting ICAM1 binding malaria parasites.
How well do the substrates KISS the enzyme? Molecular docking program selection for feruloyl esterases

Molecular docking is the most commonly used technique in the modern drug discovery process where computational approaches involving docking algorithms are used to dock small molecules into macromolecular target structures. Over the recent years several evaluation studies have been reported by independent scientists comparing the performance of the docking programs by using default 'black box' protocols supplied by the software companies. Such studies have to be considered carefully as the docking programs can be tweaked towards optimum performance by selecting the parameters suitable for the target of interest. In this study we address the problem of selecting an appropriate docking and scoring function combination (88 docking algorithm-scoring functions) for substrate specificity predictions for feruloyl esterases, an industrially relevant enzyme family. We also propose the 'Key Interaction Score System' (KISS), a more biochemically meaningful measure for evaluation of docking programs based on pose prediction accuracy.
Hyperactivity of the Ero1α Oxidase Elicits Endoplasmic Reticulum Stress but No Broad Antioxidant Response

Oxidizing equivalents for the process of oxidative protein folding in the endoplasmic reticulum (ER) of mammalian cells are mainly provided by the Ero1α oxidase. The molecular mechanisms that regulate Ero1α activity in order to harness its oxidative power are quite well understood. However, the overall cellular response to oxidative stress generated by Ero1α in the lumen of the mammalian ER is poorly characterized. Here we investigate the effects of overexpressing a hyperactive mutant (C104A/C131A) of Ero1α. We show that Ero1α hyperactivity leads to hyperoxidation of the ER oxidoreductase Erp57 and induces expression of two established unfolded protein response (UPR) targets, BiP (immunoglobulin-binding protein) and HERP (homocysteine-induced ER protein). These effects could be reverted or aggravated by N-acetylcysteine and buthionine sulfoximine, respectively. Because both agents manipulate the cellular glutathione redox buffer, we conclude that the observed effects of Ero1α-C104A/C131A overexpression are likely caused by an oxidative perturbation of the ER glutathione redox buffer. In accordance, we show that Ero1α hyperactivity affects cell viability when cellular glutathione levels are compromised. Using microarray analysis, we demonstrate that the cell reacts to the oxidative challenge caused by Ero1α hyperactivity by turning on the UPR. Moreover, this analysis allowed the identification of two new targets of the mammalian UPR, CRELD1 and c18orf45. Interestingly, a broad antioxidant response was not induced. Our findings suggest that the hyperoxidation generated by Ero1α-C104A/C131A is addressed in the ER lumen and is unlikely to exert oxidative injury throughout the cell.

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Identification of acquired antimicrobial resistance genes

Objectives: Identification of antimicrobial resistance genes is important for understanding the underlying mechanisms and the epidemiology of antimicrobial resistance. As the costs of whole-genome sequencing (WGS) continue to decline, it becomes increasingly available in routine diagnostic laboratories and is anticipated to substitute traditional methods for resistance gene identification. Thus, the current challenge is to extract the relevant information from the large amount of generated data. Methods: We developed a web-based method, ResFinder that uses BLAST for identification of acquired antimicrobial resistance genes in whole-genome data. As input, the method can use both pre-assembled, complete or partial genomes, and short sequence reads from four different sequencing platforms. The method was evaluated on 1862 GenBank files containing 1411 different resistance genes, as well as on 23 de-novo-sequenced isolates. Results: When testing the 1862 GenBank files, the method identified the resistance genes with an ID = 100% (100% identity) to the genes in ResFinder. Agreement between in silico predictions and phenotypic testing was found when the method was further tested on 23 isolates of five different bacterial species, with available phenotypes. Furthermore, ResFinder was evaluated on WGS chromosomes and plasmids of 30 isolates. Seven of these isolates were annotated to have antimicrobial resistance, and in all cases, annotations were compatible with the ResFinder results. Conclusions: A web server providing a convenient way of identifying acquired antimicrobial resistance genes in completely sequenced isolates was created. ResFinder can be accessed at www.genomicepidemiology.org. ResFinder will continuously be updated as new resistance genes are identified.

General information
Identification of a Novel UTY-Encoded Minor Histocompatibility Antigen

Minor histocompatibility antigens (mHags) encoded by the Y-chromosome (H-Y-mHags) are known to play a pivotal role in allogeneic haematopoietic cell transplantation (HCT) involving female donors and male recipients. We present a new H-Y-mHag, YYNAFHWAI (UTY139–147), encoded by the UTY gene and presented by HLA-A*24:02. Briefly, short peptide stretches encompassing multiple putative H-Y-mHags were designed using a bioinformatics predictor of peptide-HLA binding, NetMHCpan. These peptides were used to screen for peptide-specific HLA-restricted T cell responses in peripheral blood mononuclear cells obtained post-HCT from male recipients of female donor grafts. In one of these recipients, a CD8+ T cell response was observed against a peptide stretch encoded by the UTY gene. Another bioinformatics tool, HLArestrictor, was used to identify the optimal peptide and HLA-restriction element. Using peptide/HLA tetramers, the specificity of the CD8+ T cell response was successfully validated as being HLA-A*24:02-restricted and directed against the male UTY139–147 peptide. Functional analysis of these T cells demonstrated male UTY139–147 peptide-specific cytokine secretion (IFNγ, TNFα and MIP-1β) and cytotoxic degranulation (CD107a). In contrast, no responses were seen when the T cells were stimulated with patient tumour cells alone. CD8+ T cells specific for this new H-Y-mHag were found in three of five HLA-A*24:02-positive male recipients of female donor HCT grafts available for this study.
Identification of cytochrome P450 2D6 and 2C9 substrates and inhibitors by QSAR analysis

This paper presents four new QSAR models for CYP2C9 and CYP2D6 substrate recognition and inhibitor identification based on human clinical data. The models were used to screen a large data set of environmental chemicals for CYP activity, and to analyze the frequency of CYP activity among these compounds. A large fraction of these chemicals were found to be CYP active, and thus potentially capable of affecting human physiology. 20% of the compounds within the applicability domain of the models were predicted to be CYP2C9 substrates, and 17% to be inhibitors. The corresponding numbers for CYP2D6 were 9% and 21%. Where the majority of CYP2C9 active compounds were predicted to be both a substrate and an inhibitor at the same time, the CYP2D6 active compounds were primarily predicted to be only inhibitors. It was demonstrated that the models could identify compound classes with a high occurrence of specific CYP activity. An overrepresentation was seen for poly-aromatic hydrocarbons (group of procarcinogens) among CYP2C9 active and mutagenic compounds compared to CYP2C9 inactive and mutagenic compounds. The mutagenicity was predicted with a QSAR model based on Ames in vitro test data.

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Immune epitope database analysis resource

The immune epitope database analysis resource (IEDB-AR: http://tools.iedb.org) is a collection of tools for prediction and analysis of molecular targets of T- and B-cell immune responses (i.e., epitopes). Since its last publication in the NAR webserver issue in 2008, a new generation of peptide:MHC binding and T-cell epitope predictive tools have been added. As validated by different labs and in the first international competition for predicting peptide:MHC-I binding, their predictive performances have improved considerably. In addition, a new B-cell epitope prediction tool was added, and the homology mapping tool was updated to enable mapping of discontinuous epitopes onto 3D structures. Furthermore, to serve a wider range of users, the number of ways in which IEDB-AR can be accessed has been expanded. Specifically, the predictive tools can be programmatically accessed using a web interface and can also be downloaded as software packages.

General information

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Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, La Jolla Institute for Allergy & Immunology, San Diego Supercomputer Center, Shanghai Advanced Research Institute
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Immune Recognition of Latency-insitigating Pathogens by Human Dendritic Cells

Latent infections with the human pathogenic microorganisms Mycobacterium tuberculosis (Mtb) and the human immunodeficiency virus (HIV) are creating some of the most devastating pandemics to date, with great impact on the infected people’s lives, their expected lifetime, as well as general costs for society. Consequently there is a pressing need to search for new treatment strategies. Nowadays it is known that HIV-1 and Mtb have acquired the ability to escape the removal from the body by exploiting the immune system for their own benefits. Dendritic cells (DCs) determine the way the immune response unfolds by signaling other immune cells how to respond. An early deregulation of the DCs may therefore propagate into detrimental effects in later stages of the immune response, and may permit HIV-1 and Mtb to become latent. Hence, understanding the way HIV-1 and Mtb interacts with DCs could lead to novel treatment strategies. In the present work this has been examined in purified human plasmacytoid DCs (pDCs) and monocyte-derived DCs (moDCs). First it is demonstrated how Mtb exploits plasticity in moDCs to avoid production of the cytokine IL-12p70 necessary for protection against Mtb. Then it is shown that Mtb induces signaling in moDCs that misdirects the immune response into an extracellular Th17 response, even though the bacteria hide inside immune cells. Finally it is demonstrated how HIV-1 strains, capable of provoking sustained infection, induce a highmannose-independent complete necrotic eradication of the pDCs that is needed to inhibit initial infection. The results presented in this thesis provide novel insights into immune evasion strategies employed by HIV-1 and Mtb. These findings could eventually be utilized for better treatment strategies against AIDS and tuberculosis disease when specific strategies for immune cell perturbations are established.
Immunogenicity of Mycobacterium avium subsp. paratuberculosis specific peptides for inclusion in a subunit vaccine against paratuberculosis
Paratuberculosis in ruminants is caused by an infection with Mycobacterium avium subspecies paratuberculosis (MAP) and is a chronic disease characterized by granulomatous enteritis. Available vaccines against paratuberculosis consist of variations of whole bacteria with adjuvant showing various efficacies. The main problem with available vaccines is their interference with surveillance and diagnosis of bovine tuberculosis and paratuberculosis. Our ultimate aim is to develop a subunit vaccine consisting of selected MAP peptides, which allow differentiation of infected from vaccinated animals. Here, 118 peptides were identified by in silico analysis and synthesized chemically. Peptides were tested for reactivity and immunogenicity with T-cell lines generated from PBMCs isolated from MAP infected goats and with blood samples from MAP infected calves. Immunogenicity of peptides was evaluated using full blood IFN-γ release assay and ELISPOT measuring IFN-γ release of PBMCs. A number of peptides resulted in high T cell proliferative responses in T-cell lines and some peptides induced IFN-γ production measured by ELISPOT. This indicates that some of the peptides in the panel contain T cell epitopes and are immunogenic. In the near future, a panel of selected peptides will be tested for efficacy as a vaccine against paratuberculosis with calves or goats experimentally infected with MAP.

Improving the prediction of the brain disposition for orally administered drugs using BDDCS
In modeling blood–brain barrier (BBB) passage, in silico models have yielded ~80% prediction accuracy, and are currently used in early drug discovery. Being derived from molecular structural information only, these models do not take into account the biological factors responsible for the in vivo outcome. Passive permeability and P-glycoprotein (Pgp, ABCB1) efflux have been successfully recognized to impact xenobiotic extrusion from the brain, as Pgp is known to play a role in limiting the BBB penetration of oral drugs in humans. However, these two properties alone fail to explain the BBB penetration for a significant number of marketed central nervous system (CNS) agents. The Biopharmaceutics Drug Disposition Classification System (BDDCS) has proved useful in predicting drug disposition in the human body, particularly in the liver and intestine. Here we discuss the value of using BDDCS to improve BBB predictions of oral drugs. BDDCS class membership was integrated with in vitro Pgp efflux and in silico permeability data to create a simple 3-step classification tree that accurately predicted CNS disposition for more than 90% of 153 drugs in our data set. About 98% of BDDCS class 1 drugs were found to markedly distribute throughout the brain; this includes a number of BDDCS class 1 drugs shown to be Pgp substrates. This new perspective provides a further interpretation of how Pgp influences the sedative effects of H1-histamine receptor antagonists.
**Integrative data analysis of male reproductive disorders**

During the last decades a decline in male reproductive health has been observed in Nordic countries, and particularly in Denmark. Testicular cancer is the most fatal form of male reproductive disorders, and despite high remission rates it is typically accompanied with infertility. The main topic of this thesis is the identification of the molecular basis of male reproductive disorders, with a special focus on testicular cancer. To this end, clinical samples were characterized by microarray-based transcription and genomic variation assays and molecular entities were identified by computational analysis of such data in conjunction with data from publicly available repositories. This thesis presents an introduction to disease genetics and molecular systems biology, followed by four studies that each provide detailed clues to the etiology of male reproductive disorders. Finally, a fifth study illustrates the use of massively parallel nucleotide sequencing for gene expression analysis.

In paper I the similarity of testicular carcinoma in situ cells from the developing testis was investigated. We observed a close similarity to gonocytes, contributing further indications that non-spermatocytic testicular cancer arise due to disturbances in early testicular development. In paper II we analysed copy number variations (CNV) in germline DNA from four families with testicular germ cell tumors. Given the low number of samples, we aimed to improve the confidence by placing CNVs in a protein network context superimposed with established phenomic information. We thereby identified a recurrent CNV at a locus with genes encoding for the relaxin peptide hormones, indicating their potential role in testis function. Paper III presents a genome-wide association study on testicular dysgenesis syndrome. We confirmed the importance of KITLG in testicular cancer, and identified two risk loci related to the TGFβ-signaling pathway, TGFBR3 and BMP7, by using a systems biology approach that was guided by the developmental disease hypothesis, and a pathway analysis based approach, respectively. Paper IV investigate the genome-wide association data with respect to copy number variation and show that the aggregated effect of rare variants can influence the risk for testicular cancer. Paper V provides an example of the application of RNA-Seq for expression analysis of a species with an unsequenced genome. We analysed the plant Craterostigma plantagineum, which is known for its astonishing drought tolerance, and thereby provided the first transcriptomes of this species. Comparisons of unstressed to desiccated conditions indicated several pathways of interest.

In conclusion, this thesis contributes to the molecular understanding of testicular malfunction and desiccation tolerance in C. plantagineum, as well as develops and highlights the usefulness of novel systems biology methodologies.

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**General information**
- **State:** Published
- **Organisations:** Department of Systems Biology, Center for Biological Sequence Analysis
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**Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing**

**BACKGROUND:** Intratumor heterogeneity may foster tumor evolution and adaptation and hinder personalized-medicine strategies that depend on results from single tumor-biopsy samples. **METHODS** To examine intratumor heterogeneity, we performed exome sequencing, chromosome aberration analysis, and ploidy profiling on multiple spatially separated samples obtained from primary renal carcinomas and associated metastatic sites. We characterized the consequences of intratumor heterogeneity using immunohistochemical analysis, mutation functional analysis, and profiling of messenger RNA expression. **RESULTS:** Phylogenetic reconstruction revealed branched evolutionary tumor growth, with 63 to 69% of all somatic mutations not detectable across every tumor region. Intratumor heterogeneity was observed for a mutation within an autoinhibitory domain of the mammalian target of rapamycin (mTOR) kinase, correlating with S6 and 4EBP phosphorylation in vivo and constitutive activation of mTOR kinase activity in vitro. Mutational intratumor heterogeneity was seen for multiple tumor-suppressor genes converging on loss of function; SETD2, PTEN, and KDM5C underwent multiple distinct and spatially separated inactivating mutations within a single tumor, suggesting convergent phenotypic evolution. Gene-expression signatures of good and poor prognosis were detected in different regions of the same tumor. Allelic composition and ploidy profiling analysis revealed extensive intratumor heterogeneity, with 26 of 30 tumor samples from four tumors harboring divergent allelic-imbalance profiles and with ploidy heterogeneity in two of four tumors. **CONCLUSIONS:** Intratumor heterogeneity can lead to underestimation of the tumor genomics landscape portrayed from single tumor-biopsy samples and may present major challenges to personalized-medicine and biomarker development. Intratumor heterogeneity, associated with heterogeneous protein function, may foster tumor adaptation and therapeutic failure through Darwinian selection. (Funded by the Medical Research Council and others.)
Isolation of IL-12p70-competent human monocyte-derived dendritic cells

Diverse methodologies ranging from experimental immunological studies to immunotherapy involve the application of human monocyte-derived dendritic cells (moDCs). Considerable donor-dependent variations in the moDC production of IL-12p70 affect the outcome of these methodologies. It has been shown that moDCs generated under standard conditions develop into two subsets based on CD1a-expression with the CD1a+ moDCs being the main IL-12p70 producers. This has however not been generally accepted, which we show here because the subset described as CD1a-negative does express CD1a, but at a lower level than the other subset. We further characterize the phenotype of these two subsets, showing that the CD1a-hi subset has a greater immunogenic phenotype, making this subset more suitable for immunotherapy. The two subsets have previously been separated by cell sorting, but as this technique is not available to many laboratories and has incompatibility with clinical settings, a more widely useable technique is warranted. Therefore we tested if magnetic-activated cell sorting is useful for the purpose, and show that it is possible to isolate IL-12p70-competent CD1a-hi moDCs to a
Is the pan-genome also a pan-selectome?
The comparative genomics of prokaryotes has shown the presence of conserved regions containing highly similar genes (the 'core genome') and other regions that vary in gene content (the 'flexible' regions). A significant part of the latter is involved in surface structures that are phage recognition targets. Another sizeable part provides for differences in niche exploitation. Metagenomic data indicates that natural populations of prokaryotes are composed of assemblages of clonal lineages or "meta-clones" that share a core of genes but contain a high diversity by varying the flexible component. This meta-clonal diversity is maintained by a collection of phages that equalize the populations by preventing any individual clonal lineage from hoarding common resources. Thus, this polyclonal assemblage and the phages preying upon them constitute natural selection units. © 2012 Rodriguez-Valera F et al.
Knowledge engineering for health: A new discipline required to bridge the "ICT gap" between research and healthcare

Despite vast amounts of money and research being channeled toward biomedical research, relatively little impact has been made on routine clinical practice. At the heart of this failure is the information and communication technology "chasm" that exists between research and healthcare. A new focus on "knowledge engineering for health" is needed to facilitate knowledge transmission across the research-healthcare gap. This discipline is required to engineer the bidirectional flow of data: processing research data and knowledge to identify clinically relevant advances and delivering these into healthcare use; conversely, making outcomes from the practice of medicine suitably available for use by the research community. This system will be able to self-optimize in that outcomes for patients treated by decisions that were based on the latest research knowledge will be fed back to the research world. A series of meetings, culminating in the "i-Health 2011" workshop, have brought together interdisciplinary experts to map the challenges and requirements for such a system.

Here, we describe the main conclusions from these meetings. An "I4Health" interdisciplinary network of experts now exists to promote the key aims and objectives, namely "integrating and interpreting information for individualized healthcare," by developing the "knowledge engineering for health" domain. Hum Mutat 33:797–802, 2012. © 2012 Wiley Periodicals, Inc.
LeuO is a global regulator of gene expression in Salmonella enterica serovar Typhimurium

We report the first investigation of the binding of the Salmonella enterica LeuO LysR-type transcription regulator to its genomic targets in vivo. Chromatin-immunoprecipitation-on-chip identified 178 LeuO binding sites on the chromosome of S. enterica serovar Typhimurium strain SL1344. These sites were distributed across both the core and the horizontally acquired genome, and included housekeeping genes and genes known to contribute to virulence. Sixty-eight LeuO targets were co-bound by the global repressor protein, H-NS. Thus, while LeuO may function as an H-NS antagonist, these functions are unlikely to involve displacement of H-NS. RNA polymerase bound 173 of the 178 LeuO targets, consistent with LeuO being a transcription regulator. Thus, LeuO targets two classes of genes, those that are bound by H-NS and those that are not bound by H-NS. LeuO binding site analysis revealed a logo conforming to the TN11A motif common to LysR-type transcription factors. It differed in some details from a motif that we composed for Escherichia coli LeuO binding sites; 1263 and 1094 LeuO binding site locations were predicted in the S. Typhimurium SL1344 and E. coli MG1655 genomes respectively. Despite differences in motif composition, many LeuO target genes were common to both species. Thus, LeuO is likely to be a more important global regulator than previously suspected.

General information
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LocARNA-P: Accurate boundary prediction and improved detection of structural RNAs

Current genomic screens for noncoding RNAs (ncRNAs) predict a large number of genomic regions containing potential structural ncRNAs. The analysis of these data requires highly accurate prediction of ncRNA boundaries and discrimination of promising candidate ncRNAs from weak predictions. Existing methods struggle with these goals because they rely on sequence-based multiple sequence alignments, which regularly misalign RNA structure and therefore do not support identification of structural similarities. To overcome this limitation, we compute columnwise and global reliabilities of alignments based on sequence and structure similarity; we refer to these structure-based alignment reliabilities as STARs. The columnwise STARs of alignments, or STAR profiles, provide a versatile tool for the manual and automatic analysis of ncRNAs. In particular, we improve the boundary prediction of the widely used ncRNA gene finder RNAz by a factor of 3 from a median deviation of 47 to 13 nt. Post-processing RNAz predictions, LocARNA-P’s STAR score allows much stronger discrimination between true- and false-positive predictions than RNAz’s own evaluation. The improved accuracy, in this scenario increased from AUC 0.71 to AUC 0.87, significantly reduces the cost of successive analysis steps. The ready-to-use software tool LocARNA-P produces structure-based multiple RNA alignments with associated columnwise STARs and predicts ncRNA boundaries. We provide additional results, a web server for LocARNA/LocARNA-P, and the software package, including documentation and a pipeline for refining screens for structural ncRNA, at http://www.bioinf.uni-freiburg.de/Supplements/LocARNA-P/.

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Scopus rating (2013): SJR 4.397 SNIP 1.049 CiteScore 4.97
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BFI (2009): BFI-level 1
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Mapping the genome of Plasmodium falciparum on the drug-like chemical space reveals novel anti-malarial targets and potential drug leads

The parasite Plasmodium falciparum is the main agent responsible for malaria. In this study, we exploited a recently published chemical library from GlaxoSmithKline (GSK) that had previously been confirmed to inhibit parasite growth of the wild type (3D7) and the multi-drug resistance (D2d) strains, in order to uncover the weak links in the proteome of the parasite. We predicted 293 proteins of P. falciparum, including the six out of the seven verified targets for P. falciparum malaria treatment, as targets of 4645 GSK active compounds. Furthermore, we prioritized druggable targets, based on a number of factors, such as essentiality for growth, lack of homology with human proteins, and availability of experimental data on ligand activity with a non-human homologue of a parasite protein. We have additionally prioritized predicted ligands based on their polypharmacology profile, with focus on validated essential proteins and the effect of their perturbations on the metabolic network of P. falciparum, as well as indication of drug resistance emergence. Finally, we predict potential off-target effects on the human host with associations to cancer, neurological and dermatological disorders, based on integration of available chemical-protein and protein-protein interaction data. Our work suggests that a large number of the P. falciparum proteome is potentially druggable and could therefore serve as novel drug targets in the fight against malaria. At the same time, prioritized compounds from the GSK library could serve as lead compounds to medicinal chemists for further optimization.
Maternal high-fat/high-sucrose diet during lactation results in increased adipose tissue mass, and altered hepatic fatty acid metabolism at weaning.
Maternal high-fat/high-sucrose diet during lactation results in increased adipose tissue mass, and altered hepatic fatty acid metabolism at weaning

Mechanisms of G Protein-Coupled Estrogen Receptor-Mediated Spinal Nociception

Human and animal studies suggest that estrogens are involved in the processing of nociceptive sensory information and analgesic responses in the central nervous system. Rapid pronociceptive estrogenic effects have been reported, some of which likely involve G protein-coupled estrogen receptor (GPER) activation. Membrane depolarization and increases in cytosolic calcium and reactive oxygen species (ROS) levels are markers of neuronal activation, underlying pain sensitization in the spinal cord. Using behavioral, electrophysiological, and fluorescent imaging studies, we evaluated GPER involvement in spinal nociceptive processing. Intrathecal challenging of mice with the GPER agonist G-1 results in pain-related behaviors. GPER antagonism with G15 reduces the G-1-induced response. Electrophysiological recordings from superficial dorsal horn neurons indicate neuronal membrane depolarization with G-1 application, which is G15 sensitive. In cultured spinal sensory neurons, G-1 increases intracellular calcium concentration and induces mitochondrial and cytosolic ROS accumulation. In the presence of G15, G-1 does not elicit the calcium and ROS responses, confirming specific GPER involvement in this process. Cytosolic calcium concentration elevates faster and with higher amplitude following G-1 intracellular microinjections compared to extracellular exposure, suggesting subcellular GPER functionality. Thus, GPER activation results in spinal nociception, and the downstream mechanisms involve cytosolic calcium increase, ROS accumulation, and neuronal membrane depolarization. PerspectiveOur results suggest that GPER modulates pain processing in spinal sensory neurons via cytosolic calcium increase and ROS accumulation. These findings extend the current knowledge on GPER involvement in physiology and disease, providing the first evidence of its pronociceptive effects at central levels and characterizing some of the underlying mechanisms.
MicroRNA expression profiling of carcinoma in situ cells of the testis

Testicular germ cell tumours, seminoma (SE) and non-seminoma (NS), of young adult men develop from a precursor cell, carcinoma in situ (CIS), which resembles foetal gonocytes and retains embryonic pluripotency. We used microarrays to analyse microRNA (miRNA) expression in 12 human testis samples with CIS cells and compared it with miRNA expression profiles of normal adult testis, testis with Sertoli-cell-only that lacks germ cells, testis tumours (SE and embryonal carcinoma (EC), an undifferentiated component of NS) and foetal male and female gonads. Principal components analysis revealed distinct miRNA expression profiles characteristic for each of the different tissue types. We identified several miRNAs that were unique to testis with CIS cells, foetal gonads and testis tumours. These included miRNAs from the hsa-miR-371–373 and -302–367 clusters that have previously been reported in germ cell tumours and three miRNAs (hsa-miR-96, -141 and -200c) that were also expressed in human epididymis. We found several miRNAs that were upregulated in testis tumours: hsa-miR-9, -105 and -182–183–96 clusters were highly expressed in SE, while the hsa-miR-515–526 cluster was high in EC. We conclude that the miRNA expression profile changes during testis development and that the miRNA profile of adult testis with CIS cells shares characteristic similarities with the expression in foetal gonocytes.
Mining electronic health records: towards better research applications and clinical care.
Clinical data describing the phenotypes and treatment of patients represents an underused data source that has much greater research potential than is currently realized. Mining of electronic health records (EHRs) has the potential for establishing new patient-stratification principles and for revealing unknown disease correlations. Integrating EHR data with genetic data will also give a finer understanding of genotype-phenotype relationships. However, a broad range of ethical, legal and technical reasons currently hinder the systematic deposition of these data in EHRs and their mining. Here, we consider the potential for furthering medical research and clinical care using EHR data and the challenges that must be overcome before this is a reality.

General information
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Scopus rating (2008): SJR 10.816 SNIP 3.169
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Scopus rating (2006): SJR 7.151 SNIP 2.64
Scopus rating (2005): SJR 6.842 SNIP 2.396
Scopus rating (2004): SJR 7.596 SNIP 2.974
Scopus rating (2002): SJR 8.205 SNIP 2.875
Modeling of Phenoxy Acid Herbicide Mineralization and Growth of Microbial Degraders in 15 Soils Monitored by Quantitative Real-Time PCR of the Functional tfdA Gene

Mineralization potentials, rates, and kinetics of the three phenoxy acid (PA) herbicides, 2,4-dichlorophenoxyacetic acid (2,4-D), 4-chloro-2-methylphenoxyacetic acid (MCPA), and 2-(4-chloro-2-methylphenoxy)propanoic acid (MCPP), were investigated and compared in 15 soils collected from five continents. The mineralization patterns were fitted by zero/linear or exponential growth forms of the three-half-order models and by logarithmic (log), first-order, or zero-order kinetic models. Prior and subsequent to the mineralization event, tfdA genes were quantified using real-time PCR to estimate the genetic potential for degrading PA in the soils. In 25 of the 45 mineralization scenarios, ~60% mineralization was observed within 118 days. Elevated concentrations of tfdA in the range 1 × 10^5 to 5 × 10^7 gene copies g^-1 of soil were observed in soils where mineralization could be described by using growth-linked kinetic models. A clear trend was observed that the mineralization rates of the three PAs occurred in the order 2,4-D > MCPA > MCPP, and a correlation was observed between rapid mineralization and soils exposed to PA previously. Finally, for 2,4-D mineralization, all seven mineralization patterns which were best fitted by the exponential model yielded a higher tfdA gene potential after mineralization had occurred than the three mineralization patterns best fitted by the Lin model.

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BFI (2017): BFI-level 2
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 4.08
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 1.891 SNIP 1.308 CiteScore 4.14
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 1.857 SNIP 1.384 CiteScore 4.02
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 1.899 SNIP 1.414 CiteScore 4.25
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 1.975 SNIP 1.429 CiteScore 4.29
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
Motion gør dig mere sund end et vægttab
Hvis mænd vil være sunde, skal de dyrke motion hver dag og sørge for at få pulsen helt op bare nogle gange om ugen. Det gør dem sundere, end hvis de ændrer kostvaner for at tabe sig, viser ny dansk forskning

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis
Authors: Hoffmann, T. J. (Forskerdatabase), Nordby, P. (Intern)
Publication date: 2012
Main Research Area: Technical/natural sciences

Publication information
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Source: dtu
Source-ID: n::oai:DTIC-ART:dkart/388707855::35317
Publication: Research - peer-review › Journal article – Annual report year: 2012
Multilocus Sequence Typing of Total-Genome-Sequenced Bacteria

Accurate strain identification is essential for anyone working with bacteria. For many species, multilocus sequence typing (MLST) is considered the "gold standard" of typing, but it is traditionally performed in an expensive and time-consuming manner. As the costs of whole-genome sequencing (WGS) continue to decline, it becomes increasingly available to scientists and routine diagnostic laboratories. Currently, the cost is below that of traditional MLST. The new challenges will be how to extract the relevant information from the large amount of data so as to allow for comparison over time and between laboratories. Ideally, this information should also allow for comparison to historical data. We developed a Web-based method for MLST of 66 bacterial species based on WGS data. As input, the method uses short sequence reads from four sequencing platforms or preassembled genomes. Updates from the MLST databases are downloaded monthly, and the best-matching MLST alleles of the specified MLST scheme are found using a BLAST-based ranking method. The sequence type is then determined by the combination of alleles identified. The method was tested on preassembled genomes from 336 isolates covering 56 MLST schemes, on short sequence reads from 387 isolates covering 10 schemes, and on a small test set of short sequence reads from 29 isolates for which the sequence type had been determined by traditional methods. The method presented here enables investigators to determine the sequence types of their isolates on the basis of WGS data. This method is publicly available at www.cbs.dtu.dk/services/MLST.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, National Food Institute, Division of Microbiology and Risk Assessment, Center for Systems Microbiology, Novo Nordisk Foundation Center for Biosustainability, CFB - Metagenomic Systems Biology
Pages: 1355-1361
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Main Research Area: Technical/natural sciences

Publication information
Journal: Journal of Clinical Microbiology
Volume: 50
Issue number: 4
ISSN (Print): 0095-1137
Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.57 SJR 2.14 SNIP 1.417
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.204 SNIP 1.448 CiteScore 3.56
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.205 SNIP 1.538 CiteScore 3.84
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 2.414 SNIP 1.646 CiteScore 4.18
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 2.114 SNIP 1.632 CiteScore 4.11
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 2.336 SNIP 1.698 CiteScore 4.27
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
Muscle ceramide content is similar after 3 weeks' consumption of fat or carbohydrate diet in a crossover design in patients with type 2 diabetes

This study aimed at investigating the effect of prolonged adaptation to fat- or carbohydrate-rich diet on muscle ceramide in type 2 diabetes patients, using a longitudinal crossover study. Eleven type 2 diabetes patients consumed isocaloric fat- or carbohydrate-rich diet for 3 weeks in random order. After each dietary intervention period, muscle glycogen, triacylglycerol and ceramide content and plasma concentrations of insulin, adiponectin, glucose and FFA were determined. Insulin resistance was assessed by HOMA2 calculation. After the dietary period, plasma glucose and insulin, insulin sensitivity, muscle glycogen, triacylglycerol and ceramide content were similar. Plasma adiponectin concentration was significantly higher after fat compared with carbohydrate-rich diet. Results indicated that following fat-rich diet intake muscle ceramide and triacylglycerol concentrations were not different compared with that after carbohydrate-rich diet. Furthermore, plasma adiponectin concentration was higher after fat-rich compared with carbohydrate-rich diet, but insulin sensitivity remained similar despite the major difference in dietary macronutrient composition.
Mutational properties of amino acid residues: implications for evolvability of phosphorylatable residues

As François Jacob pointed out over 30 years ago, evolution is a tinkering process, and, as such, relies on the genetic diversity produced by mutation subsequently shaped by Darwinian selection. However, there is one implicit assumption that is made when studying this tinkering process; it is typically assumed that all amino acid residues are equally likely to mutate or to result from a mutation. Here, by reconstructing ancestral sequences and computing mutational probabilities for all the amino acid residues, we refute this assumption and show extensive inequalities between different residues in terms of their mutational activity. Moreover, we highlight the importance of the genetic code and physico-chemical properties of the amino acid residues as likely causes of these inequalities and uncover serine as a mutational hot spot. Finally, we explore the consequences that these different mutational properties have on phosphorylation site evolution, showing that a higher degree of evolvability exists for phosphorylated threonine and, to a lesser extent, serine in
comparison with tyrosine residues. As exemplified by the suppression of serine's mutational activity in phosphorylation sites, our results suggest that the cell can fine-tune the mutational activities of amino acid residues when they reside in functional protein regions.
Mycobacterium leprae virulence-associated peptides are indicators of exposure to M. leprae in Brazil, Ethiopia and Nepal

Silent transmission of Mycobacterium leprae, as evidenced by stable leprosy incidence rates in various countries, remains a health challenge despite the implementation of multidrug therapy worldwide. Therefore, the development of tools for the early diagnosis of M. leprae infection should be emphasised in leprosy research. As part of the continuing effort to identify antigens that have diagnostic potential, unique M. leprae peptides derived from predicted virulence-associated proteins (group IV.A) were identified using advanced genome pattern programs and bioinformatics. Based on human leukocyte antigen (HLA)-binding motifs, we selected 21 peptides that were predicted to be promiscuous HLA-class I T-cell epitopes and eight peptides that were predicted to be HLA-class II restricted T-cell epitopes for field-testing in Brazil, Ethiopia and Nepal. High levels of interferon (IFN)-gamma were induced when peripheral blood mononuclear cells (PBMCs) from tuberculoid/borderline tuberculoid leprosy patients located in Brazil and Ethiopia were stimulated with the ML2055 p35 peptide. PBMCs that were isolated from healthy endemic controls living in areas with high leprosy prevalence (EChigh) in Ethiopia also responded to the ML2055 p35 peptide. The Brazilian EChigh group recognised the ML1358 p20 and ML1358 p24 peptides. None of the peptides were recognised by PBMCs from healthy controls living in non-endemic region. In Nepal, mixtures of these peptides induced the production of IFN-gamma by the PBMCs of leprosy patients and EChigh. Therefore, the M. leprae virulence-associated peptides identified in this study may be useful for identifying exposure to M. leprae in population with differing HLA polymorphisms.
Nature of bacterial colonization influences transcription of mucin genes in mice during the first week of life

In summary, our data show that development of the expression of genes encoding secreted (Muc2/Tff3) and membrane-bound (Muc1/Muc3/Muc4) mucus regulatory proteins, respectively, is distinct and that the onset of this development may be accelerated by specific groups of bacteria present or absent at the mucosal site.

General information
State: Published
Organisations: National Food Institute, Division of Food Microbiology, Center for Biological Sequence Analysis, University of Copenhagen
Authors: Bergström, A. (Intern), Kristensen, M. B. (Intern), Bahl, M. I. (Intern), Metzdorff, S. B. (Ekstern), Fink, L. N. (Intern), Frøkiær, H. (Ekstern), Licht, T. R. (Intern)
Number of pages: 7
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Main Research Area: Technical/natural sciences

Publication information
Journal: BMC Research Notes
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Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed yes
Scopus rating (2016): CiteScore 1.29 SJR 0.608 SNIP 0.669
Web of Science (2016): Indexed yes
Scopus rating (2015): SJR 0.722 SNIP 0.734 CiteScore 1.5
Scopus rating (2014): SJR 0.649 SNIP 0.782 CiteScore 1.43
Web of Science (2014): Indexed yes
Scopus rating (2013): SJR 0.644 SNIP 0.764 CiteScore 1.55
ISI indexed (2013): ISI indexed no
Scopus rating (2012): SJR 0.613 SNIP 0.648 CiteScore 1.55
ISI indexed (2012): ISI indexed no
Web of Science (2012): Indexed yes
Navigating cancer network attractors for tumor-specific therapy.

Cells employ highly dynamic signaling networks to drive biological decision processes. Perturbations to these signaling networks may attract cells to new malignant signaling and phenotypic states, termed cancer network attractors, that result in cancer development. As different cancer cells reach these malignant states by accumulating different molecular alterations, uncovering these mechanisms represents a grand challenge in cancer biology. Addressing this challenge will require new systems-based strategies that capture the intrinsic properties of cancer signaling networks and provide deeper understanding of the processes by which genetic lesions perturb these networks and lead to disease phenotypes. Network biology will help circumvent fundamental obstacles in cancer treatment, such as drug resistance and metastasis, empowering personalized and tumor-specific cancer therapies.
Neonatal Cytokine Profile in the Airway Mucosal Lining Fluid Is Skewed by Maternal Atopy

Rationale: Heredity from mother or father may impact differently in complex diseases, such as atopy. Maternal atopy is a stronger risk factor than paternal atopy for the development of atopy in the offspring. We hypothesized that mother's and father's atopy would have a differential imprinting on the cytokines and chemokines in the upper airway mucosal lining fluid of healthy neonates. Objectives: To study parental atopic imprinting on the cytokines and chemokines in the upper airway mucosal lining fluid of healthy neonates. Methods: Eighteen cytokines and chemokines were quantified in nasal mucosal lining fluid in 309 neonates from the novel unselected Copenhagen Prospective Study on Asthma in Childhood (COPSAC) birth cohort. Measurements and Main Results: Maternal, but not paternal, atopic status (asthma, hay fever, or eczema with or without sensitization) was associated with general down-regulation of all 18 mediators assessed by principal component analysis (overall P = 0.015). Conclusions: Maternal atopy, but not paternal atopy, showed a strong linkage with a suppressed mucosal cytokine and chemokine signature in asymptomatic neonates, suggesting imprinting by the maternal milieu in utero or perinatal life.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Copenhagen University Hospital, Imperial College London, University of Copenhagen
Authors: Folsgaard, N. V. (Ekstern), Chawes, B. L. (Ekstern), Rasmussen, M. A. (Ekstern), Bischoff, A. L. (Ekstern), Carson, C. G. (Ekstern), Stokholm, J. (Ekstern), Pedersen, L. (Ekstern), Hansel, T. T. (Ekstern), Bonnelykke, K. (Ekstern), Pedersen, S. B. (Intern), Bisgaard, H. (Ekstern)
Pages: 275-280
Publication date: 2012
NetMHCons: a consensus method for the major histocompatibility complex class I predictions

A key role in cell-mediated immunity is dedicated to the major histocompatibility complex (MHC) molecules that bind peptides for presentation on the cell surface. Several in silico methods capable of predicting peptide binding to MHC class I have been developed. The accuracy of these methods depends on the data available characterizing the binding specificity of the MHC molecules. It has, moreover, been demonstrated that consensus methods defined as combinations of two or more different methods led to improved prediction accuracy. This plethora of methods makes it very difficult for
the non-expert user to choose the most suitable method for predicting binding to a given MHC molecule. In this study, we have therefore made an in-depth analysis of combinations of three state-of-the-art MHC–peptide binding prediction methods (NetMHC, NetMHCpan and PickPocket). We demonstrate that a simple combination of NetMHC and NetMHCpan gives the highest performance when the allele in question is included in the training and is characterized by at least 50 data points with at least ten binders. Otherwise, NetMHCpan is the best predictor. When an allele has not been characterized, the performance depends on the distance to the training data. NetMHCpan has the highest performance when close neighbours are present in the training set, while the combination of NetMHCpan and PickPocket outperforms either of the two methods for alleles with more remote neighbours. The final method, NetMHCcons, is publicly available at www.cbs.dtu.dk/services/NetMHCcons, and allows the user in an automatic manner to obtain the most accurate predictions for any given MHC molecule.

**General information**
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology
Authors: Karosiene, E. (Intern), Lundegaard, C. (Intern), Lund, O. (Intern), Nielsen, M. (Intern)
Pages: 177-186
Publication date: 2012
Main Research Area: Technical/natural sciences

**Publication information**
Journal: Immunogenetics
Volume: 64
Issue number: 3
ISSN (Print): 0093-7711
Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.2 SJR 1.231 SNIP 0.703
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.551 SNIP 0.819 CiteScore 2.47
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.221 SNIP 0.833 CiteScore 2.28
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.231 SNIP 0.763 CiteScore 2.48
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.365 SNIP 0.943 CiteScore 2.91
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.304 SNIP 0.888 CiteScore 2.83
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.186 SNIP 0.847
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.486 SNIP 0.847
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 1.386 SNIP 0.774
Web of Science (2008): Indexed yes
Network Medicine Strikes a Blow against Breast Cancer

Drug development for complex diseases is shifting from targeting individual proteins or genes to systems-based attacks targeting dynamic network states. Lee et al. now reveal how the progressive rewiring of a signaling network over time following EGF receptor inhibition leaves triple-negative breast tumors vulnerable to a second, later hit with DNA-damaging drugs, demonstrating that time- and order-dependent drug combinations can be more efficacious in killing cancer cells.

General information

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Copenhagen
Authors: Erler, J. T. (Forskerdatabase), Linding, R. (Intern)
Pages: 731-733
Publication date: 2012
Main Research Area: Technical/natural sciences

Publication information

Journal: Cell
Volume: 149
Issue number: 4
ISSN (Print): 0092-8674
Ratings:
BFI (2018): BFI-level 3
BFI (2017): BFI-level 2
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 22.79 SJR 26.947 SNIP 4.959
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 27.696 SNIP 5.314 CiteScore 23.62
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 28.41 SNIP 5.687 CiteScore 24.91
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 27.895 SNIP 5.887 CiteScore 24.88
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Non-O1 Vibrio cholerae unlinked to cholera in Haiti

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Harvard Medical School, Brigham and Women's Hospital, Mount Sinai School of Medicine
Authors: Mekalanos, J. J. (Ekstern), Robins, W. (Ekstern), Ussery, D. (Intern), Davis, B. M. (Ekstern), Schadt, E. (Ekstern), Waldor, M. K. (Ekstern)
Pages: E3206
Publication date: 2012
Main Research Area: Technical/natural sciences

Publication information
Volume: 109
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ISSN (Print): 0027-8424
Ratings:
BFI (2018): BFI-level 2
BFI (2017): BFI-level 2
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 8.56 SJR 6.321 SNIP 2.629
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Of possible cheminformatics futures

For over a decade, cheminformatics has contributed to a wide array of scientific tasks from analytical chemistry and biochemistry to pharmacology and drug discovery; and although its contributions to decision making are recognized, the challenge is how it would contribute to faster development of novel, better products. Here we address the future of cheminformatics with primary focus on innovation. Cheminformatics developers often need to choose between "mainstream" (i.e., accepted, expected) and novel, leading-edge tools, with an increasing trend for open science. Possible
futures for cheminformatics include the worst case scenario (lack of funding, no creative usage), as well as the best case scenario (complete integration, from systems biology to virtual physiology). As "-omics" technologies advance, and computer hardware improves, compounds will no longer be profiled at the molecular level, but also in terms of genetic and clinical effects. Among potentially novel tools, we anticipate machine learning models based on free text processing, an increased performance in environmental cheminformatics, significant decision-making support, as well as the emergence of robot scientists conducting automated drug discovery research. Furthermore, cheminformatics is anticipated to expand the frontiers of knowledge and evolve in an open-ended, extensible manner, allowing us to explore multiple research scenarios in order to avoid epistemological "local information minimum trap".

**General information**

State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, University of New Mexico
Authors: Oprea, T. I. (Ekstern), Taboureau, O. (Intern), Bologa, C. G. (Ekstern)
Pages: 107-112
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Main Research Area: Technical/natural sciences

**Publication information**

Journal: Journal of Computer - Aided Molecular Design
Volume: 26
Issue number: 1
ISSN (Print): 0920-654X
Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): SJR 1.139 SNIP 1.189 CiteScore 3.23
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.977 SNIP 1.138 CiteScore 3.02
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.015 SNIP 0.963 CiteScore 2.84
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 0.901 SNIP 0.94 CiteScore 2.82
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.011 SNIP 0.931 CiteScore 3.13
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 0.939 SNIP 0.92 CiteScore 3.17
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.156 SNIP 1.16
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.067 SNIP 0.992
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 0.972 SNIP 0.971
Scopus rating (2007): SJR 0.771 SNIP 0.857
Scopus rating (2006): SJR 0.655 SNIP 0.855
Scopus rating (2005): SJR 0.893 SNIP 0.85
Scopus rating (2004): SJR 1.039 SNIP 0.931
Scopus rating (2003): SJR 0.688 SNIP 1.23
Scopus rating (2002): SJR 0.703 SNIP 0.983
Web of Science (2002): Indexed yes
Scopus rating (2001): SJR 0.469 SNIP 0.558
Scopus rating (2000): SJR 0.762 SNIP 0.63
Partial migration in fishes: definitions, methodologies and taxonomic distribution.

Partial migration, where populations are composed of both migratory and resident individuals, is extremely widespread across the animal kingdom. Researchers studying fish movements have long recognized that many fishes are partial migrants, however, no detailed taxonomic review has ever been published. In addition, previous work and synthesis has been hampered by a varied lexicon associated with this phenomenon in fishes. In this review, definitions and important concepts in partial migration research are discussed, and a classification system of the different forms of partial migration in fishes introduced. Next, a detailed taxonomic overview of partial migration in this group is considered. Finally, methodological approaches that ichthyologists can use to study this fascinating phenomenon are reviewed. Partial migration is more widespread amongst fishes than previously thought, and given the array of techniques available to fish biologists to study migratory variation the future of the field looks promising.

General information
State: Published
Organisations: National Institute of Aquatic Resources, Section for Freshwater Fisheries Ecology, Division of Food Chemistry, Center for Biological Sequence Analysis, Studieadministrationen
Authors: Chapman, B. B. (Ekstern), Skov, C. (Intern), Hulthén, K. (Ekstern), Brodersen, J. (Forskerdatabase), Nilsson, P. A. (Intern), Hansson, L. (Intern), Brönmark, C. (Ekstern)
Pages: 479-499
Publication date: 2012
Main Research Area: Technical/natural sciences

Publication information
Journal: Journal of Fish Biology
Volume: 81
Issue number: 2
ISSN (Print): 0022-1112
Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 1.57 SJR 0.741 SNIP 0.882
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.951 SNIP 0.935 CiteScore 1.64
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.944 SNIP 0.934 CiteScore 1.76
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.049 SNIP 1.118 CiteScore 1.98
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 0.93 SNIP 1.035 CiteScore 1.88
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 0.895 SNIP 0.946 CiteScore 1.66
ISI indexed (2011): ISI indexed yes
Peptide-MHC class I stability is a better predictor than peptide affinity of CTL immunogenicity

Efficient presentation of peptide-MHC class I (pMHC-I) complexes to immune T cells should benefit from a stable peptide-MHC-I interaction. However, it has been difficult to distinguish stability from other requirements for MHC-I binding, for example, affinity. We have recently established a high-throughput assay for pMHC-I stability. Here, we have generated a large database containing stability measurements of pMHC-I complexes, and re-examined a previously reported unbiased analysis of the relative contributions of antigen processing and presentation in defining cytotoxic T lymphocyte (CTL) immunogenicity [Assarsson et al., J. Immunol. 2007. 178: 7890–7901]. Using an affinity-balanced approach, we demonstrated that immunogenic peptides tend to be more stably bound to MHC-I molecules compared with nonimmunogenic peptides. We also developed a bioinformatics method to predict pMHC-I stability, which suggested that 30% of the nonimmunogenic binders hitherto classified as “holes in the T-cell repertoire” can be explained as being unstably bound to MHC-I. Finally, we suggest that nonoptimal anchor residues in position 2 of the peptide are particularly prone to cause unstable interactions with MHC-I. We conclude that the availability of accurate predictors of pMHC-I stability might be helpful in the elucidation of MHC-I restricted antigen presentation, and might be instrumental in future search strategies for MHC-I epitopes.

General information
State: Published
Organisations: Department of Systems Biology, Novo Nordisk Foundation Center for Biosustainability, Bacterial Cell Factories, CFB - Core Flow, Center for Biological Sequence Analysis, Technical University of Denmark, University of Copenhagen
Authors: Harndahl, M. N. (Forskerdatabase), Rasmussen, M. (Ekstern), Roder, G. (Ekstern), Dalggaard Pedersen, I. (Ekstern), Sørensen, M. (Forskerdatabase), Nielsen, M. (Intern), Buus, S. (Ekstern)
Pages: 1405-1416
Publication date: 2012
Main Research Area: Technical/natural sciences
Peptide-MHC class I stability is a stronger predictor of CTL immunogenicity than peptide affinity

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b Center for Biological Sequence Analysis, Department of Systems Biology, Technical University of Denmark, Denmark

Efficient presentation of peptide-MHC class I (pMHC-I) complexes to immune T cells should benefit from a stable peptide-MHC-I interaction. However, it has been difficult to distinguish stability from other requirements for MHC-I binding e.g. affinity. We have recently established a high-throughput assay for pMHC-I stability. Here, we have generated a large database containing stability measurements of pMHC-I complexes, and re-examined a previously reported unbiased analysis of the relative contributions of antigen processing and presentation in defining cytotoxic T lymphocyte (CTL) immunogenicity Assarsson et al., 2007. Using an affinity-balanced approach, we demonstrated that immunogenic peptides tend to be more stably bound to MHC-I molecules compared with non-immunogenic peptides. We also developed a bioinformatics method to predict pMHC-I stability, which suggested that 30% of the non-immunogenic binders hitherto classified as "holes in the T cell repertoire" can be explained as being unstably bound to MHC-I. Finally, we suggest that non-optimal anchor residues in position 2 of the peptide are particularly prone to cause unstable interactions with MHC-I. We conclude that the availability of accurate predictors of pMHC-I stability might be helpful in the elucidation of MHC-I restricted antigen presentation, and might be instrumental in future search strategies for MHC-I epitopes.

Reference

Plasmodium falciparum erythrocyte membrane protein 1 domain cassettes 8 and 13 are associated with severe malaria in children

The clinical outcome of Plasmodium falciparum infections ranges from asymptomatic parasitemia to severe malaria syndromes associated with high mortality. The virulence of P. falciparum infections is associated with the type of P. falciparum erythrocyte membrane protein 1 (PfEMP1) expressed on the surface of infected erythrocytes to anchor these to the vascular lining. Although var2csa, the var gene encoding the PfEMP1 associated with placental malaria, was discovered in 2003, the identification of the var/PfEMP1 variants associated with severe malaria in children has remained elusive. To identify var/PfEMP1 variants associated with severe disease outcome, we compared var transcript levels in parasites from 88 children with severe malaria and 40 children admitted to the hospital with uncomplicated malaria. Transcript analysis was performed by RT-quantitative PCR using a set of 42 primer pairs amplifying var subtype-specific
loci covering most var/PfEMP1 subtypes. In addition, we characterized the near-full-length sequence of the most prominently expressed var genes in three patients diagnosed with severe anemia and/or cerebral malaria. The combined analysis showed that severe malaria syndromes, including severe anemia and cerebral malaria, are associated with high transcript levels of PfEMP1 domain cassette 8-encoding var genes. Transcript levels of group A var genes, including genes encoding domain cassette 13, were also significantly higher in patients with severe syndromes compared with those with uncomplicated malaria. This study specifies the var/PfEMP1 types expressed in severe malaria in children, and thereby provides unique targets for future efforts to prevent and treat severe malaria infections.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Tanga Medical Research Centre, University of Copenhagen
Authors: Lavstsen, T. (Forskerdatabase), Turner, L. (Forskerdatabase), Saguti, F. (Ekstern), Magistrado, P. A. (Forskerdatabase), Rask, T. S. (Intern), Jespersen, J. S. (Ekstern), Wang, C. W. (Ekstern), Berger, S. S. (Forskerdatabase), Baraka, V. (Ekstern), Marquard, A. M. (Ekstern), Seguin-Orlando, A. (Forskerdatabase), Willerslev, E. (Forskerdatabase), Gilbert, M. T. P. (Forskerdatabase), Lusingu, J. P. A. (Forskerdatabase), Theander, T. G. (Forskerdatabase)
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BFI (2009): BFI-level 2
Scopus rating (2009): SJR 6.913 SNIP 2.544
Web of Science (2009): Indexed yes
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We have analyzed a natural population of the marine bacterium, Alteromonas macleodii, from a single sample of seawater to evaluate the genomic diversity present. We performed full genome sequencing of four isolates and 161 metagenomic fosmid clones, all of which were assigned to A. macleodii by sequence similarity. Out of the four strain genomes, A. macleodii deep ecotype (AltDE1) represented a different genome, whereas AltDE2 and AltDE3 were identical to the previously described AltDE. Although the core genome (~80%) had an average nucleotide identity of 98.51%, both AltDE and AltDE1 contained flexible genomic islands (fGIs), that is, genomic islands present in both genomes in the same genomic context but having different gene content. Some of the fGIs encode cell surface receptors known to be phage recognition targets, such as the O-chain of the lipopolysaccharide, whereas others have genes involved in physiological traits (e.g., nutrient transport, degradation, and metal resistance) denoting microniche specialization. The presence in metagenomic fosmids of genomic fragments differing from the sequenced strain genomes, together with the presence of new fGIs, indicates that there are at least two more A. macleodii clones present. The availability of three or more sequences overlapping the same genomic region also allowed us to estimate the frequency and distribution of recombination events among these different clones, indicating that these clustered near the genomic islands. The results indicate that this natural A. macleodii population has multiple clones with a potential for different phage susceptibility and exploitation of resources, within a seemingly unstructured habitat.

Polyclonality of Concurrent Natural Populations of Alteromonas macleodii

We have analyzed a natural population of the marine bacterium, Alteromonas macleodii, from a single sample of seawater to evaluate the genomic diversity present. We performed full genome sequencing of four isolates and 161 metagenomic fosmid clones, all of which were assigned to A. macleodii by sequence similarity. Out of the four strain genomes, A. macleodii deep ecotype (AltDE1) represented a different genome, whereas AltDE2 and AltDE3 were identical to the previously described AltDE. Although the core genome (~80%) had an average nucleotide identity of 98.51%, both AltDE and AltDE1 contained flexible genomic islands (fGIs), that is, genomic islands present in both genomes in the same genomic context but having different gene content. Some of the fGIs encode cell surface receptors known to be phage recognition targets, such as the O-chain of the lipopolysaccharide, whereas others have genes involved in physiological traits (e.g., nutrient transport, degradation, and metal resistance) denoting microniche specialization. The presence in metagenomic fosmids of genomic fragments differing from the sequenced strain genomes, together with the presence of new fGIs, indicates that there are at least two more A. macleodii clones present. The availability of three or more sequences overlapping the same genomic region also allowed us to estimate the frequency and distribution of recombination events among these different clones, indicating that these clustered near the genomic islands. The results indicate that this natural A. macleodii population has multiple clones with a potential for different phage susceptibility and exploitation of resources, within a seemingly unstructured habitat.

General information
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Prediction of drug efficacy for cancer treatment based on comparative analysis of chemosensitivity and gene expression data

The NCI60 database is the largest available collection of compounds with measured anti-cancer activity. The strengths and limitations for using the NCI60 database as a source of new anti-cancer agents are explored and discussed in relation to previous studies. We selected a sub-set of 2333 compounds with reliable experimental half maximum growth inhibitions (GI50) values for 30 cell lines from the NCI60 data set and evaluated their growth inhibitory effect (chemosensitivity) with respect to tissue of origin. This was done by identifying natural clusters in the chemosensitivity data set and in a data set of expression profiles of 1901 genes for the corresponding tumor cell lines. Five clusters were identified based on the gene expression data using self-organizing maps (SOM), comprising leukemia, melanoma, ovarian and prostate, basal breast, and luminal breast cancer cells, respectively. The strong difference in gene expression between basal and luminal breast cancer cells was reflected clearly in the chemosensitivity data. Although most compounds in the data set were of low potency, high efficacy compounds that showed specificity with respect to tissue of origin could be found. Furthermore, eight potential topoisomerase II inhibitors were identified using a structural similarity search. Finally, a set of genes with expression profiles that were significantly correlated with anti-cancer drug activity was identified. Our study demonstrates that the combined data sets, which provide comprehensive information on drug activity and gene expression profiles of tumor cell lines studied, are useful for identifying potential new active compounds.
Predictions versus high-throughput experiments in T-cell epitope discovery: competition or synergy?

Prediction methods as well as experimental methods for T-cell epitope discovery have developed significantly in recent years. High-throughput experimental methods have made it possible to perform full-length protein scans for epitopes restricted to a limited number of MHC alleles. The high costs and limitations regarding the number of proteins and MHC alleles that are feasibly handled by such experimental methods have made in silico prediction models of high interest. MHC binding prediction methods are today of a very high quality and can predict MHC binding peptides with high accuracy. This is possible for a large range of MHC alleles and relevant length of binding peptides. The predictions can easily be performed for complete proteomes of any size. Prediction methods are still, however, dependent on good experimental methods for validation, and should merely be used as a guide for rational epitope discovery. We expect prediction methods as well as experimental validation methods to continue to develop and that we will soon see clinical trials of products whose development has been guided by prediction methods.
Profiles of Genomic Instability in High-Grade Serous Ovarian Cancer Predict Treatment Outcome

Purpose: High-grade serous cancer (HGSC) is the most common cancer of the ovary and is characterized by chromosomal instability. Defects in homologous recombination repair (HRR) are associated with genomic instability in HGSC, and are exploited by therapy targeting DNA repair. Defective HRR causes uniparental deletions and loss of heterozygosity (LOH). Our purpose is to profile LOH in HGSC and correlate our findings to clinical outcome, and compare HGSC and high-grade breast cancers.

Experimental Design: We examined LOH and copy number changes using single nucleotide polymorphism array data from three HGSC cohorts and compared results to a cohort of high-grade breast cancers.

Results: LOH-based clustering divided HGSC into two clusters. The major group displayed extensive LOH and was further divided into two subgroups. The second group contained remarkably less LOH. BRCA1 promoter methylation was associated with the major group. LOH clusters were reproducible when validated in two independent HGSC datasets. LOH burden in the major cluster of HGSC was similar to triple-negative, and distinct from other high-grade breast cancers. Our analysis revealed an LOH cluster with lower treatment resistance and a significant correlation between LOH burden and PFS.

Conclusions: Separating HGSC by LOH-based clustering produces remarkably stable subgroups in three different cohorts. Patients in the various LOH clusters differed with respect to chemotherapy resistance, and the extent of LOH correlated with PFS. LOH burden may indicate vulnerability to treatment targeting DNA repair, such as PARP1 inhibitors.

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QSAR model for human pregnane X receptor (PXR) binding: Screening of environmental chemicals and correlations with genotoxicity, endocrine disruption and teratogenicity

The pregnane X receptor (PXR) has a key role in regulating the metabolism and transport of structurally diverse endogenous and exogenous compounds. Activation of PXR has the potential to initiate adverse effects, causing drug–drug interactions, and perturbing normal physiological functions. Therefore, identification of PXR ligands would be valuable information for pharmaceutical and toxicological research. In the present study, we developed a quantitative structure–activity relationship (QSAR) model for the identification of PXR ligands using data based on a human PXR binding assay. A total of 631 molecules, representing a variety of chemical structures, constituted the training set of the model. Cross-validation of the model showed a sensitivity of 82%, a specificity of 85%, and a concordance of 84%. The developed model provided knowledge about molecular descriptors that may influence the binding of molecules to PXR. The model was used to screen a large inventory of environmental chemicals, of which 47% was found to be within domain of the model. Approximately 35% of the chemicals within domain were predicted to be PXR ligands. The predicted PXR ligands were found to be overrepresented among chemicals predicted to cause adverse effects, such as genotoxicity, teratogenicity, estrogen receptor activation and androgen receptor antagonism compared to chemicals not causing these effects. The developed model may be useful as a tool for predicting potential PXR ligands and for providing mechanistic information of toxic effects of chemicals.

General information
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Organisations: National Food Institute, Division of Toxicology and Risk Assessment, Center for Biological Sequence Analysis
Authors: Dybdahl, M. (Intern), Nikolov, N. G. (Intern), Wedebye, E. B. (Intern), Jónsdóttir, S. Ó. (Intern), Niemelä, J. R. (Intern)
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BFI (2013): BFI-level 2
Scopus rating (2013): SJR 1.424 SNIP 1.291 CiteScore 4.19
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Scopus rating (2012): SJR 1.574 SNIP 1.412 CiteScore 4.44
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Scopus rating (2008): SJR 1.302 SNIP 1.16
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Scopus rating (2007): SJR 1.402 SNIP 1.329
Scopus rating (2006): SJR 1.385 SNIP 1.31
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 1.194 SNIP 1.181
Scopus rating (2004): SJR 1.113 SNIP 1.069
Web of Science (2004): Indexed yes
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Recommendations for Mass Spectrometry Data Quality Metrics for Open Access Data (Corollary to the Amsterdam Principles)

Policies supporting the rapid and open sharing of proteomic data are being implemented by the leading journals in the field. The proteomics community is taking steps to ensure that data are made publicly accessible and are of high quality, a challenging task that requires the development and deployment of methods for measuring and documenting data quality metrics. On September 18, 2010, the United States National Cancer Institute convened the "International Workshop on Proteomic Data Quality Metrics" in Sydney, Australia, to identify and address issues facing the development and use of such methods for open access proteomics data. The stakeholders at the workshop enumerated the key principles underlying a framework for data quality assessment in mass spectrometry data that will meet the needs of the research community, journals, funding agencies, and data repositories. Attendees discussed and agreed up on two primary needs for the wide use of quality metrics: 1) an evolving list of comprehensive quality metrics and 2) standards accompanied by software analytics. Attendees stressed the importance of increased education and training programs to promote reliable protocols in proteomics. This workshop report explores the historic precedents, key discussions, and necessary next steps to enhance the quality of open access data. By agreement, this article is published simultaneously in the Journal of Proteome Research, Molecular and Cellular Proteomics, Proteomics, and Proteomics Clinical Applications as a public service to the research community. The peer review process was a coordinated effort conducted by a panel of referees selected by the journals.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, National Cancer Institute, Agilent Research Laboratories, Macquarie University, US National Institute of Health, University of Victoria, University of California, Institute for Systems Biology, Johns Hopkins University, Luxembourg Clinical Proteomics Center, QIMR Berghofer Medical Research Institute, Northeastern University, European Bioinformatics Institute, Thermo Fisher Scientific, AB SCIEX, European Commission, Wiley-VCH, Weinheim, Hoffmann-La Roche, Cellular and Molecular Logic Unit, University of Michigan, University of Georgia, La Trobe University, Pacific Northwest National Laboratory, Vanderbilt-Ingram Cancer Center, National Institute of Standards and Technology, The Scripps Research Institute, Agilent Technologies
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Web of Science (2008): Indexed yes
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Web of Science (2007): Indexed yes
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Web of Science (2006): Indexed yes
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Web of Science (2005): Indexed yes
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Web of Science (2004): Indexed yes
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Policies supporting the rapid and open sharing of proteomic data are being implemented by the leading journals in the field. The proteomics community is taking steps to ensure that data are made publicly accessible and are of high quality, a challenging task that requires the development and deployment of methods for measuring and documenting data quality metrics. On September 18, 2010, the United States National Cancer Institute convened the “International Workshop on Proteomic Data Quality Metrics” in Sydney, Australia, to identify and address issues facing the development and use of such methods for open access proteomics data. The stakeholders at the workshop enumerated the key principles underlying a framework for data quality assessment in mass spectrometry data that will meet the needs of the research community, journals, funding agencies, and data repositories. Attendees discussed and agreed up on two primary needs for the wide use of quality metrics: 1) an evolving list of comprehensive quality metrics and 2) standards accompanied by software analytics. Attendees stressed the importance of increased education and training programs to promote reliable protocols in proteomics. This workshop report explores the historic precedents, key discussions, and necessary next steps to enhance the quality of open access data. By agreement, this article is published simultaneously in the Journal of Proteome Research, Molecular and Cellular Proteomics, Proteomics, and Proteomics Clinical Applications as a public service to the research community. The peer review process was a coordinated effort conducted by a panel of referees selected by the journals.

**General information**
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, National Cancer Institute, Agilent Research Laboratories, Macquarie University, US National Institute of Health, University of Victoria, University of California, Institute for Systems Biology, Johns Hopkins University, Luxembourg Clinical Proteomics Center, QIMR Berghofer Medical Research Institute, Northeastern University, European Bioinformatics Institute, Thermo Fisher Scientific, AB SCIEX, European Commission, Wiley-VCH, Weinheim, Hoffmann-La Roche, Cellular and Molecular Logic Unit,
Relative entropy differences in bacterial chromosomes, plasmids, phages and genomic islands

**Background:** We sought to assess whether the concept of relative entropy (information capacity), could aid our understanding of the process of horizontal gene transfer in microbes. We analyzed the differences in information capacity between prokaryotic chromosomes, genomic islands (GI), phages, and plasmids. Relative entropy was estimated using the Kullback-Leibler measure.

**Results:** Relative entropy was highest in bacterial chromosomes and had the sequence chromosomes > GI > phage > plasmid. There was an association between relative entropy and AT content in chromosomes, phages, plasmids and GIs with the strongest association being in phages. Relative entropy was also found to be lower in the obligate intracellular Mycobacterium leprae than in the related M. tuberculosis when measured on a shared set of highly conserved genes.

**Conclusions:** We argue that relative entropy differences reflect how plasmids, phages and GIs interact with microbial host chromosomes and that all these biological entities are, or have been, subjected to different selective pressures. The rate at which amelioration of horizontally acquired DNA occurs within the chromosome is likely to account for the small differences between chromosomes and stably incorporated GIs compared to the transient or independent replicons such as phages and plasmids.

**General information**

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**Organisations:** Department of Systems Biology, Center for Biological Sequence Analysis, Norwegian School of Veterinary Science, Wageningen IMARES, National Veterinary Institute, Norwegian University of Life Sciences

**Authors:** Bohlin, J. (Ekstern), van Passel, M. W. J. (Ekstern), Snipen, L. (Ekstern), Kristoffersen, A. B. (Ekstern), Ussery, D. (Intern), Hardy, S. P. (Ekstern)

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- Scopus rating (2015): SJR 2.287 SNIP 1.172 CiteScore 4.3
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- Web of Science (2013): Indexed yes
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- Web of Science (2012): Indexed yes
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- ISI indexed (2011): ISI indexed yes
The interaction between antibodies and antigens is one of the most important immune system mechanisms for clearing infectious organisms from the host. Antibodies bind to antigens at sites referred to as B-cell epitopes. Identification of the exact location of B-cell epitopes is essential in several biomedical applications such as: rational vaccine design, development of disease diagnostics and immunotherapeutics. However, experimental mapping of epitopes is resource intensive making in silico methods an appealing complementary approach. To date, the reported performance of methods for in silico mapping of B-cell epitopes has been moderate. Several issues regarding the evaluation data sets may however have led to the performance values being underestimated: Rarely, all potential epitopes have been mapped on an antigen, and antibodies are generally raised against the antigen in a given biological context not against the antigen monomer. Improper dealing with these aspects leads to many artificial false positive predictions and hence to incorrect low performance values. To demonstrate the impact of proper benchmark definitions, we here present an updated version of the DiscoTope method incorporating a novel spatial neighborhood definition and half-sphere exposure as surface measure. Compared to other state-of-the-art prediction methods, Discotope-2.0 displayed improved performance both in cross-validation and in independent evaluations. Using DiscoTope-2.0, we assessed the impact on performance when using proper benchmark definitions. For 13 proteins in the training data set where sufficient biological information was available to make a proper benchmark redefinition, the average AUC performance was improved from 0.791 to 0.824. Similarly, the average AUC performance on an independent evaluation data set improved from 0.712 to 0.727. Our results thus demonstrate that given proper benchmark definitions, B-cell epitope prediction methods achieve highly significant predictive performances suggesting these tools to be a powerful asset in rational epitope discovery. The updated version...
Scale-free behaviour of amino acid pair interactions in folded proteins

The protein structure is a cumulative result of interactions between amino acid residues interacting with each other through space and/or chemical bonds. Despite the large number of high resolution protein structures, the "protein structure code" has not been fully identified. Our manuscript presents a novel approach to protein structure analysis in order to identify rules for spatial packing of amino acid pairs in proteins. We have investigated 8706 high resolution non-

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Scale-free behaviour of amino acid pair interactions in folded proteins

The protein structure is a cumulative result of interactions between amino acid residues interacting with each other through space and/or chemical bonds. Despite the large number of high resolution protein structures, the "protein structure code" has not been fully identified. Our manuscript presents a novel approach to protein structure analysis in order to identify rules for spatial packing of amino acid pairs in proteins. We have investigated 8706 high resolution non-
redundant protein chains and quantified amino acid pair interactions in terms of solvent accessibility, spatial and sequence distance, secondary structure, and sequence length. The number of pairs found in a particular environment is stored in a cell in an 8 dimensional data tensor. When plotting the cell population against the number of cells that have the same population size, a scale free organization is found. When analyzing which amino acid paired residues contributed to the cells with a population above 50, pairs of Ala, Ile, Leu and Val dominate the results. This result is statistically highly significant. We postulate that such pairs form “structural stability points” in the protein structure. Our data shows that they are in buried α-helices or β-strands, in a spatial distance of 3.8–4.3Å and in a sequence distance .4 residues. We speculate that the scale free organization of the amino acid pair interactions in the 8D protein structure combined with the clear dominance of pairs of Ala, Ile, Leu and Val is important for understanding the very nature of the protein structure formation. Our observations suggest that protein structures should be considered as having a higher dimensional organization.

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Authors: Petersen, S. B. (Ekstern), Neves-Petersen, M. T. (Ekstern), Mortensen, R. J. (Ekstern), Henriksen, S. B. (Ekstern), Geertz-Hansen, H. M. (Intern)
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Seq2Logo: a method for construction and visualization of amino acid binding motifs and sequence profiles including sequence weighting, pseudo counts and two-sided representation of amino acid enrichment and depletion

Seq2Logo is a web-based sequence logo generator. Sequence logos are a graphical representation of the information content stored in a multiple sequence alignment (MSA) and provide a compact and highly intuitive representation of the position-specific amino acid composition of binding motifs, active sites, etc. in biological sequences. Accurate generation of sequence logos is often compromised by sequence redundancy and low number of observations. Moreover, most methods available for sequence logo generation focus on displaying the position-specific enrichment of amino acids, discarding the equally valuable information related to amino acid depletion. Seq2logo aims at resolving these issues allowing the user to include sequence weighting to correct for data redundancy, pseudo counts to correct for low number of observations and different logotype representations each capturing different aspects related to amino acid enrichment and depletion. Besides allowing input in the format of peptides and MSA, Seq2Logo accepts input as Blast sequence profiles, providing easy access for non-expert end-users to characterize and identify functionally conserved/variable amino acids in any given protein of interest. The output from the server is a sequence logo and a PSSM. Seq2Logo is available at http://www.cbs.dtu.dk/biotools/Seq2Logo (14 May 2012, date last accessed).
Sequencing Chromosomal Abnormalities Reveals Neurodevelopmental Loci that Confer Risk across Diagnostic Boundaries

Sequencing of balanced chromosomal abnormalities, combined with convergent genomic studies of gene expression, copy-number variation, and genome-wide association, identifies 22 new loci that contribute to autism and related neurodevelopmental disorders. These data support a polygenic risk model for autism and provide new insight into how different types of mutations of the same genes can lead to variable disease phenotypes that manifest at different stages of life.

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Sharing programming resources between Bio* projects through remote procedure call and native call stack strategies.

Open-source software (OSS) encourages computer programmers to reuse software components written by others. In evolutionary bioinformatics, OSS comes in a broad range of programming languages, including C/C++, Perl, Python, Ruby, Java, and R. To avoid writing the same functionality multiple times for different languages, it is possible to share components by bridging computer languages and Bio* projects, such as BioPerl, Biopython, BioRuby, BioJava, and R/Bioconductor. In this chapter, we compare the two principal approaches for sharing software between different programming languages: either by remote procedure call (RPC) or by sharing a local call stack. RPC provides a language-independent protocol over a network interface; examples are RSOAP and Rserve. The local call stack provides a between-language mapping not over the network interface, but directly in computer memory; examples are R bindings, RPy, and languages sharing the Java Virtual Machine stack. This functionality provides strategies for sharing of software between Bio* projects, which can be exploited more often. Here, we present cross-language examples for sequence translation, and measure throughput of the different options. We compare calling into R through native R, RSOAP, Rserve, and RPy interfaces, with the performance of native BioPerl, Biopython, BioJava, and BioRuby implementations, and with call stack bindings to BioJava and the European Molecular Biology Open Software Suite. In general, call stack approaches outperform native Bio* implementations and these, in turn, outperform RPC-based approaches. To test and compare strategies, we provide a downloadable BioNode image with all examples, tools, and libraries included. The BioNode image can be run on VirtualBox-supported operating systems, including Windows, OSX, and Linux.

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snpTree - a web-server to identify and construct SNP trees from whole genome sequence data.

Background

The advances and decreasing economical cost of whole genome sequencing (WGS), will soon make this technology available for routine infectious disease epidemiology. In epidemiological studies, outbreak isolates have very little diversity and require extensive genomic analysis to differentiate and classify isolates. One of the successfully and broadly used methods is analysis of single nucleotide polymorphisms (SNPs). Currently, there are different tools and methods to identify SNPs including various options and cut-off values. Furthermore, all current methods require bioinformatic skills. Thus, we lack a standard and simple automatic tool to determine SNPs and construct phylogenetic tree from WGS data.

Results

Here we introduce snpTree, a server for online-automatic SNPs analysis. This tool is composed of different SNPs analysis suites, perl and python scripts. snpTree can identify SNPs and construct phylogenetic trees from WGS as well as from assembled genomes or contigs. WGS data in fastq format are aligned to reference genomes by BWA while contigs in fasta format are processed by Nucmer. SNPs are concatenated based on position on reference genome and a tree is constructed from concatenated SNPs using FastTree and a perl script. The online server was implemented by HTML, Java and python script.

The server was evaluated using four published bacterial WGS data sets (V. cholerae, S. aureus CC398, S. Typhimurium and M. tuberculosis). The evaluation results for the first three cases was consistent and concordant for both raw reads and assembled genomes. In the latter case the original publication involved extensive filtering of SNPs, which could not be repeated using snpTree.

Conclusions

The snpTree server is an easy to use option for rapid standardised and automatic SNP analysis in epidemiological studies also for users with limited bioinformatic experience. The web server is freely accessible at http://www.cbs.dtu.dk/services/snpTree-1.0/.

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System chemical biology studies of endocrine disruptors

Endocrine disrupting chemicals (EDCs) alter hormonal balance and other physiological systems through inappropriate developmental or adult exposure, perturbing the reproductive function of further generations. While disruption of key receptors (e.g., estrogen, androgen, and thyroid) at the ligand binding domain (LBD) has been associated with EDCs, a significant number of EDCs do not appear to influence the LBDs of these receptors. Therefore, we evaluated the potential biological effects of EDCs in humans with the aim to rationalize the etiology of certain disorders associated with the reproductive function. We compiled 675 (known or suspected) EDCs and examined chemical-protein associations via ChemProt [http://www.cbs.dtu.dk/services/ChemProt/]. Over 1000 proteins susceptible to perturbation by one or more EDCs were subject to a protein-protein interaction network evaluation. Synergistic EDC effects resulting in the perturbation of different proteins associated to particular diseases (e.g., cryptorchidism) were evaluated.

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Telomeric Allelic Imbalance Indicates Defective DNA Repair and Sensitivity to DNA-Damaging Agents

DNA repair competency is one determinant of sensitivity to certain chemotherapy drugs, such as cisplatin. Cancer cells with intact DNA repair can avoid the accumulation of genome damage during growth and also can repair platinum-induced DNA damage. We sought genomic signatures indicative of defective DNA repair in cell lines and tumors and correlated these signatures to platinum sensitivity. The number of subchromosomal regions with allelic imbalance extending to the telomere (NtAI) predicted cisplatin sensitivity in vitro and pathologic response to preoperative cisplatin treatment in patients with triple-negative breast cancer (TNBC). In serous ovarian cancer treated with platinum-based chemotherapy, higher levels of NtAI forecast a better initial response. We found an inverse relationship between BRCA1 expression and NtAI in sporadic TNBC and serous ovarian cancers without BRCA1 or BRCA2 mutation. Thus, accumulation of telomeric allelic imbalance is a marker of platinum sensitivity and suggests impaired DNA repair. SIGNIFICANCE: Mutations in BRCA genes cause defects in DNA repair that predict sensitivity to DNA damaging agents, including platinum; however, some patients without BRCA mutations also benefit from these agents. NtAI, a genomic measure of unfaithfully repaired DNA, may identify cancer patients likely to benefit from treatments targeting defective DNA repair. Cancer Discov; 2(4); 366–75. ©2012 AACR. This article is highlighted in the In This Issue feature, p. 288

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The Cancer Exome Generated by Alternative mRNA Splicing Dilutes Predicted HLA Class I Epitope Density

Several studies have shown that cancers actively regulate alternative splicing. Altered splicing mechanisms in cancer lead to cancer-specific transcripts different from the pool of transcripts occurring only in healthy tissue. At the same time, altered presentation of HLA class I epitopes is frequently observed in various types of cancer. Down-regulation of genes related to HLA class I antigen processing has been observed in several cancer types, leading to fewer HLA class I antigens on the cell surface. Here, we use a peptidome wide analysis of predicted alternative splice forms, based on a publicly available database, to show that peptides over-represented in cancer splice variants comprise significantly fewer predicted HLA class I epitopes compared to peptides from normal transcripts. Peptides over-represented in cancer transcripts are in the case of the three most common HLA class I supertype representatives consistently found to contain fewer predicted epitopes compared to normal tissue. We observed a significant difference in amino acid composition between protein sequences associated with normal versus cancer tissue, as transcripts found in cancer are enriched with hydrophilic amino acids. This variation contributes to the observed significant lower likelihood of cancer-specific peptides to be predicted epitopes compared to peptides found in normal tissue.

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The Duffy-Binding-Like β domain (DBLβ) of the Plasmodium falciparum erythrocyte membrane protein 1 (PfEMP1) variant, PFD1235w, binds ICAM1

Plasmodium falciparum is by far the most virulent human malaria parasite. P. falciparum variant erythrocyte surface antigens, known as PfEMP1, play a crucial role in malaria pathogenesis as they mediate adhesion to host endothelial receptors. The PfEMP1 variant, PFD1235w, encoded by the 3D7 group A var gene has been associated with severe malaria and erythrocytes infected with parasites expressing PFD1235w binds ICAM1. To identify the PFD1235w domain(s) responsible for ICAM1 binding we used recombinant protein (NTS, CIDR1, DBL1-CIDR1, DBLdomains, CIDR2) and ICAM1 in Enzyme-Linked Immuno-Sorbent Assay (ELISA). We identified the DBLβ3-domain 4 (D4) of the PFD1235w to be responsible for ICAM1 binding in a concentration dependent manner and the binding could be inhibited by a panel of monoclonal ICAM1 antibodies. By using 3D protein modeling we generated different PfEMP1 hybrid molecules and truncated proteins in order to determine the essential binding region of the DBLβ3-D4 involved in the ICAM1 interaction. The hybrid molecules and truncated proteins were tested for ICAM1 binding in ELISA. Results indicate that the C-terminal of DBLβ3-D4 is directly involved in the ICAM1 interaction, while the N-terminal region is necessary for correct protein conformation. These results contribute to a greater understanding of how PfEMP1 interacts with endothelial receptors such as ICAM1 and provide a model for future analysis of other PfEMP1 variants adhering to ICAM1.
The impact of network biology in pharmacology and toxicology

With the need to investigate alternative approaches and emerging technologies in order to increase drug efficacy and reduce adverse drug effects, network biology offers a novel way of approaching drug discovery by considering the effect of a molecule and protein's function in a global physiological environment. By studying drug action across multiple scales of complexity, from molecular to cellular and tissue level, network-based computational methods have the potential to improve our understanding of the impact of chemicals in human health. In this review we present the available large-scale databases and tools that allow integration and analysis of such information for understanding the properties of small molecules in the context of cellular networks. With the recent advances in the omics area, global integrative approaches are necessary to cope with the massive amounts of data, and biomedical researchers are urged to implement new types of analyses that can lead to new therapeutic interventions with increased safety and efficacy compared with existing medications.

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Scopus rating (2010): SJR 0.418 SNIP 0.88
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The role of miRNA regulation in cancer progression and drug resistance

This PhD thesis presents the work carried out at Center for Biological Sequence Analysis, Technical University of Denmark. The projects presented in this thesis are purely bioinformatic in nature. Included in this thesis are the two projects that focus on the gene regulatory events mediated by miRNAs in the context of cancer biology, drug resistance and disease progression.

The first project described in Chapter 6 addresses the problem of tamoxifen resistance, an anti-estrogen drug that is generally highly effective in the treatment of ER-positive breast cancers. The underlying molecular mechanisms for the acquired resistance to tamoxifen are not very well understood. Therefore, with the aid of miRNA and gene expression profiles for MCF7/S0.5 (tamoxifen sensitive) and three MCF7/S0.5 derived tamoxifen resistant cell lines, we obtained several miRNA-mediated regulatory events in the tamoxifen resistant cell lines. Following a systems biology approach of integrating evidences of functional interactions such as transcription factor (TF)-miRNA interactions, we have identified a number of biologically relevant pathways involved in the development of tamoxifen resistance.

Chapter 7 presents a study highlighting the role of miRNAs in the transformation of ocular mucosa associated lymphoid tissue lymphoma (MALT) to the high-grade diffuse large B-cell lymphoma (DLBCL) of eye. Several tumor suppressive miRNAs were found to be dysregulated in DLBCL, suggesting their possible role in disease transformation. Many of those were under transcriptional regulation by MYC and NFKB1, the key transcription factors involved in lymphomas. Furthermore, upstream regulators of NFKB1 were also repressed, suggesting a possible loss of regulation of NFKB1 may contribute to the activation of NF-κB signaling pathway, and thereby to the disease transformation.

In summary, this thesis focuses on regulatory role of miRNAs in drug resistance and disease progression. The findings provide hints toward various biologically and perhaps therapeutically relevant gene regulatory events. This thesis demonstrates the right choice of data analysis techniques combined with a systems biology approach provides better understanding of the complex biology.
The transcriptional landscape and small RNAs of Salmonella enterica serovar Typhimurium

More than 50 y of research have provided great insight into the physiology, metabolism, and molecular biology of Salmonella enterica serovar Typhimurium (S. Typhimurium), but important gaps in our knowledge remain. It is clear that a precise choreography of gene expression is required for Salmonella infection, but basic genetic information such as the global locations of transcription start sites (TSSs) has been lacking. We combined three RNA-sequencing techniques and two sequencing platforms to generate a robust picture of transcription in S. Typhimurium. Differential RNA sequencing identified 1,873 TSSs on the chromosome of S. Typhimurium SL1344 and 13% of these TSSs initiated antisense transcripts. Unique findings include the TSSs of the virulence regulators phoP, slyA, and invF. Chromatin immunoprecipitation revealed that RNA polymerase was bound to 70% of the TSSs, and two-thirds of these TSSs were associated with σ70 (including phoP, slyA, and invF) from which we identified the −10 and −35 motifs of σ70-dependent S. Typhimurium gene promoters. Overall, we corrected the location of important genes and discovered 18 times more promoters than identified previously. S. Typhimurium expresses 140 small regulatory RNAs (sRNAs) at early stationary phase, including 60 newly identified sRNAs. Almost half of the experimentally verified sRNAs were found to be unique to the Salmonella genus, and

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TLR2 Controls Intestinal Carcinogen Detoxication by CYP1A1.

Intestinal cytochrome P450 subclass 1A1 (CYP1A1) contributes to a metabolic "shield" protecting the host from ingested carcinogens such as polycyclic aromatic hydrocarbons (PAH). The expression of CYP1 (including CYP1A2 and CYP1B1) is considered to depend solely on a heterodimeric transcription factor consisting of the arylhydrocarbon receptor (AHR) and the AHR nuclear translocator (ARNT). So far, no interference has been noted between the regulation of CYP1 and the activation of Toll-like receptor 2 (TLR2), which modulates the inflammatory response to bacterial cell wall components in immune cells and enterocytes. Here we report that intestinal CYP1A1 is silenced in TLR2-deficient mice, even when under exposure to the carcinogenic PAH benzo[a]pyrene (BaP). In contrast, hepatic CYP1A1 was moderately induced in TLR2-deficient mice without restoring their ability to clear BaP from systemic circulation, as present in wild-type animals. After feeding of BaP for 21 days, only TLR2(-/-) mice, but not their wild type littermates developed polyps in the colon. Gene expressions and protein concentrations of AHR and ARNT in the intestine did not differ between the genotypes. In conclusion, the presence of ligands for TLR2 of bacterial origin seems to be crucial for detoxication of luminal carcinogens by CYP1A1 in the intestine. This unprecedented finding indicates a complex interplay between the immune system of the host and intestinal bacteria with detoxication mechanisms. This highlights the relevance of intestinal microbiota when trying to unravel pathways present in mammals and opens new perspectives for research in human health.
Toxicogenomics Investigation Under the eTOX Project

Attrition of drug candidates during pre-clinical development due to toxicity, especially hepatotoxicity and nephrotoxicity, is an important and continuing problem in the pharmaceutical industry. The reasons for this trend may be multifactorial and there is a need to improve toxicity testing paradigms within the industry. Microarray technologies have the ability to generate massive amounts of gene expression information as an initial step to decipher the molecular mechanisms of toxicologic changes, i.e. toxicogenomics. In the context of the eTOX consortium, one of public private partnership within the framework of the European Innovative Medicines Initiative (IMI), we will discuss here how the integration and analysis of toxicogenomics data can help to understanding the mechanism of toxicity of a compound and so reduce the risk of late-stage failure in pharmaceutical development.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Novo Nordisk Foundation Center for Biosustainability, CFB - Metagenomic Systems Biology, Wellcome Trust Genome Campus
Number of pages: 5
Publication date: 2012
Main Research Area: Technical/natural sciences

Transcriptome Dynamics of Pseudomonas putida KT2440 under Water Stress

Water deprivation can be a major stressor to microbial life in surface and subsurface soil. In unsaturated soils, the matric potential (Ψm) is often the main component of the water potential, which measures the thermodynamic availability of water. A low matric potential usually translates into water forming thin liquid films in the soil pores. Little is known of how bacteria respond to such conditions, where, in addition to facing water deprivation that might impair their metabolism, they have to adapt their dispersal strategy as swimming motility may be compromised. Using the pressurized porous surface model (PPSM), which allows creation of thin liquid films by controlling Ψm, we examined the transcriptome dynamics of Pseudomonas putida KT2440. We identified the differentially expressed genes in cells exposed to a mild matric stress (–0.4 MPa) for 4, 24, or 72 h. The major response was detected at 4 h before gradually disappearing. Upregulation of alginate genes was notable in this early response. Flagellar genes were not downregulated, and the microarray data even suggested increasing expression as the stress prolonged. Moreover, we tested the effect of polyethylene glycol 8000 (PEG 8000), a nonpermeating solute often used to simulate Ψm, on the gene expression profile and detected a different profile than that observed by directly imposing Ψm. This study is the first transcriptome profiling of KT2440 under directly controlled Ψm and also the first to show the difference in gene expression profiles between a PEG 8000-simulated and a directly controlled Ψm.

General information
State: Published
Organisations: Environmental Chemistry, Department of Environmental Engineering, Center for Biological Sequence Analysis, Department of Systems Biology
Authors: Güleiz, G. (Intern), Dechesne, A. (Intern), Workman, C. (Intern), Smets, B. F. (Intern)
Pages: 676-683
Publication date: 2012
Main Research Area: Technical/natural sciences
Issue number: 3
ISSN (Print): 0099-2240
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  BFI (2018): BFI-level 2
  BFI (2017): BFI-level 2
  Web of Science (2017): Indexed yes
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  Scopus rating (2016): CiteScore 4.08
  Web of Science (2016): Indexed yes
  BFI (2015): BFI-level 2
  Scopus rating (2015): SJR 1.891 SNIP 1.308 CiteScore 4.14
  Web of Science (2015): Indexed yes
  BFI (2014): BFI-level 2
  Scopus rating (2014): SJR 1.857 SNIP 1.384 CiteScore 4.02
  Web of Science (2014): Indexed yes
  BFI (2013): BFI-level 2
  Scopus rating (2013): SJR 1.899 SNIP 1.414 CiteScore 4.25
  ISI indexed (2013): ISI indexed yes
  Web of Science (2013): Indexed yes
  BFI (2012): BFI-level 2
  Scopus rating (2012): SJR 1.975 SNIP 1.429 CiteScore 4.29
  ISI indexed (2012): ISI indexed yes
  Web of Science (2012): Indexed yes
  BFI (2011): BFI-level 2
  Scopus rating (2011): SJR 1.914 SNIP 1.455 CiteScore 4.12
  ISI indexed (2011): ISI indexed yes
  Web of Science (2011): Indexed yes
  BFI (2010): BFI-level 2
  Scopus rating (2010): SJR 1.887 SNIP 1.436
  Web of Science (2010): Indexed yes
  BFI (2009): BFI-level 2
  Scopus rating (2009): SJR 1.972 SNIP 1.528
  Web of Science (2009): Indexed yes
  BFI (2008): BFI-level 2
  Scopus rating (2008): SJR 2.156 SNIP 1.572
  Web of Science (2008): Indexed yes
  Scopus rating (2007): SJR 2.043 SNIP 1.647
  Web of Science (2007): Indexed yes
  Scopus rating (2006): SJR 2.054 SNIP 1.602
  Web of Science (2006): Indexed yes
  Scopus rating (2005): SJR 2.074 SNIP 1.653
  Web of Science (2005): Indexed yes
  Scopus rating (2004): SJR 2.108 SNIP 1.648
  Web of Science (2004): Indexed yes
  Scopus rating (2003): SJR 2.097 SNIP 1.821
  Web of Science (2003): Indexed yes
  Scopus rating (2002): SJR 2.046 SNIP 1.754
  Web of Science (2002): Indexed yes
  Scopus rating (2001): SJR 1.989 SNIP 1.736
  Web of Science (2001): Indexed yes
  Scopus rating (2000): SJR 1.957 SNIP 1.758
  Web of Science (2000): Indexed yes
  Scopus rating (1999): SJR 2.3 SNIP 1.732
Two novel methods for using genome sequences to infer taxonomy

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University College Dublin
Authors: Ussery, D. (Intern), Gordon, S. V. (Ekstern)
Pages: 1414
Publication date: 2012
Main Research Area: Technical/natural sciences

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Journal: Microbiology
Volume: 158
Issue number: Pt 6
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Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 1.56 SJR 0.805 SNIP 0.648
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.136 SNIP 0.834 CiteScore 2.05
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.448 SNIP 0.978 CiteScore 2.69
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 1.652 SNIP 1.031 CiteScore 3.34
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 1.596 SNIP 0.974 CiteScore 3.12
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 1.636 SNIP 1.036 CiteScore 3.18
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 1.774 SNIP 0.988
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 1.69 SNIP 0.994
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 1.709 SNIP 1.009
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 1.719 SNIP 1.059
Uncovering the Molecular Machinery of the Human Spindle—An Integration of Wet and Dry Systems Biology

The mitotic spindle is an essential molecular machine involved in cell division, whose composition has been studied extensively by detailed cellular biology, high-throughput proteomics, and RNA interference experiments. However, because of its dynamic organization and complex regulation it is difficult to obtain a complete description of its molecular composition. We have implemented an integrated computational approach to characterize novel human spindle components and have analysed in detail the individual candidates predicted to be spindle proteins, as well as the network of predicted relations connecting known and putative spindle proteins. The subsequent experimental validation of a number of predicted novel proteins confirmed not only their association with the spindle apparatus but also their role in mitosis. We found that 75% of our tested proteins are localizing to the spindle apparatus compared to a success rate of 35% when expert knowledge alone was used. We compare our results to the previously published MitoCheck study and see that our approach does validate some findings by this consortium. Further, we predict so-called "hidden spindle hubs", proteins whose network of interactions is still poorly characterised by experimental means and which are thought to influence the functionality of the mitotic spindle on a large scale. Our analyses suggest that we are still far from knowing the complete repertoire of functionally important components of the human spindle network. Combining integrated bio-computational approaches and single gene experimental follow-ups could be key to exploring the still hidden regions of the human spindle system.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Novo Nordisk Foundation Center for Biosustainability, CFB - Metagenomic Systems Biology, Centro Nacional de Investigaciones Oncológicas, Max Planck Institute, University of Malaga, Memorial Sloan-Kettering Cancer Center, University College London
Pages: e31813
Publication date: 2012
Main Research Area: Technical/natural sciences

Publication information
Journal: PLoS One
Upregulation of TGF-beta 1 in neonates of mothers receiving Influenza A (H1N1) vaccination during pregnancy

Background: Influenza vaccination of pregnant women is generally considered safe, but the effects on the immune system of the unborn child are unknown. Objectives: Our primary objective was to explore differences in cytokine and chemokine levels in nasal mucosal lining fluid in neonates of mothers vaccinated during or after pregnancy. Method: IFN-c, IL-1b, IL-2, -4, -5, -10, -12p70, -13, -17, TNF-a, IL-8, eotaxin-1, eotaxin-3, IP-10, MCP-1, MCP-4, MDC, MIP-1b, TGF-b1 and TARC were quantified in nasal mucosal lining fluid in neonates of mothers receiving Influenza A (H1N1v) vaccine during (n = 52) or after pregnancy (n = 118) in our unselected Copenhagen Prospective Study on Asthma in Childhood 2010 birth-cohort. Result: Neonates of mothers vaccinated during pregnancy showed a significant up-regulation of the immune-regulatory TGF-b1 (P = 0.0004), significant down regulation (P < 0.05) of TARC, IL-5, IL-10, IFN-c, MDC, IFN-c and non-significant down regulation of nearly all other mediators except for MCP-4, IL-17, eotaxin-3 compared to neonates of mothers vaccinated after pregnancy. Results are adjusted for season; airway colonization S. pneumoniae, H. influenzae, M. catarrhalis, and S. aureus; older siblings; furred animals in home; smoking during 3rd trimester; and mothers’ atopic disease. Conclusion: These findings suggest that Influenza A (H1N1) vaccination during pregnancy affects the mucosal immune competence of the unborn child. The up-regulation of TGF-b1 and down-regulation of nearly all essential contributors to protective immunity reflect an imprinting suggestive of immune inhibition that may affect the neonates’ ability to combat respiratory tract infections.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Copenhagen University Hospital, University of Copenhagen
Authors: Bischoff, A. L. (Forskerdatabase), Folsgaard, N. (Ekstern), Bisgaard, H. (Ekstern), Rasmussen, M. (Ekstern), Pedersen, S. B. (Intern)
Pages: 475
Publication date: 2012
Conference: 31 Congress of the European Academy of Allergy and Clinical Immunology, Geneva, Switzerland, 16/06/2012 - 16/06/2012
Main Research Area: Technical/natural sciences

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Journal: Allergy
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ISSN (Print): 0105-4538
Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 6.23 SJR 2.724 SNIP 2.475
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 3.13 SNIP 2.127 CiteScore 5.73
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.464 SNIP 2.121 CiteScore 5.51
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 2.195 SNIP 1.902 CiteScore 4.91
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 2.008 SNIP 1.818 CiteScore 4.81
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 2.328 SNIP 1.781 CiteScore 4.89
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.826 SNIP 1.845
Wide Distribution of Closely Related, Antibiotic-Producing Arthrobacter Strains throughout the Arctic Ocean

We isolated 16 antibiotic-producing bacterial strains throughout the central Arctic Ocean, including seven Arthrobacter spp. with almost identical 16S rRNA gene sequences. These strains were numerically rare, as revealed using 454 pyrosequencing libraries. Arthrobacter spp. produced arthrobacilins A to C under different culture conditions, but other, unidentified compounds likely contributed to their antibiotic activity.

General information
State: Published
Organisations: National Food Institute, Department of Systems Biology, Center for Microbial Biotechnology, Center for Biological Sequence Analysis, Novo Nordisk Foundation Center for Biosustainability, CFB - Metagenomic Systems Biology, Division of Industrial Food Research
Authors: Wietz, M. (Intern), Månsson, M. (Intern), Bowman, J. S. (Ekstern), Blom, N. (Intern), Ng, Y. (Intern), Gram, L. (Intern)
Pages: 2039-2042
Publication date: 2012
Main Research Area: Technical/natural sciences

Publication information
Journal: Applied and Environmental Microbiology
Volume: 78
Issue number: 6
ISSN (Print): 0099-2240
Ratings:
BFI (2018): BFI-level 2
BFI (2017): BFI-level 2
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 4.08
Integrative Systems Biology: Elucidating Complex Traits
Prediction of protein structural features by use of artificial neural networks

In the past decades we have seen an exponential growth of biological sequence data. The cost for DNA sequencing has dropped significantly since the announcement of the first sequenced genome and newly sequenced genomes are published almost every week. Publicly available genetic sequence databases like for example GenBank are increasing considerably in size and GenBank currently contains more than 132 million sequences. Similar the Protein Data Bank currently contains more than 71,000 experimentally determined structures of nucleic acids, proteins and nucleic acid/protein complexes. There is a huge over-representation of DNA sequences when comparing the amount of experimentally verified proteins with the amount of DNA sequences. The academic and industrial research community therefore has to rely on structure predictions instead of waiting for the time consuming experimentally determined structure data. This thesis describes the development of two new tools to study such genetic sequence data. NetSurfP was developed to predict the surface accessibility of amino acids in amino acid sequences. Knowledge of the degree of surface exposure of an amino acid is valuable and has been used to enhance the understanding of a variety of biological problems, including protein-protein interaction, prediction of epitopes and active sites. Following NetSurfP, NetTurnp was developed for the prediction of turn occurrence. Using secondary structure and surface accessibility predictions from NetSurfP, a better understanding and improvement of the performance for the prediction of turns was obtained. Turns are very interesting in the way that they are the most abundant type of turn structures, and approximately 25% of all amino acids in protein structures are located in a turn. In bioinformatics speed and accuracy is an important factor, hence the developed tools are expected to return a result in a rapid and efficient manner. Our way of solving that problem was to pre calculate protein sequence data. Currently, more than 500,000 protein sequences are in the local cache. In relation to surface exposure, a third project dealt with the prediction of discontinuous B-cell epitopes. Here Half Sphere Exposure (HSE) was integrated in an existing prediction method. HSE is a measure of solvent exposure where the upper and lower epitope contacts to a given residue can be weighted differently. The integration of HSE showed to improve previously obtained results. Lastly, I present an attempt to predict the HIV-1 Protease specificity. As the protease is essential for the life cycle of the HIV virus, the protease is of great interest as a target for the rational design of drugs against HIV. We show that it is possible to predict the specificity of the HIV protease with a high performance. In the process we also identified new possible cleavage sites which will further be verified experimentally in the lab. In summary, the thesis presented in this work has greatly contributed to the development of new tools in bioinformatics that will hopefully aid in future scientific discoveries.
Relationship of Extreme Chromosomal Instability with Long-term Survival in a Retrospective Analysis of Primary Breast Cancer

Background: Chromosomal instability (CIN) is thought to be associated with poor prognosis in solid tumors; however, evidence from preclinical and mouse tumor models suggest that CIN may paradoxically enhance or impair cancer cell fitness. Breast cancer prognostic expression signature sets, which reflect tumor CIN status, efficiently delineate outcome in estrogen receptor ER-positive breast cancer in contrast to ER-negative breast cancer, suggesting that the relationship of CIN with prognosis differs in these two breast cancer subtypes. Methods: Direct assessment of CIN requires single-cell analysis methods, such as centromeric FISH, aimed at determining the variation around the modal number of two or more chromosomes within individual tumor nuclei. Here, we document the frequency of tumor CIN by dual centromeric FISH analysis in a retrospective primary breast cancer cohort of 246 patients with survival outcome. Results: There was increased CIN and clonal heterogeneity in ER-negative compared with ER-positive breast cancer. Consistent with a negative impact of CIN on cellular fitness, extreme CIN in ER-negative breast cancer was an independent variable associated with improved long-term survival in multivariate analysis. In contrast, a linear relationship of increasing CIN with poorer prognosis in ER-positive breast cancer was observed, using three independent measures of CIN. Conclusions: The paradoxical relationship between extreme CIN and cancer outcome in the ER-negative cohorts may explain why prognostic expression signatures, reflecting tumor CIN status, fail to predict outcome in this subgroup. Impact: Assessment of tumor CIN status may support risk stratification in ER-negative breast cancer and requires prospective validation. Cancer Epidemiol Biomarkers Prev; 20(10); 2183–94. 2011 AACR
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 2.086 SNIP 1.374
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 2.382 SNIP 1.407
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 2.342 SNIP 1.377
Scopus rating (2006): SJR 1.916 SNIP 1.221
Scopus rating (2005): SJR 2.108 SNIP 1.421
Scopus rating (2004): SJR 2.248 SNIP 1.485
Web of Science (2004): Indexed yes
Scopus rating (2003): SJR 2.107 SNIP 1.515
Web of Science (2003): Indexed yes
Scopus rating (2002): SJR 2.295 SNIP 1.515
Web of Science (2002): Indexed yes
Scopus rating (2001): SJR 1.891 SNIP 1.331
Scopus rating (2000): SJR 1.736 SNIP 1.512
Scopus rating (1999): SJR 1.531 SNIP 1.286
Original language: English
DOIs: 10.1158/1055-9965.EPI-11-0343
Source: dtu
Source-ID: u::5465
Publication: Research - peer-review › Journal article – Annual report year: 2012

Using Compound-Protein Interactions and Systems Biology to Study Environmental Effects on diseases development

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology
Authors: Weinhold, N. (Intern), Brunak, S. (Intern)
Publication date: Jun 2011

Publication information
Place of publication: Kgs. Lyngby, Denmark
Publisher: Technical University of Denmark (DTU)
Original language: English
Main Research Area: Technical/natural sciences
Source: orbit
Source-ID: 314206
Publication: Research › Ph.D. thesis – Annual report year: 2011

Protein Interactions and Phenotype Association for Disease Finding

General information
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis
Authors: Roque, F. J. S. S. A. (Intern), Brunak, S. (Intern)
Publication date: Apr 2011

Publication information
Place of publication: Kgs. Lyngby, Denmark
Publisher: Technical University of Denmark (DTU)
Original language: English
Main Research Area: Technical/natural sciences
Electronic versions: Francisco Roque, PhD thesis version 2.pdf
Source: orbit
Source-ID: 314221
Publication: Research › Ph.D. thesis – Annual report year: 2011
A breast cancer meta-analysis of two expression measures of chromosomal instability reveals a relationship with younger age at diagnosis and high risk histopathological variables. Breast cancer in younger patients often presents with adverse histopathological features, including increased frequency of estrogen receptor negative and lymph node positive disease status. Chromosomal instability (CIN) is increasingly recognised as an important prognostic variable in solid tumours. In a breast cancer meta-analysis of 2423 patients we examine the relationship between clinicopathological parameters and two distinct chromosomal instability gene expression signatures in order to address whether younger age at diagnosis is associated with increased tumour genome instability. We find that CIN, assessed by the two independently derived CIN expression signatures, is significantly associated with increased tumour size, ER negative or HER2 positive disease, higher tumour grade and younger age at diagnosis in ER negative breast cancer. These data support the hypothesis that chromosomal instability may be a defining feature of breast cancer biology and clinical outcome.

A Closer Look at Bacteroides: Phylogenetic Relationship and Genomic Implications of a Life in the Human Gut

The human gut is extremely densely inhabited by bacteria mainly from two phyla, Bacteroidetes and Firmicutes, and there is a great interest in analyzing whole-genome sequences for these species because of their relation to human health and disease. Here, we do whole-genome comparison of 105 Bacteroidetes/Chlorobi genomes to elucidate their phylogenetic relationship and to gain insight into what is separating the gut living Bacteroides and Parabacteroides genera from other Bacteroidetes/Chlorobi species. A comprehensive analysis shows that Bacteroides species have a higher number of extracytoplasmic function σ factors (ECF σ factors) and two component systems for extracellular signal transduction.
compared to other Bacteroidetes/Chlorobi species. A whole-genome phylogenetic analysis shows a very little difference between the Parabacteroides and Bacteroides genera. Further analysis shows that Bacteroides and Parabacteroides species share a large common core of 1,085 protein families. Genome atlases illustrate that there are few and only small unique areas on the chromosomes of four Bacteroides/Parabacteroides genomes. Functional classification to clusters of orthologous groups show that Bacteroides species are enriched in carbohydrate transport and metabolism proteins. Classification of proteins in KEGG metabolic pathways gives a detailed view of the genome’s metabolic capabilities that can be linked to its habitat. Bacteroides pectinophilus and Bacteroides capillosus do not cluster together with other Bacteroides species, based on analysis of 16S rRNA sequence, whole-genome protein families and functional content, 16S rRNA sequences of the two species suggest that they belong to the Firmicutes phylum. We have presented a more detailed and precise description of the phylogenetic relationships of members of the Bacteroidetes/Chlorobi phylum by whole genome comparison. Gut living Bacteroides have an enriched set of glycan, vitamin, and cofactor enzymes important for diet digestion.

**General information**

- **State:** Published
- **Organisations:** Center for Biological Sequence Analysis, Department of Systems Biology, Chalmers University of Technology
- **Authors:** Karlsson, F. H. (Ekstern), Ussery, D. (Intern), Nielsen, J. (Ekstern), Nookaew, I. (Ekstern)
- **Pages:** 473-485
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- **Main Research Area:** Technical/natural sciences

**Publication information**

- **Journal:** Microbial Ecology
- **Volume:** 61
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- **ISSN (Print):** 0095-3628
- **Ratings:**
  - BFI (2018): BFI-level 1
  - BFI (2017): BFI-level 1
  - Web of Science (2017): Indexed Yes
  - BFI (2016): BFI-level 1
  - Scopus rating (2016): CiteScore 3.55 SJR 1.295 SNIP 1.116
  - Web of Science (2016): Indexed yes
  - BFI (2015): BFI-level 2
  - Scopus rating (2015): SJR 1.334 SNIP 1.021 CiteScore 3.13
  - BFI (2014): BFI-level 2
  - Scopus rating (2014): SJR 1.316 SNIP 1.136 CiteScore 3.08
  - Web of Science (2014): Indexed yes
  - BFI (2013): BFI-level 2
  - Scopus rating (2013): SJR 1.408 SNIP 1.245 CiteScore 3.7
  - ISI indexed (2013): ISI indexed yes
  - BFI (2012): BFI-level 2
  - Scopus rating (2012): SJR 1.417 SNIP 1.279 CiteScore 3.36
  - ISI indexed (2012): ISI indexed yes
  - Web of Science (2012): Indexed yes
  - BFI (2011): BFI-level 2
  - Scopus rating (2011): SJR 1.299 SNIP 1.186 CiteScore 3.04
  - ISI indexed (2011): ISI indexed yes
  - Web of Science (2011): Indexed yes
  - BFI (2010): BFI-level 2
  - Scopus rating (2010): SJR 1.299 SNIP 1.158
  - Web of Science (2010): Indexed yes
  - BFI (2009): BFI-level 1
  - Scopus rating (2009): SJR 1.464 SNIP 1.168
  - Web of Science (2009): Indexed yes
  - BFI (2008): BFI-level 2
  - Scopus rating (2008): SJR 1.253 SNIP 1.058
  - Scopus rating (2007): SJR 1.283 SNIP 1.157
An Aboriginal Australian Genome Reveals Separate Human Dispersals into Asia

We present an Aboriginal Australian genomic sequence obtained from a 100-year-old lock of hair donated by an Aboriginal man from southern Western Australia in the early 20th century. We detect no evidence of European admixture and estimate contamination levels to be below 0.5%. We show that Aboriginal Australians are descendants of an early human dispersal into eastern Asia, possibly 62,000 to 75,000 years ago. This dispersal is separate from the one that gave rise to modern Asians 25,000 to 38,000 years ago. We also find evidence of gene flow between populations of the two dispersal waves prior to the divergence of Native Americans from modern Asian ancestors. Our findings support the hypothesis that present-day Aboriginal Australians descend from the earliest humans to occupy Australia, likely representing one of the oldest continuous populations outside Africa.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Novo Nordisk Foundation Center for Biosustainability, CFB - Metagenomic Systems Biology, BGI-Shenzhen, University of California, University of Tartu, Imperial College Faculty of Medicine, University of Cambridge, Chinese Academy of Sciences, Stanford University, Murdoch University, Goldfields Land and Sea Council Aboriginal Corporation, University of Western Australia, Kitasato University, Universität Bern, University of Chicago, Universite de Toulouse, Leiden University, University College London, Griffith University, Institute for Forensic Genetics, Max Planck Institute, University of Copenhagen
Pages: 94-98
Publication date: 2011
Main Research Area: Technical/natural sciences

Publication information
Journal: Science
Volume: 334
Issue number: 6052
ISSN (Print): 0036-8075
Ratings:
Application of computational systems biology to explore environmental toxicity hazards.

Background: Computer-based modeling is part of a new approach to predictive toxicology. Objectives: We investigated the usefulness of an integrated computational systems biology approach in a case study involving the isomers and metabolites of the pesticide dichlorodiphenyltrichloroethane (DDT) to ascertain their possible links to relevant adverse effects.

Methods: We extracted chemical-protein association networks for each DDT isomer and its metabolites using ChemProt, a disease chemical biology database that includes both binding and gene expression data, and we explored protein-protein interactions using a human interactome network. To identify associated dysfunctions and diseases, we integrated protein-disease annotations into the protein complexes using the Online Mendelian Inheritance in Man database and the Comparative Toxicogenomics Database.

Results: We found 175 human proteins linked to p,p'-DDT, and 187 to o,p'-DDT. Dichlorodiphenyldichloroethylene (p,p'-DDE) was the metabolite with the highest number of links, with 52. We grouped proteins for each compound based on their disease annotations. Although the two data sources differed in linkage to diseases, integrated results predicted that most diseases were linked to the two DDT isomers. Asthma was uniquely linked with p,p'-DDT, and autism with o,p'-DDT. Several reproductive and neurobehavioral outcomes and cancer types were linked to all three compounds.

Conclusions: Computer-based modeling relies on available information. Although differences in linkages to proteins may be due to incomplete data, our results appear meaningful and suggest that the parent DDT compounds may be responsible for more disease connections than the metabolites. The findings illustrate the potential use of computational approaches to toxicology.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, University of Southern Denmark
Authors: Audouze, K. M. L. (Intern), Grandjean, P. (Ekstern)
Pages: 1754-1759
Publication date: 2011
Main Research Area: Technical/natural sciences

Publication information
Journal: Environmental Health Perspectives
Volume: 119
Issue number: 12
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Ratings:
BFI (2018): BFI-level 2
BFI (2017): BFI-level 2
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 5.62 SJR 3.067 SNIP 2.362
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 3.569 SNIP 2.363 CiteScore 5.58
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 3.244 SNIP 2.319 CiteScore 5.13
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 3.059 SNIP 2.354 CiteScore 4.92
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 2.949 SNIP 2.319 CiteScore 4.77
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 3.125 SNIP 2.314 CiteScore 4.56
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
A randomized controlled intervention with fish oil versus sunflower oil from 9 to 18 months of age: exploring changes in growth and skinfold thicknesses

n-3 long-chain polyunsaturated fatty acids (n-3 LCPUFA), from fish oil (FO), in rodents have been shown to reduce adipogenesis. Evidence of an effect on adipose tissue mass in humans is limited, and no studies have specifically aimed to elucidate this in infancy. To explore whether n-3 LCPUFA intake affects adipose tissue growth, we randomly allocated 154 healthy infants to daily supplementation with FO or sunflower oil (SO) from 9 to 18 mo of age and measured z-score changes in various anthropometric assessments of body size and skinfold thicknesses and plasma adipokine concentrations. Among the 133 completing infants, erythrocyte n-3 PUFA increased more in those receiving FO than in infants receiving SO [12.2 ± 0.7 (mean ± SE) versus 2.0 ± 0.4 fatty acid percentage (FA%), p < 0.001] with a concomitant larger decrease in n-6 PUFA (-8.9 ± 0.7 versus -0.9 ± 0.6 FA%, p <0.001). We found no association between FO consumption relative to SO consumption and any of the anthropometric measures related to the size of the fat mass, but infants in the FO group had a lower skinfold ratio (triceps/subscapular) at 18 mo than those in SO group (p = 0.02). Our findings do not support the hypothesis that dietary n-3 LCPUFA is important for infant fat mass, but future studies testing this specifically are warranted. ABBREVIATIONS::
Are NOD2 polymorphisms linked to a specific disease endophenotype of Crohn's disease?

The complex and yet unknown etiology of Crohn's disease (CD) might consist of various disease endophenotypes, each of which represent their own pathogenesis. This review focuses on the disease endophenotype linked to polymorphisms in the nucleotide-binding oligomerization domain containing 2 (NOD2) protein and on the importance of established adherent-invasive E. coli (AIEC) in ileal mucosa. To date, there are several reports pointing to the implications of NOD2 polymorphisms in epithelial and immunological responses against microbes, but the pathological significance of NOD2 mutations in CD is not yet clarified. The enhanced number of pathogenic E. coli in the ileal mucosa of CD as compared to...
healthy controls may result from a genetically based failure in one of the intestinal bacteria sensing systems, like NOD2, making the ileal epithelium more prone to colonization with microbes harboring specific properties such as AIEC. Increasing the focus on defining subgroups of patients with similar disease initiations, mechanisms of action, and manifestations in CD may be pivotal for the development and implementation of future individualized treatment strategies of benefit for the single patient at an early stage. (Inflamm Bowel Dis 2011;)

**General information**
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Copenhagen University Hospital
Authors: Jensen, S. R. (Intern), Nielsen, O. H. (Ekstern), Pedersen, S. B. (Intern)
Pages: 2392-2401
Publication date: 2011
Main Research Area: Technical/natural sciences

**Publication information**
Journal: Inflammatory Bowel Diseases
Volume: 17
Issue number: 11
ISSN (Print): 1078-0998
Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): SJR 1.916 SNIP 1.247 CiteScore 3.82
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.348 SNIP 1.331 CiteScore 4.14
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.362 SNIP 1.551 CiteScore 4.14
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 2.879 SNIP 1.782 CiteScore 4.38
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 2.131 SNIP 1.582 CiteScore 3.77
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.659 SNIP 1.494 CiteScore 3.16
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.504 SNIP 1.485
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.587 SNIP 1.44
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 1.861 SNIP 1.254
Scopus rating (2007): SJR 1.717 SNIP 1.352
Scopus rating (2006): SJR 1.368 SNIP 1.154
Scopus rating (2005): SJR 0.953 SNIP 1.033
Scopus rating (2004): SJR 1.167 SNIP 1.331
Scopus rating (2003): SJR 1.232 SNIP 1.244
Scopus rating (2002): SJR 1.092 SNIP 1.129
Scopus rating (2001): SJR 0.883 SNIP 1.272
Scopus rating (2000): SJR 1.008 SNIP 1.18
Scopus rating (1999): SJR 0.29 SNIP 0.469
Original language: English
NOD2, Crohn’s disease, Paneth cells, Gut-associated lymphoid tissue, Adherent-invasive E. coli, Antimicrobials
Associating Drugs, Targets and Clinical Outcomes into an Integrated Network Affords a New Platform for Computer-Aided Drug Repurposing

Finding new uses for old drugs is a strategy embraced by the pharmaceutical industry, with increasing participation from the academic sector. Drug repurposing efforts focus on identifying novel modes of action, but not in a systematic manner. With intensive data mining and curation, we aim to apply bio- and cheminformatics tools using the DRUGS database, containing 3837 unique small molecules annotated on 1750 proteins. These are likely to serve as drug targets and antitargets (i.e., associated with side effects, SE). The academic community, the pharmaceutical sector and clinicians alike could benefit from an integrated, semantic-web compliant computer-aided drug repurposing (CADR) effort, one that would enable deep data mining of associations between approved drugs (D), targets (T), clinical outcomes (CO) and SE. We report preliminary results from text mining and multivariate statistics, based on 7684 approved drug labels, ADL (Dailymed) via text mining. From the ADL corresponding to 988 unique drugs, the “adverse reactions” section was mapped onto 174 SE, then clustered via principal component analysis into a 5 x 5 self-organizing map that was integrated into a Cytoscape network of SE-D-T-CO. This type of data can be used to streamline drug repurposing and may result in novel insights that can lead to the identification of novel drug actions.

General information

State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, University of New Mexico
Authors: Oprea, T. (Intern), Nielsen, S. K. (Intern), Ursu, O. (Ekstern), Yang, J. J. (Ekstern), Taboureau, O. (Intern), Mathias, S. L. (Ekstern), Kouskoumvekaki, I. (Intern), Sklar, L. A. (Ekstern), Bologa, C. G. (Ekstern)
Pages: 100-111
Publication date: 2011
Main Research Area: Technical/natural sciences

Publication information
Journal: Molecular Informatics
Volume: 30
Issue number: 2-3
ISSN (Print): 1868-1743
Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): SJR 0.642 SNIP 0.62 CiteScore 1.85
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.594 SNIP 0.6 CiteScore 1.83
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.509 SNIP 0.593 CiteScore 1.58
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 0.695 SNIP 0.755 CiteScore 2.23
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 0.53 SNIP 0.664 CiteScore 2.17
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 0.493 SNIP 0.77 CiteScore 2.13
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 0.582 SNIP 0.572
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 0.804 SNIP 0.777
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 0.901 SNIP 0.74
A Systematic Study of Site-specific GalNAc-type O-Glycosylation Modulating Proprotein Convertase Processing

Site-specific GalNAc-type O-glycosylation is emerging as an important co-regulator of proprotein convertase (PC) processing of proteins. PC processing is crucial in regulating many fundamental biological pathways and O-glycans in or immediately adjacent to processing sites may affect recognition and function of PCs. Thus, we previously demonstrated that deficiency in site-specific O-glycosylation in a PC site of the fibroblast growth factor, FGF23, resulted in marked reduction in secretion of active unprocessed FGF23, which cause familial tumoral calcinosis and hyperostosis hyperphosphatemia. GalNAc-type O-glycosylation is found on serine and threonine amino acids and up to 20 distinct polypeptide GalNAc transferases catalyze the first addition of GalNAc to proteins making this step the most complex and differentially regulated steps in protein glycosylation. There is no reliable prediction model for O-glycosylation especially of isolated sites, but serine and to a lesser extent threonine residues are frequently found adjacent to PC processing sites. In the present study we used in vitro enzyme assays and ex vivo cell models to systematically address the boundaries of the region within site-specific O-glycosylation affect PC processing. The results demonstrate that O-glycans within at least ±3 residues of the RXXR furin cleavage site may affect PC processing suggesting that site-specific O-glycosylation is a major co-regulator of PC processing.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, University of Copenhagen
Authors: Schjoldager, K. T. G. (Ekstern), Vester-Christensen, M. B. (Ekstern), Goth, C. K. (Ekstern), Petersen, T. N. (Intern), Brunak, S. (Intern), Bennett, E. P. (Ekstern), Levery, S. B. (Ekstern), Clausen, H. (Ekstern)
Pages: 40122-40132
Publication date: 2011
Main Research Area: Technical/natural sciences

Publication information
Journal: Journal of Biological Chemistry
Volume: 286
Issue number: 46
ISSN (Print): 0021-9258
Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 2
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 4.17 SJR 2.755 SNIP 1.125
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 3.121 SNIP 1.184 CiteScore 4.4
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 3.254 SNIP 1.222 CiteScore 4.5
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
A systems biology approach to identify potential health risk from chemical exposure

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology
Authors: Audouze, K. M. L. (Intern)
Pages: 19-25
Publication date: 2011
Main Research Area: Technical/natural sciences

Publication information
Journal: Miljø og Sundhed
Back to the Roots: Prediction of Biologically Active Natural Products from Ayurveda Traditional Medicine

Ayurveda, the traditional Indian medicine is one of the most ancient, yet living medicinal traditions. In the present work, we developed an in silico library of natural products from Ayurveda medicine, coupled with structural information, plant origin and traditional therapeutic use. Following this, we compared their structures with those of drugs from DrugBank and we constructed a structural similarity network. Information on the traditional therapeutic use of the plants was integrated in the network in order to provide further evidence for the predicted biologically active natural compounds. We hereby present a number of examples where the traditional medicinal use of the plant matches with the medicinal use of the drug that is structurally similar to a plant component. With this approach, we have brought to light a number of obscure compounds of natural origin (e.g. kanugin, norruffscine, isoazadirolide) that could provide the basis and inspiration for further lead development. Apart from the identification of novel natural leads in drug discovery, we envisage that this integrated in silico ethnopharmacology approach could find applications in the elucidation of the molecular basis of Ayurveda medicine and in drug repurposing.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Technical University of Denmark, National Medicinal Plants Board
Authors: Polur, H. (Ekstern), Joshi, T. (Intern), Workman, C. (Intern), Lavekar, G. (Ekstern), Kouskoumvekaki, I. (Intern)
Pages: 181-187
Publication date: 2011
Main Research Area: Technical/natural sciences

Publication information
Journal: Molecular Informatics
Volume: 30
Issue number: 2-3
ISSN (Print): 1868-1743
Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): SJR 0.642 SNIP 0.62 CiteScore 1.85
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.594 SNIP 0.6 CiteScore 1.83
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.509 SNIP 0.593 CiteScore 1.58
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 0.695 SNIP 0.755 CiteScore 2.23
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 0.53 SNIP 0.664 CiteScore 2.17
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 0.493 SNIP 0.77 CiteScore 2.13
Web of Science (2011): Indexed yes
Here, we compile the Biopharmaceutics Drug Disposition Classification System (BDDCS) classification for 927 drugs, which include 30 active metabolites. Of the 897 parent drugs, 78.8% (707) are administered orally. Where the lowest measured solubility is found, this value is reported for 72.7% (513) of these orally administered drugs and a dose number is recorded. The measured values are reported for percent excreted unchanged in urine, LogP, and LogD 7.4 when available. For all 927 compounds, the in silico parameters for predicted Log solubility in water, calculated LogP, polar surface area, and the number of hydrogen bond acceptors and hydrogen bond donors for the active moiety are also provided, thereby allowing comparison analyses for both in silico and experimentally measured values. We discuss the potential use of BDDCS to estimate the disposition characteristics of novel chemicals (new molecular entities) in the early stages of drug discovery and development. Transporter effects in the intestine and the liver are not clinically relevant for BDDCS class 1 drugs, but potentially can have a high impact for class 2 (efflux in the gut, and efflux and uptake in the liver) and class 3 (uptake and efflux in both gut and liver) drugs. A combination of high dose and low solubility is likely to cause BDDCS class 4 to be underpopulated in terms of approved drugs (N = 53 compared with over 200 each in classes 1–3). The influence of several measured and in silico parameters in the process of BDDCS category assignment is discussed in detail.

**General information**

**State:** Published  
**Organisations:** Center for Biological Sequence Analysis, Department of Systems Biology, University of California, San Francisco  
**Authors:** Benet, L. Z. (Ekstern), Broccatelli, F. (Ekstern), Oprea, T. (Intern)  
**Pages:** 519-547  
**Publication date:** 2011  
**Main Research Area:** Technical/natural sciences

**Publication information**

**Journal:** The A A P S Journal. Annual Meeting Abstracts  
**Volume:** 13  
**Issue number:** 4  
**ISSN (Print):** 1551-1081  
**Ratings:**  
**ISI indexed (2013):** ISI indexed no  
**ISI indexed (2012):** ISI indexed no  
**ISI indexed (2011):** ISI indexed no  
**Original language:** English  
**Permeability rate, Extent of metabolism, Biowaiver, BDDCS, Dose number**
Bioinformatics-Driven Identification and Examination of Candidate Genes for Non-Alcoholic Fatty Liver Disease

Objective: Candidate genes for non-alcoholic fatty liver disease (NAFLD) identified by a bioinformatics approach were examined for variant associations to quantitative traits of NAFLD-related phenotypes. Research Design and Methods: By integrating public database text mining, trans-organism protein-protein interaction transferal, and information on liver protein expression a protein-protein interaction network was constructed and from this a smaller isolated interactome was identified. Five genes from this interactome were selected for genetic analysis. Twenty-one tag single-nucleotide polymorphisms (SNPs) which captured all common variation in these genes were genotyped in 10,196 Danes, and analyzed for association with NAFLD-related quantitative traits, type 2 diabetes (T2D), central obesity, and WHO-defined metabolic syndrome (MetS). Results: 273 genes were included in the protein-protein interaction analysis and EHHADH, ECHS1, HADHA, HADHB, and ACADL were selected for further examination. A total of 10 nominal statistical significant associations (P <0.05) to quantitative metabolic traits were identified. Also, the case-control study showed associations between variation in the five genes and T2D, central obesity, and MetS, respectively. Bonferroni adjustments for multiple testing negated all associations. Conclusions: Using a bioinformatics approach we identified five candidate genes for NAFLD. However, we failed to provide evidence of associations with major effects between SNPs in these five genes and NAFLD-related quantitative traits, T2D, central obesity, and MetS.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Hagedorn Research Institute, Steno Diabetes Centre, University of Lausanne, University of Copenhagen
Pages: e16542
Publication date: 2011
Main Research Area: Technical/natural sciences

Publication information
Journal: P L o S One
Volume: 6
Issue number: 1
ISSN (Print): 1932-6203
Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.11 SJR 1.201 SNIP 1.092
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.414 SNIP 1.131 CiteScore 3.32
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.545 SNIP 1.141 CiteScore 3.54
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.74 SNIP 1.147 CiteScore 3.94
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.945 SNIP 1.142 CiteScore 4.15
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
Bistability in autoimmune diseases

Autoimmune diseases damage host tissue, which, in turn, may trigger a stronger immune response. Systems characterized by such positive feedback loops can display co-existing stable steady states. In a mathematical model of autoimmune disease, one steady state may correspond to the healthy state and another to an autoimmune steady state characterized by widespread tissue damage and immune activation. We show how a triggering event may move the system from the healthy to the autoimmune state and how transient immunosuppressive treatment can move the system back to the healthy state.

General information

State: Published
Organisations: Department of Physics, Center for Biological Sequence Analysis, Department of Systems Biology, University of Copenhagen
Authors: Rapin, N. (Ekstern), Mosekilde, E. (Intern), Lund, O. (Intern)
Pages: 256-260
Publication date: 2011
Main Research Area: Technical/natural sciences

Publication information

Journal: Autoimmunity
Volume: 44
Issue number: 4
ISSN (Print): 0891-6934
Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): SJR 0.757 SNIP 0.79 CiteScore 2.5
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.86 SNIP 0.91 CiteScore 2.91
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.672 SNIP 0.694 CiteScore 2.3
Bovine colostrum is superior to enriched formulas in stimulating intestinal function and necrotising enterocolitis resistance in preterm pigs

Milk contains immunomodulatory compounds that may be important to protect the immature intestine in preterm neonates from harmful inflammatory reactions involved in disorders like necrotising enterocolitis (NEC). We hypothesised that bovine colostrum and milk formulas enriched with sialic acids (SL), gangliosides (Gang) or osteopontin (OPN) would improve gastrointestinal function and NEC resistance in preterm neonates. Forty-seven caesarean-delivered preterm pigs were given total parenteral nutrition for 2 d followed by 1.5 d of enteral feeding. In Expt 1, a control formula was compared with an OPN-enriched formula (n 13), while Expt 2 compared a control formula with bovine colostrum or formulas enriched with Gang or SL (n 4-6). OPN enrichment decreased NEC severity relative to control formula (P
Cancer stem cell overexpression of nicotinamide N-methyltransferase enhances cellular radiation resistance

Background: Cancer stem cells are thought to be a radioresistant population and may be the seeds for recurrence after radiotherapy. Using tumorigenic clones of retroviral immortalized human mesenchymal stem cell with small differences in their phenotype, we investigated possible genetic expression that could explain cancer stem cell radiation resistance.

Methods: Tumorigenic mesenchymal cancer stem cell clones BB3 and CE8 were irradiated at varying doses and assayed for clonogenic surviving fraction. Altered gene expression before and after 2Gy was assessed by Affymetric exon chip analysis and further validated with q-RT-PCR using TaqMan probes. Results: The CE8 clone was more radiation resistant than the BB3 clone. From a pool of 15 validated genes with altered expression in the CE8 clone, we found the enzyme nicotinamide N-methyltransferase (NNMT) more than 5-fold upregulated. In-depth pathway analysis found the genes involved in cancer, proliferation, DNA repair and cell death.

Conclusions: The higher radiation resistance in clone CE8 is likely due to NNMT overexpression. The higher levels of NNMT could affect the cellular damage resistance through depletion of the accessible amounts of nicotinamide, which is a known inhibitor of cellular DNA repair mechanisms.
ChemProt: a disease chemical biology database

Systems pharmacology is an emergent area that studies drug action across multiple scales of complexity, from molecular and cellular to tissue and organism levels. There is a critical need to develop network-based approaches to integrate the growing body of chemical biology knowledge with network biology. Here, we report ChemProt, a disease chemical biology database, which is based on a compilation of multiple chemical-protein annotation resources, as well as disease-associated protein-protein interactions (PPIs). We assembled more than 700,000 unique chemicals with biological annotation for 30,578 proteins. We gathered over 2-million chemical-protein interactions, which were integrated in a quality scored human PPI network of 428,429 interactions. The PPI network layer allows for studying disease and tissue specificity through each protein complex. ChemProt can assist in the in silico evaluation of environmental chemicals, natural products and approved drugs, as well as the selection of new compounds based on their activity profile against most known biological targets, including those related to adverse drug events. Results from the disease chemical biology database associate citalopram, an antidepressant, with osteogenesis imperfect and leukemia and bisphenol A, an endocrine disruptor, with certain types of cancer, respectively. The server can be accessed at http://www.cbs.dtu.dk/services/ChemProt/.

General information

State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Romanian Academy
Pages: D367-372
Publication date: 2011
Main Research Area: Technical/natural sciences

Publication information

Journal: Nucleic Acids Research
Volume: 39
Issue number: Issue Suppl. 1
ISSN (Print): 0305-1048
Ratings:
BFI (2018): BFI-level 2
BFI (2017): BFI-level 2
Web of Science (2017): Indexed yes
Comparative analysis of a large panel of non-starch polysaccharides reveals structures with selective regulatory properties in dendritic cells

Scope: Structural-based recognition of foreign molecules is essential for activation of dendritic cells (DCs) that play a key role in regulation of gut mucosal immunity. Orally ingested non-starch polysaccharides (NSP) are ascribed many health-promoting properties, but currently we lack insight into the impact of structure and size for their capacity to affect immune responses. Methods and results: This study addresses the importance of chemical structure, size, origin and presence of contaminants for the capacity of both dietary and non-food NSP to modulate DC. Of 28 NSP products, β-glucans of microbial and plant origin and the galactomannan guar gum were found to modulate the DC cytokine pattern induced by the Toll-like receptor 4-ligand LPS giving rise to reduced IL-12p70 and increased IL-10 levels, whereas IL-6 production was unaffected. A large proportion of the tested NSP were able to down-regulate LPS-induced IL-12p70 production. The most potent NSP induced up-regulation of CD86 on DC independently of LPS stimulation. Cereal-based β-glucans showed less potency than β-glucans of microbial origin, but proper molecular weight composition and preparation may improve effectiveness. Conclusions: Collectively, this comparative study revealed that some plant-derived NSP besides those of microbial origin exert modulation of the DC phenotype, with the exact structure being important for the activity.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Department of Chemical and Biochemical Engineering
Authors: Wismar, R. (Intern), Pedersen, S. B. (Intern), Lærke, H. N. (Ekstern), Frøkiær, H. (Intern)
Pages: 443-454
Publication date: 2011
Main Research Area: Technical/natural sciences

Publication information
Journal: Molecular Nutrition & Food Research
Volume: 55
Issue number: 3
ISSN (Print): 1613-4125
Ratings:
BFI (2018): BFI-level 2
BFI (2017): BFI-level 2
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 4.48 SJR 1.554 SNIP 1.284
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 1.719 SNIP 1.417 CiteScore 4.53
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 1.683 SNIP 1.456 CiteScore 4.55
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 1.672 SNIP 1.501 CiteScore 4.92
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 1.556 SNIP 1.593 CiteScore 4.5
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 1.519 SNIP 1.485 CiteScore 4.54
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 1.55 SNIP 1.518
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.306 SNIP 1.336
Complete Genome Sequence of the Commensal Enterococcus faecalis 62, Isolated from a Healthy Norwegian Infant

The genome of Enterococcus faecalis 62, a commensal isolate from a healthy Norwegian infant, revealed multiple adaptive traits to the gastrointestinal tract (GIT) environment and the milk-containing diet of breast-fed infants. Adaptation to a commensal existence was emphasized by lactose and other carbohydrate metabolism genes within genomic islands, accompanied by the absence of virulence traits.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Norwegian University of Life Sciences, University of Oslo
Authors: Brede, D. A. (Ekstern), Snipen, L. G. (Ekstern), Ussery, D. (Intern), Nederbragt, A. J. (Ekstern), Nes, I. F. (Ekstern)
Pages: 2377-2378
Publication date: 2011
Main Research Area: Technical/natural sciences

Publication information
Journal: Journal of Bacteriology
Volume: 193
Issue number: 9
ISSN (Print): 0021-9193
Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.08 SJR 1.908 SNIP 0.884
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.151 SNIP 0.959 CiteScore 2.84
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.069 SNIP 0.937 CiteScore 2.72
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Computational methods in epitope discovery: Abstract

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology
Authors: Lundegaard, C. (Intern)
Pages: S54
Publication date: 2011
Conference: World Congress on Advances in Oncology and International Symposium on Molecular Medicine, Rhodes Island, Greece, 01/01/2011
Main Research Area: Technical/natural sciences
Conservation analysis of dengue virus-cell epitope-based vaccine candidates using peptide block entropy

Broad coverage of the pathogen population is particularly important when designing CD8+ T-cell epitope vaccines against viral pathogens. Traditional approaches are based on combinations of highly conserved T-cell epitopes. Peptide block entropy analysis is a novel approach for assembling sets of broadly covering antigens. Since T-cell epitopes are recognized as peptides rather than individual residues, this method is based on calculating the information content of blocks of peptides from a multiple sequence alignment of homologous proteins rather than using the information content of individual residues. The block entropy analysis provides broad coverage of variant antigens. We applied the block entropy analysis method to the proteomes of the four serotypes of dengue virus (DENV) and found 1,551 blocks of 9-mer peptides, which cover 99% of available sequences with five or fewer unique peptides. In contrast, the benchmark study by Khan et al. (2008) resulted in 165 conserved 9-mer peptides. Many of the conserved blocks are located consecutively in the proteins. Connecting these blocks resulted in 78 conserved regions. Of the 1551 blocks of 9-mer peptides 110 comprised predicted HLA binder sets. In total, 457 subunit peptides that encompass the diversity of all sequenced DENV strains of which 333 are T-cell epitope candidates.
Consistent metagenes from cancer expression profiles yield agent specific predictors of chemotherapy response

BACKGROUND: Genome scale expression profiling of human tumor samples is likely to yield improved cancer treatment decisions. However, identification of clinically predictive or prognostic classifiers can be challenging when a large number of genes are measured in a small number of tumors. RESULTS: We describe an unsupervised method to extract robust, consistent metagenes from multiple analogous data sets. We applied this method to expression profiles from five "double negative breast cancer" (DNBC) (not expressing ESR1 or HER2) cohorts and derived four metagenes. We assessed these metagenes in four similar but independent cohorts and found strong associations between three of the metagenes and agent-specific response to neoadjuvant therapy. Furthermore, we applied the method to ovarian and early stage lung cancer, two tumor types that lack reliable predictors of outcome, and found that the metagenes yield predictors of survival for both. CONCLUSIONS: These results suggest that the use of multiple data sets to derive potential biomarkers can filter out data set-specific noise and can increase the efficiency in identifying clinically accurate biomarkers.
Cost-effective multiplexing before capture allows screening of 25 000 clinically relevant SNPs in childhood acute lymphoblastic leukemia

Genetic variants, including single-nucleotide polymorphisms (SNPs), are key determiners of interindividual differences in treatment efficacy and toxicity in childhood acute lymphoblastic leukemia (ALL). Although up to 13 chemotherapeutic agents are used in the treatment of this cancer, it remains a model disease for exploring the impact of genetic variation due to well-characterized cytogenetics, drug response pathways and precise monitoring of minimal residual disease. Here, we have selected clinically relevant genes and SNPs through literature screening, and on the basis of associations with key pathways, protein-protein interactions or downstream partners that have a role in drug disposition and treatment efficacy in childhood ALL. This allows exploration of pathways, where one of several genetic variants may lead to similar clinical phenotypes through related molecular mechanisms. We have designed a cost-effective, high-throughput capture assay of ≈25 000 clinically relevant SNPs, and demonstrated that multiple samples can be tagged and pooled before genome capture in targeted enrichment with a sufficient sequencing depth for genotyping. This multiplexed, targeted sequencing method allows exploration of the impact of pharmacogenetics on efficacy and toxicity in childhood ALL treatment, which will be of importance for personalized chemotherapy.

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General information

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Novo Nordisk Foundation Center for Biosustainability, CFB - Metagenomic Systems Biology, Panum Institute, Copenhagen University Hospital
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Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): SJR 4.929 SNIP 2.213 CiteScore 6.47
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 5.148 SNIP 2.276 CiteScore 6.43
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 4.66 SNIP 1.968 CiteScore 5.83
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 4.643 SNIP 1.744 CiteScore 5.78
ISI indexed (2013): ISI indexed yes
Diversion of flux toward sesquiterpene production in Saccharomyces cerevisiae by fusion of host and heterologous enzymes.

The ability to transfer metabolic pathways from the natural producer organisms to the well-characterized cell factory Saccharomyces cerevisiae is well documented. However, as many secondary metabolites are produced by collaborating enzymes assembled in complexes, metabolite production in yeast may be limited by the inability of the heterologous enzymes to collaborate with the native yeast enzymes. This may cause loss of intermediates by diffusion or degradation or due to conversion of the intermediate through competitive pathways. To bypass this problem, we have pursued a strategy in which key enzymes in the pathway are expressed as a physical fusion. As a model system, we have constructed several fusion protein variants in which farnesyl diphosphate synthase (FPPS) of yeast has been coupled to patchoulol synthase (PTS) of plant origin (Pogostemon cablin). Expression of the fusion proteins in S. cerevisiae increased the production of patchoulol, the main sesquiterpene produced by PTS, up to 2-fold. Moreover, we have demonstrated that the fusion strategy can be used in combination with traditional metabolic engineering to further increase the production of patchoulol. This simple test case of synthetic biology demonstrates that engineering the spatial organization of metabolic enzymes around a branch point has great potential for diverting flux toward a desired product. ©American Society for Microbiology. All rights reserved.
DNA methyltransferase 1 and DNA methylation patterning contribute to germinal center B-cell differentiation

The phenotype of germinal center (GC) B cells includes the unique ability to tolerate rapid proliferation and the mutagenic actions of activation induced cytosine deaminase (AICDA). Given the importance of epigenetic patterning in determining cellular phenotypes, we examined DNA methylation and the role of DNA methyltransferases in the formation of GCs. DNA methylation profiling revealed a marked shift in DNA methylation patterning in GC B cells versus resting/naive B cells. This shift included significant differential methylation of 235 genes, with concordant inverse changes in gene expression affecting most notably genes of the NFkB and MAP kinase signaling pathways. GC B cells were predominantly hypomethylated compared with naive B cells and AICDA binding sites were highly overrepresented among hypomethylated loci. GC B cells also exhibited greater DNA methylation heterogeneity than naive B cells. Among DNA methyltransferases (DNMTs), only DNMT1 was significantly up-regulated in GC B cells. Dnmt1 hypomorphic mice displayed deficient GC formation and treatment of mice with the DNA methyltransferase inhibitor decitabine resulted in failure to form GCs after immune stimulation. Notably, the GC B cells of Dnmt1 hypomorphic animals showed evidence of increased DNA damage, suggesting dual roles for DNMT1 in DNA methylation and double strand DNA break repair.

General information

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Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Weill Cornell Medical College, Dana-Farber Cancer Institute, Virginia Commonwealth University, Karolinska Institutet, University of Chicago
Pages: 3559-3569
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Main Research Area: Technical/natural sciences
Drug repurposing from an academic perspective

Academia and small business research units are poised to play an increasing role in drug discovery, with drug repurposing as one of the major areas of activity. Here we summarize project status for several drugs or classes of drugs: raltegravir, cyclobenzaprine, benzbromarone, mometasone furoate, astemizole, R-naproxen, ketorolac, tolfenamic acid, phenothiazines, methylergonovine maleate and beta-adrenergic receptor drugs, respectively. On the basis of this multi-year, multi-project experience we discuss strengths and weaknesses of academic-based drug repurposing research. Translational, target and disease foci are strategic advantages fostered by close proximity and frequent interactions between basic and clinical scientists, which often result in discovering new modes of action for approved drugs. By contrast, lack of integration with pharmaceutical sciences and toxicology, lack of appropriate intellectual coverage and issues related to dosing and safety may lead to significant drawbacks. The development of a more streamlined regulatory process worldwide, and the development of precompetitive knowledge transfer systems such as a global healthcare database focused on regulatory and scientific information for drugs worldwide, are among the ideas proposed to improve the process of academic drug discovery and repurposing, and to overcome the ‘valley of death’ by bridging basic to clinical sciences.

General information

State: Published
Organisations: Center for Biological Sequence Analysis, University of New Mexico, La Jolla Institute for Allergy & Immunology, Carnegie Mellon University, University of Florida
Pages: 61-69
Effect of dairy fat on plasma phytanic acid in healthy volunteers - a randomized controlled study

BACKGROUND: Phytanic acid produced in ruminants from chlorophyll may have preventive effects on the metabolic syndrome, partly due to its reported RXR and PPAR-α agonist activity. Milk from cows fed increased levels of green plant material, contains increased phytanic acid concentrations, but it is unknown to what extent minor increases in phytanic acid content in dairy fat leads to higher circulating levels of phytanic acid in plasma of the consumers. OBJECTIVE: To investigate if cow feeding regimes affects concentration of plasma phytanic acid and risk markers of the metabolic syndrome in human. DESIGN: In a double-blind, randomized, 4 wk, parallel intervention study 14 healthy young subjects were given 45 g milk fat/d from test butter and cheese with 0.24 wt% phytanic acid or a control diet with 0.13 wt% phytanic acid. Difference in phytanic acid was obtained by feeding roughage with low or high content of chlorophyll. RESULTS: There tended to be a difference in plasma phytanic acid (P = 0.0730) concentration after the dietary intervention. Plasma phytanic acid increased significantly within both groups with the highest increase in control group (24%) compared to phytanic acid group (15%). There were no significant effects of phytanic acid on risk markers for the metabolic syndrome. CONCLUSIONS: The results indicate that increased intake of dairy fat modify the plasma phytanic acid concentration, regardless of cows feeding regime and the minor difference in dietary phytanic acid. Whether the phytanic acid has potential to affects the risk markers of the metabolic syndrome in human still remain to be elucidated.
Effect of industrially produced trans fat on markers of systemic inflammation: evidence from a randomized trial in women

Consumption of industrially produced trans fatty acids (IP-TFA) has been positively associated with systemic markers of low-grade inflammation and endothelial dysfunction in cross-sectional studies, but results from intervention studies are inconclusive. Therefore, we conducted a 16 week double-blind parallel intervention study with the objective to examine the effect of IP-TFA intake on biomarkers of inflammation, oxidative stress, and endothelial dysfunction. Fifty-two healthy overweight postmenopausal women (49 completers) were randomly assigned to receive either partially hydrogenated soybean oil (15.7 g/day IP-TFA) or control oil without IP-TFA. After 16 weeks, IP-TFA intake increased baseline-adjusted serum tumor necrosis factor (TNF) α by 12% [95% confidence interval (CI): 5–20; P = 0.002] more in the IP-TFA group compared with controls. Plasma soluble TNF receptors 1 and 2 were also increased by IP-TFA [155 pg/ml (CI: 63–247); P <0.001 and 480 pg/ml (CI: 72–887); P = 0.02, respectively]. Serum C-reactive protein, interleukin (IL) 6 and adiponectin and subcutaneous abdominal adipose tissue mRNA expression of IL6, IL8, TNFα, and adiponectin as well as ceramide content were not affected by IP-TFA, nor was urinary 8-iso-prostaglandin-F2α. In conclusion, this dietary trial indicates that the mechanisms linking dietary IP-TFA to cardiovascular disease may involve activation of the TNFα system.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Gentofte University Hospital, Uppsala University, United States Department of Agriculture, Copenhagen University Hospital, University of Copenhagen
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Scopus rating (2016): SJR 2.533 SNIP 1.344 CiteScore 4.46
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 2.583 SNIP 1.329 CiteScore 4.42
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 2.514 SNIP 1.318 CiteScore 4.5
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 2.364 SNIP 1.364 CiteScore 4.93
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 2.618 SNIP 1.549 CiteScore 5.39
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BFI (2011): BFI-level 1
Scopus rating (2011): SJR 2.922 SNIP 1.458 CiteScore 4.68
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 2.766 SNIP 1.491
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 2.402 SNIP 1.293
BFI (2008): BFI-level 1
Effects of Topical Corticosteroid and Tacrolimus on Ceramides and Irritancy to Sodium Lauryl Sulphate in Healthy Skin

The skin barrier, located in the stratum corneum, is influenced mainly by the lipid and protein composition of this layer. In eczematous diseases impairment of the skin barrier is thought to be of prime importance. Topical anti-inflammatory drugs and emollients are the most widely used eczema treatments. The aim of this study was to examine the effects of topically applied corticosteroid, tacrolimus and emollient on stratum corneum lipids and barrier parameters. Nineteen healthy volunteers participated in the study. Both forearms of the subjects were divided into four areas, which were treated twice daily for one week with betamethasone, tacrolimus, emollient, or left untreated, respectively. After one week each area was challenged with a 24 h sodium lauryl sulphate patch test. The lipids were collected using the cyanoacrylate method and evaluated by high performance thin layer chromatography. For evaluation of the skin barrier, transepidermal water loss, erythema and electrical capacitance were measured. The ceramide/cholesterol ratio was increased in betamethasone- (p = 0.008) and tacrolimus-treated (p = 0.025) skin compared with emollient-treated skin. No differences in ceramide subgroups were found between treatment regimes. Pretreatment with betamethasone (p = 0.01) or with tacrolimus (p = 0.001) causes a decreased inflammatory response to sodium lauryl sulphate compared with emollient. In conclusion, treatment with betamethasone and tacrolimus has a positive effect on the ceramide/cholesterol ratio and susceptibility to irritant reaction compared with an emollient.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, University of Copenhagen, Copenhagen University Hospital
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Scopus rating (2015): SJR 1.082 SNIP 1.293 CiteScore 1.58
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.078 SNIP 1.204 CiteScore 1.5
Enterotypes of the human gut microbiome

Our knowledge of species and functional composition of the human gut microbiome is rapidly increasing, but it is still based on very few cohorts and little is known about variation across the world. By combining 22 newly sequenced faecal metagenomes of individuals from four countries with previously published data sets, here we identify three robust clusters (referred to as enterotypes hereafter) that are not nation or continent specific. We also confirmed the enterotypes in two published, larger cohorts, indicating that intestinal microbiota variation is generally stratified, not continuous. This indicates further the existence of a limited number of well-balanced host-microbial symbiotic states that might respond differently to diet and drug intake. The enterotypes are mostly driven by species composition, but abundant molecular functions are not necessarily provided by abundant species, highlighting the importance of a functional analysis to understand microbial communities. Although individual host properties such as body mass index, age, or gender cannot explain the observed enterotypes, data-driven marker genes or functional modules can be identified for each of these host properties. For example, twelve genes significantly correlate with age and three functional modules with the body mass index, hinting at a diagnostic potential of microbial markers.

General information
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Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Novo Nordisk Foundation Center for Biosustainability, CFB - Metagenomic Systems Biology, European Molecular Biology Laboratory, Commissariat a l’Energie Atomique, INRA Institut National de La Recherche Agronomique, University Hospital Vall d’Hebron, Barcelona Supercomputing Center, University of Tokyo, University of Miyazaki, Wageningen IMARES, Tokyo Institute of Technology, BGI-Shenzhen, Institut Mériteux, UCB Pharma SA, Danone Research, Technical University of Denmark, Strasbourg University, Wellcome Trust Sanger Institute, Istituto Europeo di Oncologia, University of Copenhagen
Authors: Arumugam, M. (Ekstern), Raes, J. (Ekstern), Pelletier, E. (Ekstern), Le Paslier, D. (Ekstern), Yamada, T. (Ekstern), Mende, D. R. (Ekstern), Fernandes, G. R. (Ekstern), Tap, J. (Ekstern), Bruls, T. (Ekstern), Batto, J. (Ekstern),
Evolutionary dynamics of bacteria in a human host environment

Laboratory evolution experiments have led to important findings relating organism adaptation and genomic evolution. However, continuous monitoring of long-term evolution has been lacking for natural systems, limiting our understanding of these processes in situ. Here we characterize the evolutionary dynamics of a lineage of a clinically important opportunistic bacterial pathogen, Pseudomonas aeruginosa, as it adapts to the airways of several individual cystic fibrosis patients over 200,000 bacterial generations, and provide estimates of mutation rates of bacteria in a natural environment. In contrast to predictions based on in vitro evolution experiments, we document limited diversification of the evolving lineage despite a highly structured and complex host environment. Notably, the lineage went through an initial period of rapid adaptation caused by a small number of mutations with pleiotropic effects, followed by a period of genetic drift with limited phenotypic change and a genomic signature of negative selection, suggesting that the evolving lineage has reached a major adaptive peak in the fitness landscape. This contrasts with previous findings of continued positive selection from long-term in vitro evolution experiments. The evolved phenotype of the infecting bacteria further suggests that the opportunistic pathogen has transitioned to become a primary pathogen for cystic fibrosis patients.
Experience with the use of online lectures, video Modules, and wiki-websites in engineering education

We here present our experience with three computer-based teaching methodologies that we have used for a number of years in engineering education: Online lectures, video modules, and wiki websites. The aim is to provide the reader with concrete tools that can be used directly in teaching situations, and to inspire further use of information technologies.

General information

State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology
Authors: Pedersen, A. G. (Intern), Wernersson, R. (Intern)
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Publisher: Technical University of Denmark (DTU)
Ex vivo intestinal adhesion of Escherichia coli LF82 in Crohn's disease

Adherent-invasive Escherichia coli (AIEC) are reported to inhabit the gut mucosa in Crohn's disease (CD), however, little is known about the importance of host factors for the interplay between AIEC and the human gut. To examine if differences in bacterial adhesion patterns are disease associated, the AIEC-prototype strain LF82 was evaluated for its ability to adhere to ileal and colonic biopsies from CD and healthy controls (HC). Moreover, the efficacy of the non-pathogenic E. coli Nissle 1917 (ECN) in averting LF82 adhesion to ileal mucosa was assessed. Similar numbers of LF82 adhered to biopsies from CD and HC. A significantly greater LF82 attachment to ileal versus colonic mucosa was found in HC (P < 0.01), however, not in CD. ECN did not reduce the adhesion of LF82 to ileal specimens in CD or HC. These results show that enhanced bacterial adhesion ability is unlikely to play any significant role in CD, thus implying that other host protective factors may be impaired in CD. Further, exclusion of LF82 attachment by ECN co-incubation does not appear to represent a relevant treatment regimen.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Copenhagen University Hospital
Authors: Jensen, S. R. (Intern), Fink, L. N. (Intern), Nielsen, O. H. (Ekstern), Brynskov, J. (Ekstern), Pedersen, S. B. (Intern)
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BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.12 SJR 0.768 SNIP 0.752
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Scopus rating (2015): SJR 0.911 SNIP 0.764 CiteScore 1.99
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.928 SNIP 0.749 CiteScore 1.89
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ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 0.899 SNIP 0.696 CiteScore 2.01
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 0.87 SNIP 0.706 CiteScore 2.09
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.097 SNIP 0.678
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.098 SNIP 0.804
BACKGROUND: Although, systematic analysis of gene annotation is a powerful tool for interpreting gene expression data, it sometimes is blurred by incomplete gene annotation, missing expression response of key genes and secondary gene expression responses. These shortcomings may be partially circumvented by instead matching gene expression signatures to signatures of other experiments. FINDINGS: To facilitate this we present the Functional Association Response by Overlap (FARO) server, that match input signatures to a compendium of 242 gene expression signatures, extracted from more than 1700 Arabidopsis microarray experiments. CONCLUSIONS: Hereby we present a publicly available tool for robust characterization of Arabidopsis gene expression experiments which can point to similar experimental factors in other experiments. The server is available at http://www.cbs.dtu.dk/services/faro/.
Fish oil combined with SCFA synergistically prevent tissue accumulation of NEFA during weight loss in obese mice

Based on their proposed metabolic effects, we examined whether fish oil (FO) and SCFA, alone or in combination, accelerate weight loss and the resultant metabolic improvements. Obesity was induced in male C57BL/6J mice by high-energy feeding for 10 weeks. The mice were transferred to a low-fat diet (2.5w%) for 4 weeks, the source of fat being either FO, a lard–safflower oil mix (control), or both types combined with SCFA. Weight, fasting insulin, tissue and serum lipid concentrations, as well as mRNA amount of genes related to adipose inflammation and hepatic fat oxidation were determined. All groups lost weight and showed reduced fasting insulin concentrations and reduced liver TAG. However, weight loss on the control-fat diet caused significant increase in hepatic and cardiac NEFA. Substituting 20 % of the fat with SCFA increased weight loss by 48 % and reduced fasting insulin 1.5-fold more than the no-SCFA diets. It furthermore significantly increased the amount of mRNA for PPAR-α, and decreased the mRNA amount for NF-κB in the liver and white adipose tissue. The FO diets enhanced improvement of tissue lipid levels. Thus, FO improved liver TAG and NEFA levels compared with weight loss on the control diet. Combining FO and SCFA further reduced tissue NEFA accumulation. In conclusion, we found that dietary SCFA had a significant impact on gene expression in the liver and adipose tissue, and that the effect of FO on tissue NEFA content was modified by SCFA. Thus, interactions between fatty acids should be considered when studying the effects of specific fatty acids.

General information
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Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, University of Copenhagen
Authors: Pedersen, M. H. (Intern), Lauritzen, L. (Ekstern), Hellgren, L. (Intern)
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Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.583 SNIP 1.446 CiteScore 3.52
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BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.468 SNIP 1.278 CiteScore 3.18
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 2.72 SNIP 2.521 CiteScore 3.61
Background: The flavivirus genus is unusually large, comprising more than 70 species, of which more than half are known human pathogens. It includes a set of clinically relevant infectious agents such as dengue, West Nile, yellow fever, and Japanese encephalitis viruses. Although these pathogens have been studied extensively, safe and efficient vaccines lack for the majority of the flaviviruses.

Results: We have assembled a database that combines antigenic data of flaviviruses, specialized analysis tools, and...
workflows for automated complex analyses focusing on applications in immunology and vaccinology. FLAVIdB contains 12,858 entries of flavivirus antigen sequences, 184 verified T-cell epitopes, 201 verified B-cell epitopes, and 4 representative molecular structures of the dengue virus envelope protein. FLAVIdB was assembled by collection, annotation, and integration of data from GenBank, GenPept, UniProt, IEDB, and PDB. The data were subject to extensive quality control (redundancy elimination, error detection, and vocabulary consolidation). Further annotation of selected functionally relevant features was performed by organizing information extracted from the literature. The database was incorporated into a web-accessible data mining system, combining specialized data analysis tools for integrated analysis of relevant data categories (protein sequences, macromolecular structures, and immune epitopes). The data mining system includes tools for variability and conservation analysis, T-cell epitope prediction, and characterization of neutralizing components of B-cell epitopes. FLAVIdB is accessible at cvc.dfci.harvard.edu/flavi/

Conclusion: FLAVIdB represents a new generation of databases in which data and tools are integrated into a data mining infrastructures specifically designed to aid rational vaccine design by discovery of vaccine targets.

General information
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Dana-Farber Cancer Institute
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Scopus rating (2013): SJR 1.454 SNIP 1.086
ISI indexed (2013): ISI indexed no
Scopus rating (2012): SJR 0.712 SNIP 0.505
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Functional analysis of frequently expressed Chinese rhesus macaque MHC class I molecules Mamu-A1*02601 and Mamu-B*08301 reveals HLA-A2 and HLA-A3 supertypic specificities
The Simian immunodeficiency virus (SIV)-infected Indian rhesus macaque (Macaca mulatta) is the most established model of HIV infection and AIDS-related research, despite the potential that macaques of Chinese origin is a more relevant model. Ongoing efforts to further characterize the Chinese rhesus macaques' major histocompatibility complex (MHC) for composition and function should facilitate greater utilization of the species. Previous studies have demonstrated that Chinese-origin M. mulatta (Mamu) class I alleles are more polymorphic than their Indian counterparts, perhaps inferring a model more representative of human MHC, human leukocyte antigen (HLA). Furthermore, the Chinese rhesus
macaque class I allele Mamu-A1*02201, the most frequent allele thus far identified, has recently been characterized and shown to be an HLA-B7 supertype analog, the most frequent supertype in human populations. In this study, we have characterized two additional alleles expressed with high frequency in Chinese rhesus macaques, Mamu-A1*02601 and Mamu-B*08301. Upon the development of MHC–peptide-binding assays and definition of their associated motifs, we reveal that these Mamu alleles share peptide-binding characteristics with the HLA-A2 and HLA-A3 supertypes, respectively, the next most frequent human supertypes after HLA-B7. These data suggest that Chinese rhesus macaques may indeed be a more representative model of HLA gene diversity and function as compared to the species of Indian origin and therefore a better model for investigating human immune responses.

General information
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Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, La Jolla Institute for Allergy & Immunology, University of Wisconsin-Madison, University of Oklahoma
Authors: Southwood, S. (Ekstern), Solomon, C. (Ekstern), Hoof, I. (Intern), Rudersdorf, R. (Ekstern), Sidney, J. (Ekstern), Peters, B. (Ekstern), Wahl, A. (Ekstern), Hawkins, O. (Ekstern), Hildebrand, W. (Ekstern), Mothé, B. R. (Ekstern), Sette, A. (Ekstern)
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Scopus rating (2008): SJR 1.386 SNIP 0.774
Although CD8(+) T cells help control Mycobacterium tuberculosis infection, their M. tuberculosis Ag repertoire, in vivo frequency, and functionality in human tuberculosis (TB) remains largely undefined. We have performed genome-based bioinformatics searches to identify new M. tuberculosis epitopes presented by major HLA class I supertypes A2, A3, and B7 (covering 80% of the human population). A total of 432 M. tuberculosis peptides predicted to bind to HLA-A*0201, HLA-A*0301, and HLA-B*0702 (representing the above supertypes) were synthesized and HLA-binding affinities determined. Peptide-specific CD8(+) T cell proliferation assays (CFSE dilution) in 41 M. tuberculosis-responsive donors identified 70 new M. tuberculosis epitopes. Using HLA/peptide tetramers for the 18 most prominently recognized HLA-A*0201-binding M. tuberculosis peptides, recognition by cured TB patients' CD8(+) T cells was validated for all 18 epitopes. Intracellular cytokine staining for IFN-gamma, IL-2, and TNF-alpha revealed mono-, dual-, as well as triple-positive CD8(+) T cells, indicating these M. tuberculosis peptide-specific CD8(+) T cells were (poly) functional. Moreover, these T cells were primed during natural infection, because they were absent from M. tuberculosis-noninfected individuals. Control CMV peptide/HLA-A*0201 tetramers stained CD8(+) T cells in M. tuberculosis-infected and noninfected individuals equally, whereas Ebola peptide/HLA-A*0201 tetramers were negative. In conclusion, the M. tuberculosis-epitope/Ag repertoire for human CD8(+) T cells is much broader than hitherto suspected, and the newly identified M. tuberculosis Ags are recognized by (poly) functional CD8(+) T cells during control of infection. These results impact on TB-vaccine design and biomarker identification. The Journal of Immunology, 2011, 186: 1068-1080.
Genome Sequence of Campylobacter jejuni strain 327, a strain isolated from a turkey slaughterhouse

Campylobacter is one of the leading causes of food-borne gastroenteritis and has a high prevalence in poultry. Campylobacter jejuni subsp. jejuni 327 is a subspecies of the genus Campylobacter of the family Campylobacteraceae in the phylum Proteobacteria. The microaerophilic, spiral shaped, catalase positive bacterium obtains energy from the metabolism of amino acids and Krebs cycle intermediates. Strain 327 was isolated from a turkey slaughter production line and is considered environmentally sensitive to food processing (cold, heat, drying) and storage conditions. The 327 whole genome shotgun sequence of 1,618,613 bp long consists of 1,740 protein-coding genes, 46 tRNA genes and 3 rRNA operons. A protein based BLAST analysis places the turkey isolate 327 close to the human clinical strain 81116 (NCTC 11828).

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Freie Universität Berlin, University of Copenhagen
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Genome sequences of two stress-tolerant Campylobacter jejuni poultry strains, 305 and DFVF1099.

Campylobacter jejuni is a food-borne pathogen with a high prevalence in poultry meat, which in fresh unfrozen condition is the major source of campylobacteriosis. C. jejuni strains DFVF1099 and 305 are considered tolerant to several environmental stresses (T. Birk et al., J. Food Prot. 73:258–265, 2010; S. L. On et al., Int. J. Med. Microbiol. 296:353–363, 2006). Here, we report the genome sequences of C. jejuni 305 and DFVF1099, a turkey and a chicken isolate, respectively. ©American Society for Microbiology. All rights reserved.
"Good teaching practice" at DTU Systems Biology - sustaining quality in teaching and learning

Success in developing teaching and learning in engineering education in general, as well as in a CDIO context, depends on continuous development of teaching competences among faculty members. Thus, it is essential to develop systems that promote understanding of how teaching and assessment can support student learning within disciplinary knowledge as well as development of professional skills. Development and maintenance of high quality teaching and learning furthermore requires that teachers have the ability to reflect critically on their teaching activities and understand its impact on the students’ learning process. To succeed in reaching these goals, development of teaching competences and knowledge in the fields of teaching and learning must be combined with continuous possibilities to reflect on teaching practice in a structured way. Development of successful teaching also requires that faculty members are inspired and encouraged to try new ways and methods in teaching, and gaining an extended understanding in how students learning can be efficiently supported. In this paper we describe a novel initiative, a concept of Good Teaching Practice, that has been developed through a process involving faculty at the department of Systems Biology at the Technical University of Denmark. The GTP initiative addresses important factors for effective teaching and enhancement of student learning. On the surface GTP is structured as an online tool, which makes six statements about important factors that support student learning that the teachers at the department are supposed to consider. This is coupled to a wiki-based web resource for sharing good examples from teaching practice among faculty. By formulating a teaching and learning profile at the department level the importance of teaching for the department are emphasized and at the same time, the wiki-based resource for sharing teaching experience shows that teaching is a shared responsibility among the entire faculty. On the website, the theoretical framework underlying GTP provides a shorthand introduction to the important prerequisites for students learning and provides definitions that provide the faculty members with a common language to use in discussions of teaching and learning. The GTP concept addresses standard 10 in the CDIO context which focuses on the enhancement of the development of teaching and learning at department level and provides the teachers with tools to conduct teaching proficiently.

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Heterozygous deletion at the RLN1 locus in a family with testicular germ cell cancer identified by integrating copy number variation data with phenome and interactome information
To search for disease-related copy number variations (CNVs) in families with a high frequency of germ cell tumours (GCT), we analysed 16 individuals from four families by array comparative genomic hybridization (aCGH) and applied an integrative systems biology algorithm that prioritizes risk-associated genes among loci targeted by CNVs. The top-ranked
candidate, RLN1, encoding a Relaxin-H1 peptide, although only detected in one of the families, was selected for further investigations. Validation of the CNV at the RLN1 locus was performed as an association study using qPCR with 106 sporadic testicular GCT patients and 200 healthy controls. Observed CNV frequencies of 1.9% among cases and 1.5% amongst controls were not significantly different and this was further confirmed by CNV data extracted from a genome-wide analysis of 189 cases and 380 controls, where similar frequencies of 2.2% were observed in both groups (p = 1). Immunohistochemistry for Relaxin-H1 (RLN1), Relaxin-H2 (RLN2) and their cognate receptor, RXFP1, detected one, and in some cases both, of the relaxins in Leydig cells, Sertoli cells and a subset of neoplastic germ cells, whereas the receptor was present in Leydig cells and spermatids. Collectively, the findings show that a heterozygous loss at the RLN1 locus is not a genetic factor mediating high population-wide risk for testicular germ cell tumour, but do not exclude a contribution of this aberration in some cases of cancer. The preliminary expression data suggest a possible role of the relaxin peptides in spermatogenesis and warrant further studies.
Traditionally, T cell epitope discovery requires considerable amounts of tedious, slow, and costly experimental work. During the last decade, prediction tools have emerged as essential tools allowing researchers to select a manageable list of epitope candidates to test from a larger peptide, protein, or even proteome. However, no current tools address the complexity caused by the highly polymorphic nature of the restricting HLA molecules, which effectively individualizes T cell responses. To fill this gap, we here present an easy-to-use prediction tool named HLArestrictor (http://www.cbs.dtu.dk/services/HLArestrictor), which is based on the highly versatile and accurate NetMHCpan predictor, which here has been optimized for the identification of both the MHC restriction element and the corresponding minimal epitope of a T cell response in a given individual. As input, it requires high-resolution (i.e., 4-digit) HLA typing of the individual. HLArestrictor then predicts all 8-11mer peptide binders within one or more larger peptides and provides an overview of the predicted HLA restrictions and minimal epitopes. The method was tested on a large dataset of HIV IFNγ ELISpot peptide responses and was shown to identify HLA restrictions and minimal epitopes for about 90% of the positive peptide/patient pairs while rejecting more than 95% of the negative peptide-HLA pairs. Furthermore, for 18 peptide/HLA tetramer validated responses, HLArestrictor in all cases predicted both the HLA restriction element and minimal epitope. Thus, HLArestrictor should be a valuable tool in any T cell epitope discovery process aimed at identifying new epitopes from infectious diseases and other disease models.
Human Leukocyte Antigen (HLA) Class I Restricted Epitope Discovery In Yellow Fever and Dengue Viruses: Importance of HLA Binding Strength.

Epitopes from all available full-length sequences of yellow fever virus (YFV) and dengue fever virus (DENV) restricted by Human Leukocyte Antigen class I (HLA-I) alleles covering 12 HLA-I supertypes were predicted using the NetCTL algorithm. A subset of 179 predicted YFV and 158 predicted DENV epitopes were selected using the EpiSelect algorithm to allow for optimal coverage of viral strains. The selected predicted epitopes were synthesized and approximately 75% were found to bind the predicted restricting HLA molecule with an affinity, K(D), stronger than 500 nM. The immunogenicity of 25 HLA-A*02:01, 28 HLA-A*2402 and 28 HLA-B*07:02 binding peptides was tested in three HLA-transgenic mice models and led to the identification of 17 HLA-A*02:01, 4 HLA-A*2402 and 4 HLA-B*07:02 immunogenic peptides. The immunogenic peptides bound HLA significantly stronger than the non-immunogenic peptides. All except one of the immunogenic peptides had K(D) below 100 nM and the peptides with K(D) below 5 nM were more likely to be immunogenic. In addition, all the immunogenic peptides that were identified as having a high functional avidity had K(D) below 20 nM. A*02:01 transgenic mice were also inoculated twice with the 17DD YFV vaccine strain. Three of the YFV A*02:01 restricted peptides activated T-cells from the infected mice in vitro. All three peptides that elicited responses had an HLA binding affinity of 2 nM or less. The results indicate the importance of the strength of HLA binding in shaping the immune response.
Huntingtin-interacting protein 14 is a type 1 diabetes candidate protein regulating insulin secretion and β-cell apoptosis

Type 1 diabetes (T1D) is a complex disease characterized by the loss of insulin-secreting β-cells. Although the disease has a strong genetic component, and several loci are known to increase T1D susceptibility risk, only few causal genes have currently been identified. To identify disease-causing genes in T1D, we performed an in silico "phenome–interactome analysis" on a genome-wide linkage scan dataset. This method prioritizes candidates according to their physical interactions at the protein level with other proteins involved in diabetes. A total of 11 genes were predicted to be likely disease genes in T1D, including the INS gene. An unexpected top-scoring candidate gene was huntingtin-interacting protein (HIP)-14/ZDHHC17. Immunohistochemical analysis of pancreatic sections demonstrated that HIP14 is almost exclusively expressed in insulin-positive cells in islets of Langerhans. RNAi knockdown experiments established that HIP14 is an antiapoptotic protein required for β-cell survival and glucose-stimulated insulin secretion. Proinflammatory cytokines (IL-1β and IFN-γ) that mediate β-cell dysfunction in T1D down-regulated HIP14 expression in insulin-secreting INS-1 cells and in isolated rat and human islets. Overexpression of HIP14 was associated with a decrease in IL-1β–induced NF-κB activity and protection against IL-1β–mediated apoptosis. Our study demonstrates that the current network biology approach is a valid method to identify genes of importance for T1D and may therefore embody the basis for more rational and targeted therapeutic approaches.
Major histocompatibility complex (MHC) class I restricted cytotoxic T lymphocytes (CTL) are known to play an important role in the control of Mycobacterium tuberculosis infection so identification of CTL epitopes from M. tuberculosis is of importance for the development of effective peptide-based vaccines. In the present work, bioinformatics technology was employed to predict binding motifs of 9mer peptides derived from M. tuberculosis for the 12 HLA-I supertypes. Subsequently, the predicted peptides were synthesized and assayed for binding to HLA-I molecules in a biochemically based system. The antigenicity of a total of 157 peptides with measured affinity for HLA-I molecules of KD ≤ 500 nm were evaluated using peripheral blood T cells from strongly purified protein derivative reactive healthy donors. Of the 157 peptides, eight peptides (5%) were found to induce T-cell responses. As judged from blocking with HLA class I and II subtype antibodies in the ELISPOT assay culture, none of the eight antigenic peptides induced HLA class I restricted CD8+ T-cell responses. Instead all responses were blocked by pan-HLA class II and anti-HLA-DR antibodies. In addition, CD4+ T-cell depletion before the 10 days of expansion, resulted in total loss of reactivity in the ELISPOT culture for most peptide specificities. FACS analyses with intracellular interferon-γ staining of T cells expanded in the presence of M. tuberculosis peptides confirmed that the responsive cells were indeed CD4+. In conclusion, T-cell immunity against HLA-I binding 9mer M. tuberculosis-derived peptides might in many cases turn out to be mediated by CD4+ T cells and restricted by HLA-II molecules. The use of 9mer peptides recognized by both CD8+ and CD4+ T cells might be of importance for the development of future M. tuberculosis peptide-based vaccines.
Ileal adhesion of virulent E. coli LF82 is not enhanced in Crohn’s disease.

General information
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Ileal adhesion of virulent E. coli LF82 is not enhanced in Crohn's disease

Adherent-invasive Escherichia coli (AIEC) comprise a new group of E. coli species named from their distinctive ability to adhere to and invade the intestinal epithelium. The AIEC strains have been associated to the ileal mucosa in Crohn's disease (CD), and the impact of AIEC in the pathogenesis of CD has been further strengthened from the evidence that the ileum in CD harbors an abnormally high number of E. coli species. S16 2010 IBD Abstracts The aim of this study was to examine the adhesion of the AIEC reference strain, LF82, to tissue samples from ileum and colon in CD and healthy controls. A second purpose was to assess the probiotic efficacy of E. coli Nissle 1917 (ECN) in averting LF82 adhesion to ileal mucosa. Ileal and colonic specimens were obtained from patients with CD ileitis and controls (n¼10). A model was developed to investigate bacterial adhesion to intestinal biopsies and comprised: 1) incubation of tissue (inclusive of mucous) with 107 bacteria or buffer for 1 hour, 2) removal of non-adhered bacteria by extensive washing, and 3) absolute quantification of tissue-adhered LF82 and indigenous E. coli by a pre-validated assay including quantitative real-time PCR. Selective primers- and probes were designed specifically for targeting the pMT1-like plasmid in LF82 and E. coli 16S ribosomal DNA for quantifying the general E. coli population. Bacterial numbers were related to tissue weight. A thoroughly validated model with a coefficient of variation <2 % was developed and employed for investigation of the bacterial adherence to human intestinal specimens. LF82 adhered to intestinal biopsies in both CD and controls. Enhanced adhesion was, however, not observed in the ileum as compared to the colon in CD, which was in contradiction to controls that had a significantly higher LF82-attachment to the ileal epithelium as compared to that of the colon (P <0.01). The variation in LF82 adhesion between ileal and colonic specimens was more prominent in CD than in controls. Although not statistically significant, a trend towards higher counts of indigenous E. coli was observed in the ileum as compared to the colon of CD, and the number of indigenous LF82 and total E. coli bacteria tended to be inversely correlated in both ileum and colon tissue. Further, ECN did not avert the adhesion of LF82 to ileal specimens, but instead ECN likely favoured LF82 adhesion particularly in CD. Conclusively it was shown that LF82 preferentially adhere to ileal tissue in controls, but not in CD suggesting that the intestinal microenvironment of the colon is changed in terminal ileitis. Co-incubation with ECN tended to increase ileal LF82 adhesion, thus highlighting that careful mechanistic studies are warranted before including ECN in clinical studies. The current study demonstrates a great variability in host LF82 interactions within the group of patients with CD ileitis, thus stressing individual response patterns against LF82.

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Immune system simulation online

MOTIVATION: The recognition of antigenic peptides is a major event of an immune response. In current mesoscopic-scale simulators of the immune system, this crucial step has been modeled in a very approximated way. RESULTS: We have equipped an agent-based model of the immune system with immuno-informatics methods to allow the simulation of the cardinal events of the antigenic recognition, going from single peptides to whole proteomes. The recognition process accounts for B cell-epitopes prediction through Parker-scale affinity estimation, class I and II HLA peptide prediction and binding through position-specific scoring matrices based on information from known HLA epitopes prediction tools, and TCR binding to HLA–peptide complex calculated as the averaged sum of a residue–residue contact potential. These steps are executed for all lymphocytes agents encountering the antigen in a wide-reaching Monte Carlo simulation.

AVAILABILITY: http://www.cbs.dtu.dk/services/C-ImmSim-10.1/ CONTACT: f.castiglione@iac.cnr.it
Immunogenic CTL Epitopes Tend to be Stably Bound to MHC Class I Molecules: Implications for 'Holes in the Stably Bound MHC-I Repertoire'

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BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.898 SNIP 0.666 CiteScore 1.91
Web of Science (2014): Indexed yes
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Scopus rating (2013): SJR 0.86 SNIP 0.712 CiteScore 2.05
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Web of Science (2011): Indexed yes
Improved glucose tolerance after intensive life style intervention occurs without changes in muscle ceramide or triacylglycerol in morbidly obese subjects

Aim: This study investigated the effect of a 15-week life style intervention (hypocaloric diet and regular exercise) on glucose tolerance, skeletal muscle lipids and muscle metabolic adaptations in 14 female and 9 male morbidly obese subjects (age: 32.5 +/- 2.3 years, BMI: 46.1 +/- 1.9 kg m(-2)). Method: Before and after the life style intervention an oral glucose tolerance test (OGTT) was performed and a muscle biopsy was obtained in the fasted state. Maximal oxygen uptake was measured by an indirect test. Results: After the intervention body weight was decreased (P
Induction of Foot-and-Mouth Disease Virus-Specific Cytotoxic T Cell Killing by Vaccination

Foot-and-mouth disease (FMD) continues to be a significant threat to the health and economic value of livestock species. This acute infection is caused by the highly contagious FMD virus (FMDV), which infects cloven-hoofed animals including large and small ruminants and swine. Current vaccine strategies are all directed toward the induction of neutralizing antibody responses. However, the role of cytotoxic T lymphocytes (CTLs) has not received a great deal of attention, in part because of the technical difficulties associated with establishing a reliable assay of cell killing for this highly cytopathic virus. Here, we have used recombinant human adenovirus vectors as a means of delivering FMDV antigens in a T cell-directed vaccine in pigs. We tested the hypothesis that impaired processing of the FMDV capsid would enhance cytolytic activity, presumably by targeting all proteins for degradation and effectively increasing the class I MHC/FMDV peptide concentration for stimulation of a CTL response. We compared such a T cell targeting vaccine with the parental vaccine, previously shown to effectively induce a neutralizing antibody response. Our results show induction of FMDV-specific CD8(+) CTL killing of MHC matched target cells in an antigen specific manner. Further, we confirm these results by MHC tetramer staining. This work presents the first demonstration of FMDV specific, CTL killing and confirmation by MHC tetramer staining in response to vaccination against FMDV.
In Silico Predictions of hERG Channel Blockers in Drug Discovery: From Ligand-Based and Target-Based Approaches to Systems Chemical Biology

The risk for cardiotoxic side effects represents a major problem in clinical studies of drug candidates and regulatory agencies have explicitly recommended that all new drug candidates should be tested for blockage of the human Ether-a-go-go Related-Gene (hERG) potassium channel. Indeed, several drugs with different therapeutic indications and recognized as hERG blockers were recently withdrawn due to the risk of QT prolongation, arrhythmia and Torsade de Pointes. In silico techniques can provide a priori knowledge of hERG blockers, thus reducing the costs associated with screening assays. Significant progress has been made in structure-based and ligand-based drug design and a number of models have been developed to predict hERG blockage. Although approaches such as homology modeling in combination with docking and molecular dynamics bring us closer to understand the drug-channel interactions whereas QSAR and classification models provide a faster assessment and detection of hERG-related drug toxicity, limitation on the applicability domain of the current models and integration of data from diverse in vitro approaches are still issues to challenge. Therefore, this review will emphasize on current methods to predict hERG blockers and the need of consistent data to improve the quality and performance of the in silico models. Finally, integration of network-based analysis on drugs inducing potentially long-QT syndrome and arrhythmia will be discussed as a new perspective for a better understanding of the drug responses in systems chemical biology.
Integrating phenotypic data from electronic patient records with molecular level systems biology: Abstract of invited lecture

Electronic patient records remain a rather unexplored, but potentially rich data source for discovering correlations between diseases. We describe a general approach for gathering phenotypic descriptions of patients from medical records in a systematic and non-cohort dependent manner. By extracting phenotype information from the free-text in such records we demonstrate that we can extend the information contained in the structured record data, and use it for producing fine-grained patient stratification and disease co-occurrence statistics. The approach uses a dictionary based on the International Classification of Disease ontology and is therefore in principle language independent. As a use case we show how records from a Danish psychiatric hospital lead to the identification of disease correlations, which subsequently are mapped to systems biology frameworks.

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis
Authors: Brunak, S. (Intern)
Interdisciplinary Evaluation of Broadly-Reactive HLA Class II Restricted Epitopes Eliciting HIV-Specific CD4+T Cell Responses: Abstract of poster presentation

Background: CD4+ T cells orchestrate immune protection by "helping" other cells of our immune system to clear viral infections. It is well known that the preferential infection and depletion of CD4+ T cells contributes to hampered systemic T cell help following HIV infection. However, the functional and immunodominant discrepancies of CD4+ T cell responses targeting promiscuous MHC II restricted HIV epitopes remains poorly defined. Thus, utilization of interdisciplinary approaches might aid revealing broadly reactive peptides eliciting CD4+ T cell responses. Methods: We utilized the novel
bioinformatic prediction program NetMHCIIpan to select 64 optimized MHC II restricted epitopes located in the HIV Gag, Pol, Env, Nef and Tat regions. The epitopes were selected to cover the global diversity of the virus (multiple subtypes) and the human immune system (diverse MHC II types). Optimized polychromatic flow cytometry analysis, including the functional markers IFNγ, IL-2, IL-21, MIP-1β and TNFα, revealed immunogenicity of the individual epitopes. The study subjects (n = 38) were of diverse ethnical background infected by different HIV subtypes. High resolution HLA typing and sequences of the HIV-Gag and Nef regions were obtained. Results: The FACS analysis revealed immunogenicity against 73% of the epitopes. All subjects, except one, recognized at least one epitope. Interestingly, almost all epitopes located in Gag (15/15) and Nef (14/15) elicited responses, while epitopes in Pol (10/15) and Env (5/15) revealed restricted CD4+ T cell immunogenicity. This difference in immunogenicity between the regions was significant (One-way ANOVA: p <0.001). Additionally, Gag and Nef epitopes generated greater polyfunctionality than Poland Env-specific CD4+ T cells. Importantly, we found that the use of optimized epitopes improved the polyfunctionality compared with overlapping HIV Gag (p55) peptides. Conclusion: Using an unbiased approach where we have predicted peptides with same prerequisites, we demonstrate that HIV-specific CD4+ T cell immunodominance is heavily skewed, targeting particularly Gag and Nef.

General information
State: Published
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Intrauterine exposure to mild analgesics is a risk factor for development of male reproductive disorders in human and rat.

**BACKGROUND:** More than half of pregnant women in the Western world report intake of mild analgesics, and some of these drugs have been associated with anti-androgenic effects in animal experiments. Intrauterine exposure to anti-androgens is suspected to contribute to the recent increase in male reproductive problems, and many of the anti-androgenic compounds are like the mild analgesics potent inhibitors of prostaglandin synthesis. Therefore, it appears imperative to further investigate the potential endocrine disrupting properties of mild analgesics.

**METHODS:** In a prospective birth cohort study, 2297 Danish and Finnish pregnant women completed a questionnaire and 491 of the Danish mothers participated in a telephone interview, reporting on their use of mild analgesics during pregnancy. The testicular position of newborns was assessed by trained paediatricians. In rats, the impact of mild analgesics on anogenital distance (AGD) after intrauterine exposure was examined together with the effect on ex vivo gestational day 14.5 testes.

**RESULTS:** In the Danish birth cohort, the use of mild analgesics was dose-dependently associated with congenital cryptorchidism. In particular, use during the second trimester increased the risk. This risk was further increased after the simultaneous use of different analgesics. The association was not found in the Finnish birth cohort. Intrauterine exposure of rats to paracetamol led to a reduction in the AGD and mild analgesics accordingly reduced testosterone production in ex vivo fetal rat testes.

**CONCLUSION:** There was an association between the timing and the duration of mild analgesic use during pregnancy and the risk of cryptorchidism. These findings were supported by anti-androgenic effects in rat models leading to impaired masculinization. Our results suggest that intrauterine exposure to mild analgesics is a risk factor for development of male reproductive disorders.
Jetset: selecting the optimal microarray probe set to represent a gene

Background: Interpretation of gene expression microarrays requires a mapping from probe set to gene. On many Affymetrix gene expression microarrays, a given gene may be detected by multiple probe sets, which may deliver inconsistent or even contradictory measurements. Therefore, obtaining an unambiguous expression estimate of a pre-specified gene can be a nontrivial but essential task. Results: We developed scoring methods to assess each probe set for specificity, splice isoform coverage, and robustness against transcript degradation. We used these scores to select a single representative probe set for each gene, thus creating a simple one-to-one mapping between gene and probe set. To test this method, we evaluated concordance between protein measurements and gene expression values, and between sets of genes whose expression is known to be correlated. For both test cases, we identified genes that were nominally detected by multiple probe sets, and we found that the probe set chosen by our method showed stronger concordance. Conclusions: This method provides a simple, unambiguous mapping to allow assessment of the expression levels of specific genes of interest.

General information

State: Published
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Leptin levels in the young offspring from dams fed hypercaloric diets during gestation are decoupled from body-weight, regardless of maternal post-natal diets

Linking Genotype and Phenotype of Saccharomyces cerevisiae Strains Reveals Metabolic Engineering Targets and Leads to Triterpene Hyper-Producers

Background: Metabolic engineering is an attractive approach in order to improve the microbial production of drugs. Triterpenes is a chemically diverse class of compounds and many among them are of interest from a human health perspective. A systematic experimental or computational survey of all feasible gene modifications to determine the genotype yielding the optimal triterpene production phenotype is a laborious and time-consuming process.

Methodology/Principal Findings: Based on the recent genome-wide sequencing of Saccharomyces cerevisiae CEN. PK 113-7D and its phenotypic differences with the S288C strain, we implemented a strategy for the construction of a beta-amyrin production platform. The genes Erg8, Erg9 and HFA1 contained non-silent SNPs that were computationally analyzed to evaluate the changes that cause in the respective protein structures. Subsequently, Erg8, Erg9 and HFA1 were correlated with the increased levels of ergosterol and fatty acids in CEN. PK 113-7D and single, double, and triple gene over-expression strains were constructed. Conclusions: The six out of seven gene over-expression constructs had a considerable impact on both ergosterol and beta-amyrin production. In the case of beta-amyrin formation the triple over-expression construct exhibited a nearly 500% increase over the control strain making our metabolic engineering strategy the most successful design of triterpene microbial producers.
Machine learning competition in immunology – Prediction of HLA class I binding peptides

Experimental studies of immune system and related applications such as characterization of immune responses against pathogens, vaccine design, or optimization of therapies are combinatorially complex, time-consuming and expensive. The main methods for large-scale identification of T-cell epitopes from pathogens or cancer proteomes involve either reverse immunology or high-throughput mass spectrometry (HTMS). Reverse immunology approaches involve pre-screening of proteomes by computational algorithms, followed by experimental validation of selected targets ([Mora et al., 2006], [De Groot et al., 2008] and [Larsen et al., 2010]). HTMS involves HLA typing, immunoaffinity chromatography of HLA
molecules, HLA extraction, and chromatography combined with tandem mass spectrometry, followed by the application of computational algorithms for peptide characterization (Bassani-Sternberg et al., 2010). Hundreds of naturally processed HLA class I associated peptides have been identified in individual studies using HTMS in normal (Escobar et al., 2008), cancer ([Antwi et al., 2009] and [Bassani-Sternberg et al., 2010]), autoimmunity-related (Ben Dror et al., 2010), and infected samples (Wahl et al., 2010). Computational algorithms are essential steps in high-throughput identification of T-cell epitope candidates using both reverse immunology and HTMS approaches. Peptide binding to MHC molecules is the single most selective step in defining T cell epitope and the accuracy of computational algorithms for prediction of peptide binding, therefore, determines the accuracy of the overall method. Computational predictions of peptide binding to HLA, both class I and class II, use a variety of algorithms ranging from binding motifs to advanced machine learning techniques ([Brusic et al., 2004] and [Lafuente and Reche, 2009]) and standards for their assessments have been developed. The assessments of computational servers that predict peptide binding to several common HLA class I alleles have been performed by different groups (see [Peters et al., 2006], [Lin et al., 2008] and [Gowthaman et al., 2010]). Some of these models were reported to be highly accurate while others need improvement.
Many Putative Endocrine Disruptors Inhibit Prostaglandin Synthesis

Background: Prostaglandins (PGs) play key roles in development and maintenance of homeostasis of the adult body. Despite these important roles, it remains unclear whether the PG pathway is a target for endocrine disruption. However, several known endocrine disrupting compounds (EDCs) share a high degree of structural similarity with mild analgesics. Objectives/Methods: Using cell-based transfection and transduction experiments, mass spectrometry, and organotypic assays together with molecular modeling, we investigated whether inhibition of the PG pathway by known EDCs could be a novel point of endocrine disruption. Results: We found that many known EDCs inhibit the PG pathway in a mouse Sertoli cell line and in human primary mast cells. The EDCs also reduced PG synthesis in ex vivo rat testis and it was correlated with a reduced testosterone production. The inhibition of PG synthesis occurs without involvement of canonical prostaglandin receptors or the peroxisome proliferator-activator receptors (PPARs), which have previously been described as targets of EDCs. Instead, our results suggest that the compounds may bind directly into the active site of the cyclooxygenase (COX) enzymes, thereby obstructing the conversion of arachidonic acid to PG precursors without interfering with the expression of the COX enzymes. A common feature of the PG inhibitory EDCs is the presence of aromatic groups that may stabilize binding in the hydrophobic active site of the COX enzymes. Conclusion: Our findings suggest a hitherto unknown mode of action by EDCs through inhibition of the PG pathway and suggest new avenues to investigate effects of EDCs on reproductive and immunological disorders that have become increasingly common in recent decades.
Maternal energy intake during lactation and gestation has an effect on leptin levels in the young and adult pups

Meta-analysis of heterogeneous data sources for genome-scale identification of risk genes in complex phenotypes

Meta-analyses of large-scale association studies typically proceed solely within one data type and do not exploit the potential complementarities in other sources of molecular evidence. Here, we present an approach to combine heterogeneous data from genome-wide association (GWA) studies, protein-protein interaction screens, disease similarity, linkage studies, and gene expression experiments into a multi-layered evidence network which is used to prioritize the entire protein-coding part of the genome identifying a shortlist of candidate genes. We report specifically results on bipolar disorder, a genetically complex disease where GWA studies have only been moderately successful. We validate one such candidate experimentally, YWHAH, by genotyping five variations in 640 patients and 1,377 controls. We found a significant allelic association for the rs1049583 polymorphism in YWHAH (adjusted \( P = 5.6e^{-3} \)) with an odds ratio of 1.28 [1.12–1.48], which replicates a previous case-control study. In addition, we demonstrate our approach's general applicability by use of type 2 diabetes data sets. The method presented augments moderately powered GWA data, and represents a validated, flexible, and publicly available framework for identifying risk genes in highly polygenic diseases.

Metatranscriptomics of the human gut microbiome

Our ‘other’ genome is the collective genetic information in all of the microorganisms that are living on and within us. Collectively known as the microbiome, these microbial cells outnumber human cells in the body by more than 10 to 1, and the genes carried by these organisms outnumber the genes in the human genome by more than 100 to 1.

How these organisms contribute to and affect human health is poorly understood, but the emerging field of metagenomics promises a more comprehensive and complete understanding of the human microbiome. In the European-funded Metagenomics of the Human Intestinal Tract (MetaHIT) project [1], we combined next-generation sequencing with high-density microarrays, generating metagenomic and metatranscriptomic data for more than 400 individuals.

The combined data reveal clusters of coexisting species with differences in pathway and gene function activity, suggesting that there is a division of labor between the bacterial species in the human gut microbiome.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Novo Nordisk Foundation Center for Biosustainability, CFB - Metagenomic Systems Biology, Department of Systems Biology, Center for Biological sequence analysis
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BFI (2018): BFI-level 2
Microbial community structure of Arctic multiyear sea ice and surface seawater by 454 sequencing of the 16S RNA gene. Dramatic decreases in the extent of Arctic multiyear ice (MYI) suggest this environment may disappear as early as 2100, replaced by ecologically different first-year ice. To better understand the implications of this loss on microbial biodiversity, we undertook a detailed census of the microbial community in MYI at two sites near the geographic North Pole using parallel tag sequencing of the 16S rRNA gene. Although the composition of the MYI microbial community has been characterized by previous studies, microbial community structure has not been. Although richness was lower in MYI than in underlying surface water, we found diversity to be comparable using the Simpson and Shannon's indices (for Simpson t=0.65, P=0.56; for Shannon t=0.25, P=0.84 for a Student's t-test of mean values). Cyanobacteria, comprising 6.8% of reads obtained from MYI, were observed for the first time in Arctic sea ice. In addition, several low-abundance clades not
previously reported in sea ice were present, including the phylum TM7 and the classes Spartobacteria and Opitutae. Members of Coraliomargarita, a recently described genus of the class Opitutae, were present in sufficient numbers to suggest niche occupation within MYI.

**General information**

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- Web of Science (2016): Indexed yes
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- Web of Science (2011): Indexed yes
- BFI (2010): BFI-level 2
- Scopus rating (2010): SJR 3.245 SNIP 1.626
- Web of Science (2010): Indexed yes
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- Scopus rating (2009): SJR 2.563 SNIP 1.445
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MicroRNA-130a–mediated down-regulation of Smad4 contributes to reduced sensitivity to TGF-β1 stimulation in granulocytic precursors

Smad4 is important in the TGF-β pathway and required for transcriptional activation and inhibition of cell growth after TGF-β1 stimulation. We demonstrate that miR-130a is differentially expressed during granulopoiesis and targets Smad4 mRNA. The transcript for Smad4 is present throughout neutrophil maturation, but Smad4 protein is undetectable in the most immature cells, where miR-130a is highly expressed. Two miR-130a binding sites were identified in the 3'-untranslated region of the Smad4 mRNA. Overexpression of miR-130a in HEK293, A549, and 32Dcl3 cells repressed synthesis of Smad4 protein without affecting Smad4 mRNA level. Repression of Smad4 synthesis in a granulocytic cell line by miR-130a reduced its sensitivity to TGF-β1–induced growth inhibition. This effect was reversed by inhibiting the activity of miR-130a with an antisense probe or by expressing a Smad4 mRNA lacking miR-130a binding sites. High endogenous miR-130a and Smad4 mRNA levels and low expression of Smad4 protein were found in the t(8;21)(q22;q22) acute myelogenous leukemia–derived cell line Kasumi-1. When miR-130a was inhibited by an antisense RNA, the amount of Smad4 protein increased in Kasumi-1 cells and rendered it susceptible for TGF-β1–mediated cell growth inhibition. Our data indicate that miR-130a is involved in cell cycle regulation of granulocytic cells through engagement of Smad4 in the TGF-β pathway.
Mir-130a-Mediated Downregulation of SMAD4 Contributes to Reduced Sensitivity to TGF beta Stimulation in Promyelocytic Cells

MicroRNAs (miRNA) are noncoding RNA molecules that regulate the synthesis of proteins and, if dysregulated, can result in development of various form of cancers. We have found that miR-130a is highly expressed in immature proliferating granulocytic precursors. In more mature granulocytes the miR-130a expression is significant lower. In acute myeloid leukemia the granulocyte precursors have lost the ability to undergo terminal maturation, leading to accumulation of non-functional, immature granulocytes (myeloblasts). We hypothesize that a sustained high expression of miR-130a during granulopoiesis may sustain continuous cell proliferation. TGF-beta is a strong inhibitor of cell proliferation and lack of TGF-beta expression is associated with various form of cancer. Smad4 is an essential compound in the TGF-beta signaling pathway. Using microRNA target-prediction software, we identified Smad4 as a putative target for miR-130a. This was confirmed experimentally by demonstrating that transient overexpression of miR-130a results in reduction in the amount of Smad4 protein. Luciferase reporter constructs with the 3'-UTR of Stnad4 also respond to miR-130a - an effect that is abolished by point mutations in the miRNA-binding site. In agreement, we observed that stable overexpression of miR-130a in a granulocytic cell line reduces the level of Smad4 protein, and render the cells less sensitive to TGF-beta-induced growth inhibition. This was also confirmed with cell cycles analysis. Furthermore, the effect was diminished when transfecting the same clones with SMAD4 lacking the 3-UTR. In line with our hypothesis, the most immature granulocyte precursors demonstrate the highest expression of miR-130a is highest, and the lowest. expression of Smad4 protein. As the granulocyte precursors mature, the expression of miR-130a decreases dramatically whereas the level of Smad4 protein expression increases demonstrating inverse correlation between miR-130a and Smad4 protein. The level of Stnad4 mRNA is comparable at all stages of granulopoiesis. High miR-130a levels and low or no expression of Smad4 was found in primary cells from patients with acute myeloid leukemia and in a cell line (Kasumi-1) with the t(8:21)(q22;q22) chromosomal translocation. The level of Smad4 increased in Kasumi-1 cells when the endogenous level of miR-130a was inhibited by anti-miR-130a LNA. Our data indicate that miR-130a is involved in cell cycle regulation of normal and malignant granulocytic cells through engagement of Smad4 in the TGF-beta-pathway. Grant acknowledgment: Lundbeck foundation, Carlsberg foundation, Swedish Research Council.

General information
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MULTIPRED2: A computational system for large-scale identification of peptides predicted to bind to HLA supertypes and alleles
MULTIPRED2 is a computational system for facile prediction of peptide binding to multiple alleles belonging to human leukocyte antigen (HLA) class I and class II DR molecules. It enables prediction of peptide binding to products of individual HLA alleles, combination of alleles, or HLA supertypes. NetMHCPan and NetMHCIIpan are used as prediction engines. The 13 HLA Class I supertypes are A1, A2, A3, A24, B7, B8, B27, B44, B58, B62, C1, and C4. The 13 HLA Class II DR supertypes are DR1, DR3, DR4, DR6, DR7, DR8, DR9, DR11, DR12, DR13, DR14, DR15, and DR16. In total, MULTIPRED2 enables prediction of peptide binding to 1077 variants representing 26 HLA supertypes. MULTIPRED2 has visualization modules for mapping promiscuous T-cell epitopes as well as those regions of high target concentration – referred to as T-cell epitope hotspots. Novel graphic representations are employed to display the predicted binding peptides and immunological hotspots in an intuitive manner and also to provide a global view of results as heat maps. Another function of MULTIPRED2, which has direct relevance to vaccine design, is the calculation of population coverage. Currently it calculates population coverage in five major groups in North America. MULTIPRED2 is an important tool to complement wet-lab experimental methods for identification of T-cell epitopes. It is available at http://cvc.dfci.harvard.edu/multipred2/.
The genus Mycobacterium represents more than 120 species including important pathogens of human and cause major public health problems and illnesses. Further, with more than 100 genome sequences from this genus, comparative genome analysis can provide new insights for better understanding the evolutionary events of these species and improving drugs, vaccines, and diagnostics tools for controlling Mycobacterial diseases. In this present study we aim to outline a comparative genome analysis of fourteen Mycobacterial genomes: M. avium subsp. paratuberculosis K—10, M. bovis AF2122/97, M. bovis BCG str. Pasteur 1173P2, M. leprae Br4923, M. marinum M, M. sp. KMS, M. sp. MCS, M. tuberculosis CDC1551, M. tuberculosis H37Ra, M. tuberculosis H37Rv, M. tuberculosis KZN 1435, M. ulcerans Agy99, and M. vanbaalenii PYR—1. For this purpose a comparison has been done based on their length of genomes, GC content, number of genes in different data bases (Genbank, Refseq, and Prodigal). The BLAST matrix of these genomes has been figured to give a lot of information about the similarity between species in a simple scheme. As a result of multiple genome analysis, the pan and core genome have been defined for twelve Mycobacterial species. We have also introduced the genome atlas of the reference strain M. tuberculosis H37Rv which can give a good overview of this genome. And for examining the phylogenetic relationships among these bacteria, a phylogenetic tree has been constructed from 16S rRNA gene for tuberculosis and non tuberculosis Mycobacteria to understand the evolutionary events of these species.

**General information**

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Natural genetic engineering: intelligence & design in evolution?

There are many things that I like about James Shapiro's new book "Evolution: A View from the 21st Century" (FT Press Science, 2011). He begins the book by saying that it is the creation of novelty, and not selection, that is important in the history of life. In the presence of heritable traits that vary, selection results in the evolution of a population towards an optimal composition of those traits. But selection can only act on changes - and where does this variation come from?

Historically, the creation of novelty has been assumed to be the result of random chance or accident. And yet, organisms seem 'designed'. When one examines the data from sequenced genomes, the changes appear NOT to be random or accidental, but one observes that whole chunks of the genome come and go. These 'chunks' often contain functional units, encoding sets of genes that together can perform some specific function. Shapiro argues that what we see in genomes is 'Natural Genetic Engineering', or designed evolution: "Thinking about genomes from an informatics perspective, it is apparent that systems engineering is a better metaphor for the evolutionary process than the conventional view of evolution as a select-biased random walk through limitless space of possible DNA configurations" (page 6). In this review, I will have a look at four topics: 1.) why I think genomics is not the whole story; 2.) my own perspective of E. coli genomics, and how I think it relates to this book; 3.) a brief discussion on "Intelligence, Design, and Evolution"; and finally, 4.) a section "in defense of the central dogma".

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology
Authors: Ussery, D. (Intern)
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Publication information
NNAlign: A Web-Based Prediction Method Allowing Non-Expert End-User Discovery of Sequence Motifs in Quantitative Peptide Data

Recent advances in high-throughput technologies have made it possible to generate both gene and protein sequence data at an unprecedented rate and scale thereby enabling entirely new "omics"-based approaches towards the analysis of complex biological processes. However, the amount and complexity of data that even a single experiment can produce seriously challenges researchers with limited bioinformatics expertise, who need to handle, analyze and interpret the data before it can be understood in a biological context. Thus, there is an unmet need for tools allowing non-bioinformatics users to interpret large data sets. We have recently developed a method, NNAlign, which is generally applicable to any biological problem where quantitative peptide data is available. This method efficiently identifies underlying sequence patterns by simultaneously aligning peptide sequences and identifying motifs associated with quantitative readouts. Here, we provide a web-based implementation of NNAlign allowing non-expert end-users to submit their data (optionally adjusting method parameters), and in return receive a trained method (including a visual representation of the identified motif) that subsequently can be used as prediction method and applied to unknown proteins/peptides. We have successfully applied this method to several different data sets including peptide microarray-derived sets containing more than 100,000 data points. NNAlign is available online at http://www.cbs.dtu.dk/services/NNAlign.
OpenFreezer: a reagent information management software system.

General information
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Mount Sinai Hospital, Indiana University-Purdue
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Chromosomal instability (CIN) is associated with poor prognosis in human cancer. However, in certain animal tumor models elevated CIN negatively impacts upon organism fitness, and is poorly tolerated by cancer cells. To better understand this seemingly contradictory relationship between CIN and cancer cell biological fitness and its relationship with clinical outcome, we applied the CIN70 expression signature, which correlates with DNA-based measures of structural chromosomal complexity and numerical CIN in vivo, to gene expression profiles of 2,125 breast tumors from 13 published cohorts. Tumors with extreme CIN, defined as the highest quartile CIN70 score, were predominantly of the estrogen receptor negative (ER-), basal-like phenotype and displayed the highest chromosomal structural complexity and chromosomal numerical instability. We found that the extreme CIN/ER- tumors were associated with improved prognosis relative to tumors with intermediate CIN70 scores in the third quartile. We also observed this paradoxical relationship between CIN and prognosis in ovarian, gastric, and non-small cell lung cancer, with poorest outcome in tumors with intermediate, rather than extreme, CIN70 scores. These results suggest a nonmonotonic relationship between gene signature expression and HR for survival outcome, which may explain the difficulties encountered in the identification of prognostic expression signatures in ER- breast cancer. Furthermore, the data are consistent with the intolerance of excessive CIN in carcinomas and provide a plausible strategy to define distinct prognostic patient cohorts with ER- breast cancer. Inclusion of a surrogate measurement of CIN may improve cancer risk stratification and future therapeutic approaches. Cancer Res; 71(10): 3447-52. (C) 2011 AACR.
Parallel selection of chemotherapy-resistant cell lines to illuminate mechanisms of drug resistance in human tumors:

Abstract of paper from the IMPAKT Breast Cancer Conference

Treatment of cancer often involves the use of chemotherapeutic agents that preferentially target tumor cells. The idea behind personalized medicine is to characterize differences between individual cancer cases that will and to direct the therapy to those most likely to respond. This will require the identification of reliable predictive biomarkers for each drug. Currently, we are developing a framework for systematic biomarker discovery by using a combination of gene expression and CGH arrays to keep track of consistent changes that take place during resistance acquisition in cell lines towards two anti-cancer drugs: doxorubicin and paclitaxel. By monitoring changes at two different levels (DNA and RNA) of the genome and developing multiple cell lines developing resistance against the same drug under identical conditions, we were able to separate relevant changes from spurious ones and thus reducing the noise of the experimental system.

Doxorubicin is an anthracycline that exerts its anticancer effect through intercalation into DNA and inhibition of topoisomerase II, whereas paclitaxel stabilizes microtubules and disrupts the mitotic spindle. We use expression and copy number data from two cell lines, MDA-231 and MCF-7, that were grown in the presence of doxorubicin (n=16) or paclitaxel (n=11), vehicle control (n=2). We have observed a distinct pattern of chemotherapy-induced genomic changes. Doxorubicin-induced changes involve greater genomic rearrangements than paclitaxel, which is with accordance to their mode of action. Our findings are validated on already existing gene expression profiles of patient cohorts treated with the drugs in question, and the most promising ones will be chosen for functional validation by RNAi knock down. Successful validation will improve understanding of drug resistance mechanisms, suggest future drug targets, and enable more efficacious treatment of cancer patients.
Pervasive Sharing of Genetic Effects in Autoimmune Disease

Genome-wide association (GWA) studies have identified numerous, replicable, genetic associations between common single nucleotide polymorphisms (SNPs) and risk of common autoimmune and inflammatory (immune-mediated) diseases, some of which are shared between two diseases. Along with epidemiological and clinical evidence, this suggests that some genetic risk factors may be shared across diseases—as is the case with alleles in the Major Histocompatibility Locus. In this work we evaluate the extent of this sharing for 107 immune disease-risk SNPs in seven diseases: celiac disease, Crohn’s disease, multiple sclerosis, psoriasis, rheumatoid arthritis, systemic lupus erythematosus, and type 1 diabetes. We have developed a novel statistic for Cross Phenotype Meta-Analysis (CPMA) which detects association of a SNP to multiple, but not necessarily all, phenotypes. With it, we find evidence that 47/107 (44%) immune-mediated disease risk SNPs are associated to multiple—but not all-immune-mediated diseases (SNP-wise P-CPMA)
Pharmacophore-driven identification of PPARγ agonists from natural sources

In a search for more effective and safe anti-diabetic compounds, we developed a pharmacophore model based on partial agonists of PPARγ. The model was used for the virtual screening of the Chinese Natural Product Database (CNPD), a library of plant-derived natural products primarily used in folk medicine. From the resulting hits, we selected methyl oleononate, a compound found, among others, in Pistacia lentiscus var. Chia oleoresin (Chios mastic gum). The acid of methyl oleononate, oleononic acid, was identified as a PPARγ agonist through bioassay-guided chromatographic fractionations of Chios mastic gum fractions, whereas some other sub-fractions exhibited also biological activity towards PPARγ. The results from the present work are two-fold: on the one hand we demonstrate that the pharmacophore model we developed is able to select novel ligand scaffolds that act as PPARγ agonists; while at the same time it manifests that natural products are highly relevant for use in virtual screening-based drug discovery.
PHUSER (Primer Help for USER): a novel tool for USER fusion primer design

Uracil-Specific Exision Reagent (USER) fusion is a recently developed technique that allows for assembly of multiple DNA fragments in a few simple steps. However, designing primers for USER fusion is both tedious and time consuming. Here, we present the Primer Help for USER (PHUSER) software, a novel tool for designing primers specifically for USER fusion and USER cloning applications. We also present proof-of-concept experimental validation of its functionality. PHUSER offers quick and easy design of PCR optimized primers ensuring directionally correct fusion of fragments into a plasmid containing a customizable USER cassette. Designing primers using PHUSER ensures that the primers have similar annealing temperature (Tm), which is essential for efficient PCR. PHUSER also avoids identical overhangs, thereby ensuring correct order of assembly of DNA fragments. All possible primers are individually analysed in terms of GC content, presence of GC clamp at 3'-end, the risk of primer dimer formation, the risk of intra-primer complementarity (secondary structures) and the presence of polyN stretches. Furthermore, PHUSER offers the option to insert linkers between DNA fragments, as well as highly flexible cassette options. PHUSER is publicly available at http://www.cbs.dtu.dk/services/phuser/.
PINTA: a web server for network-based gene prioritization from expression data

PINTA (available at http://www.esat.kuleuven.be/pinta/; this web site is free and open to all users and there is no login requirement) is a web resource for the prioritization of candidate genes based on the differential expression of their neighborhood in a genome-wide protein–protein interaction network. Our strategy is meant for biological and medical researchers aiming at identifying novel disease genes using disease specific expression data. PINTA supports both candidate gene prioritization (starting from a user defined set of candidate genes) as well as genome-wide gene...
prioritization and is available for five species (human, mouse, rat, worm and yeast). As input data, PINTA only requires
disease specific expression data, whereas various platforms (e.g. Affymetrix) are supported. As a result, PINTA computes
a gene ranking and presents the results as a table that can easily be browsed and downloaded by the user.

**General information**
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Katholieke Universiteit,
Knowledge Discovery and Bioinformatics group
Authors: Nitsch, D. (Ekstern), Tranchevent, L. (Ekstern), Goncalves, J. P. (Ekstern), Vogt, J. K. (Intern), Madeira, S. C.
(Ekstern), Moreau, Y. (Ekstern)
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Web of Science (2017): Indexed yes
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Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 6.576 SNIP 2.568 CiteScore 8.74
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Scopus rating (2013): SJR 6.582 SNIP 2.266 CiteScore 8.46
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 6.13 SNIP 2.392 CiteScore 8.62
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 5.758 SNIP 2.172 CiteScore 7.86
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 5.24 SNIP 2.034
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 5.571 SNIP 1.869
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 4.641 SNIP 1.557
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 4.86 SNIP 1.787
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 4.55 SNIP 2.04
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 4.992 SNIP 2.152
Plug 'n' Play with DNA

Synthetic biology has evolved dramatically within the past decade, which calls for a revolution of the Standard Assembly method that makes the foundation of BioBricks. We believe that iGEM should be about fast assembly of BioBricks, where any thinkable part, device or existing BioBrick can be combined for any type of organism within one day. Therefore, we have designed a new BioBrick Kit based on a novel assembly standard; called "Plug 'n' Play with DNA".

General information
State: Published
Organisations: Department of Systems Biology, Center for Microbial Biotechnology, Center for Biological Sequence Analysis, Technical University of Denmark
Authors: Lund, A. M. (Intern), Andreasen, E. W. (Ekstern), Korgaard, J. V. (Ekstern), Rank, J. (Intern), Knudsen, M. S. (Intern)
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Plug 'n' Play with DNA

Synthetic biology has evolved dramatically within the past decade, which calls for a revolution of the Standard Assembly method that makes the foundation of BioBricks. We believe that iGEM should be about fast assembly of BioBricks, where any thinkable part, device or existing BioBrick can be combined for any type of organism within one day. Therefore, we have designed a new BioBrick Kit based on a novel assembly standard; called "Plug 'n' Play with DNA".

General information
State: Published
Organisations: Department of Systems Biology, Center for Microbial Biotechnology, Center for Biological Sequence Analysis, Technical University of Denmark
Authors: Lund, A. M. (Intern), Andreasen, E. W. (Ekstern), Korgaard, J. V. (Ekstern), Rank, J. (Intern), Knudsen, M. S. (Intern)
Publication date: 2011
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Electronic versions:
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Publication: Research - peer-review › Poster – Annual report year: 2011
Porcine major histocompatibility complex (MHC) class I molecules and analysis of their peptide-binding specificities

In all vertebrate animals, CD8+ cytotoxic T lymphocytes (CTLs) are controlled by major histocompatibility complex class I (MHC-I) molecules. These are highly polymorphic peptide receptors selecting and presenting endogenously derived epitopes to circulating CTLs. The polymorphism of the MHC effectively individualizes the immune response of each member of the species. We have recently developed efficient methods to generate recombinant human MHC-I (also known as human leukocyte antigen class I, HLA-I) molecules, accompanying peptide-binding assays and predictors, and HLA tetramers for specific CTL staining and manipulation. This has enabled a complete mapping of all HLA-I specificities ("the Human MHC Project"). Here, we demonstrate that these approaches can be applied to other species. We systematically transferred domains of the frequently expressed swine MHC-I molecule, SLA-1*0401, onto a HLA-I molecule (HLA-A*11:01), thereby generating recombinant human/swine chimeric MHC-I molecules as well as the intact SLA-1*0401 molecule. Biochemical peptide-binding assays and positional scanning combinatorial peptide libraries were used to analyze the peptide-binding motifs of these molecules. A pan-specific predictor of peptide–MHC-I binding, NetMHCpan, which was originally developed to cover the binding specificities of all known HLA-I molecules, was successfully used to predict the specificities of the SLA-1*0401 molecule as well as the porcine/human chimeric MHC-I molecules. These data indicate that it is possible to extend the biochemical and bioinformatics tools of the Human MHC Project to other vertebrate species.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, United States Department of Agriculture, University of Copenhagen
Authors: Pedersen, L. E. (Intern), Harndahl, M. (Ekstern), Rasmussen, M. (Ekstern), Lamberth, K. (Ekstern), Golde, W. T. (Ekstern), Lund, O. (Intern), Nielsen, M. (Intern), Buus, S. (Ekstern)
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Main Research Area: Technical/natural sciences

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Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.2 SJR 1.231 SNIP 0.703
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.551 SNIP 0.819 CiteScore 2.47
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.221 SNIP 0.833 CiteScore 2.28
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.231 SNIP 0.763 CiteScore 2.48
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.365 SNIP 0.943 CiteScore 2.91
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.304 SNIP 0.888 CiteScore 2.83
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Prediction of epitopes using neural network based methods

In this paper, we describe the methodologies behind three different aspects of the NetMHC family for prediction of MHC class I binding, mainly to HLAs. We have updated the prediction servers, NetMHC-3.2, NetMHCpan-2.2, and a new consensus method, NetMHCcons, which, in their previous versions, have been evaluated to be among the very best performing MHC-peptide binding predictors available. Here we describe the background for these methods, and the rationale behind the different optimization steps implemented in the methods. We go through the practical use of the methods, which are publicly available in the form of relatively fast and simple web interfaces. Furthermore, we will review results obtained in actual epitope discovery projects where previous implementations of the described methods have been used in the initial selection of potential epitopes. Selected potential epitopes were all evaluated experimentally using ex vivo assays.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology
Authors: Lundegaard, C. (Intern), Lund, O. (Intern), Nielsen, M. (Intern)
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Journal: Journal of Immunological Methods
Volume: 374
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BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 1.92 SJR 1.061 SNIP 0.655
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.068 SNIP 0.76 CiteScore 2.07
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.013 SNIP 0.832 CiteScore 1.99
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.08 SNIP 0.837 CiteScore 2.31
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.172 SNIP 0.94 CiteScore 2.49
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.168 SNIP 0.886 CiteScore 2.4
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.085 SNIP 0.866
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.182 SNIP 0.892
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 1.021 SNIP 0.778
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 1.032 SNIP 0.876
Scopus rating (2006): SJR 1.287 SNIP 0.952
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 1.307 SNIP 0.972
Scopus rating (2004): SJR 1.167 SNIP 0.981
Web of Science (2004): Indexed yes
Scopus rating (2003): SJR 1.283 SNIP 1
Scopus rating (2002): SJR 1.275 SNIP 0.955
Scopus rating (2001): SJR 0.974 SNIP 0.772
Scopus rating (2000): SJR 1.058 SNIP 0.989
Web of Science (2000): Indexed yes
Scopus rating (1999): SJR 1.012 SNIP 0.911
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Probiotika

General information
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University Hospital Herlev
Authors: Pedersen, S. B. (Intern), Nielsen, O. H. (Forskerdatabase), Kjeldsen, H. C. (Ekstern), Johannessen, T. (Ekstern), Løge, I. (Ekstern)
Publication date: 2011

Host publication information
Protein Interaction-Based Genome-Wide Analysis of Incident Coronary Heart Disease

Background-Network-based approaches may leverage genome-wide association (GWA) analysis by testing for the aggregate association across several pathway members. We aimed to examine if networks of genes that represent experimentally determined protein-protein interactions (PPIs) are enriched in genes associated with risk of coronary heart disease (CHD). Methods and Results-Genome-wide association analyses of approximately 700 000 single-nucleotide polymorphisms in 899 incident CHD cases and 1823 age-and sex-matched controls within the Nurses’ Health and the Health Professionals Follow-up Studies were used to assign genewise P values. A large database of PPIs was used to assemble 8351 unbiased protein complexes and corresponding gene sets. Superimposed genewise P values were used to rank gene sets based on their enrichment in genes associated with CHD. After correcting for the number of complexes tested, 1 gene set was overrepresented in CHD-associated genes (P = 0.002). Centered on the beta 1-adrenergic receptor gene (ADRB1), this complex included 18 protein interaction partners that have not been identified as candidate loci for CHD. Of the 19 genes in the top complex, 5 are involved in abnormal cardiovascular system physiological features based on knockout mice (4-fold enrichment; Fisher exact test, P = 0.006). Ingenuity pathway analysis revealed that canonical pathways, especially related to blood pressure regulation, were significantly enriched in the genes from the top complex. Conclusions-The integration of a GWA study with PPI data successfully identifies a set of candidate susceptibility genes for incident CHD that would have been missed in single-marker GWA analysis. (Circ Cardiovasc Genet. 2011; 4:549-556.)

General information
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Novo Nordisk Foundation Center for Biosustainability, CFB - Metagenomic Systems Biology, Harvard School of Public Health, Merck Research Laboratories, Harvard University
Authors: Jensen, M. K. (Forskerdatabase), Pers, T. H. (Intern), Dworzynski, P. (Intern), Girman, C. J. (Ekstern), Brunak, S. (Intern), Rimm, E. B. (Ekstern)
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Web of Science (2017): Indexed Yes
Scopus rating (2016): SJR 2.494 SNIP 1.227 CiteScore 3.82
Scopus rating (2015): SJR 2.564 SNIP 1.17 CiteScore 3.43
Web of Science (2015): Indexed yes
Scopus rating (2014): SJR 2.404 SNIP 1.184 CiteScore 3.6
Scopus rating (2013): SJR 3.328 SNIP 1.36 CiteScore 4.65
Scopus rating (2012): SJR 3.644 SNIP 1.451 CiteScore 5.06
ISI indexed (2012): ISI indexed yes
Scopus rating (2011): SJR 3.821 SNIP 1.608 CiteScore 5.4
ISI indexed (2011): ISI indexed no
Web of Science (2011): Indexed yes
Scopus rating (2010): SJR 3.232 SNIP 0.871
Scopus rating (2009): SJR 1.201
Original language: English
CARDIAC, GENETICS, ARTERY-DISEASE, ASSOCIATION ANALYSIS, SUSCEPTIBILITY LOCUS, INTERACTION DATABASE, INTERACTION NETWORKS, PATHWAY, POPULATION, RESOURCE, GENES, IDENTIFICATION
Proteins Encoded in Genomic Regions Associated with Immune-Mediated Disease Physically Interact and Suggest Underlying Biology

Genome-wide association studies (GWAS) have defined over 150 genomic regions unequivocally containing variation predisposing to immune-mediated disease. Inferring disease biology from these observations, however, hinges on our ability to discover the molecular processes being perturbed by these risk variants. It has previously been observed that different genes harboring causal mutations for the same Mendelian disease often physically interact. We sought to evaluate the degree to which this is true of genes within strongly associated loci in complex disease. Using sets of loci defined in rheumatoid arthritis (RA) and Crohn's disease (CD) GWAS, we build protein-protein interaction (PPI) networks for genes within associated loci and find abundant physical interactions between protein products of associated genes. We apply multiple permutation approaches to show that these networks are more densely connected than chance expectation. To confirm biological relevance, we show that the components of the networks tend to be expressed in similar tissues relevant to the phenotypes in question, suggesting the network indicates common underlying processes perturbed by risk loci. Furthermore, we show that the RA and CD networks have predictive power by demonstrating that proteins in these networks, not encoded in the confirmed list of disease associated loci, are significantly enriched for association to the phenotypes in question in extended GWAS analysis. Finally, we test our method in 3 non-immune traits to assess its applicability to complex traits in general. We find that genes in loci associated to height and lipid levels assemble into significantly connected networks but did not detect excess connectivity among Type 2 Diabetes (T2D) loci beyond chance. Taken together, our results constitute evidence that, for many of the complex diseases studied here, common genetic associations implicate regions encoding proteins that physically interact in a preferential manner, in line with observations in Mendelian disease.
PSICQUIC and PSISCORE: accessing and scoring molecular interactions

General information
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Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, University of Oslo, Max Planck Institute, Simon Fraser University, Institute for Research in Biomedicine, Centre National de la Recherche Scientifique, Universidad de Salamanca, Cancer Research Center, Fondazione S. Lucia, J. Craig Venter Institute, University of British Columbia, University of Toronto, Radboud University Nijmegen, Animal and Grassland Research Innovation Centre, University of California, University of Zurich, University of Edinburgh, Ontario Institute for Cancer Research, European Molecular Biology Laboratory
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BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 11.58 SJR 19.544 SNIP 5.24
Quantification of specific E. coli in gut mucosa from Crohn's disease patients
We here present a method based on qRT-PCR to quantify E. coli LF82 in intestinal human samples. Two different primer-probe sets were designed to detect LF82, and a third to target total E. coli. The assay showed high robustness and specificity for detection of LF82 in the presence of intestinal tissue.

General information
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Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Center for Systems Microbiology, Division of Microbiology and Risk Assessment, National Food Institute, Statens Serum Institut, Copenhagen University Hospital
Authors: Jensen, S. R. (Intern), Fink, L. N. (Intern), Struve, C. (Ekstern), Sternberg, C. (Intern), Andersen, J. B. (Intern), Brynskov, J. (Ekstern), Nielsen, O. H. (Ekstern), Pedersen, S. B. (Intern)
Pages: 111-114
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Main Research Area: Technical/natural sciences

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Volume: 86
Issue number: 1
Rational Discovery of T Helper Epitopes Specific for Bovine Infections with Mycobacterium avium ssp paratuberculosis

Paratuberculosis, a chronic wasting disease in ruminants, is causing significant losses to both EU dairy and meat producers, due to a decreasing milk yield, loss of body weight and early replacements. The absence of adequate diagnostic tools for early detection of subclinically infected livestock severely interferes with animal welfare and effective eradication initiatives. Currently three strains of M. bovis and one MAP strain (K10) have been fully sequenced and deposited in NCBI genbank. We have sequenced a Danish clinical isolate, Ejlskov2007, which is not yet published. State of the art bioinformatics tools has been used to identify peptides in the MAP genome, which are predicted to bind to bovine MHC (BoLA) class II antigen presenting molecules. Comparative genomics tools has been used to further select MAP specific peptides 100% conserved in the two MAP strains and with low similarity to peptides from any of the M. bovis strains according to available sequence data. Unique MAP specific predicted epitopes is selected and is to be synthesized as 15–20 aa peptides. In addition we will select peptides specifically from antigens, which have previously shown to induce a CD4+ T cell response, again with the emphasis of avoiding similarities to M. bovis sequences. Blood from cattle experimentally infected with MAP will be used for proliferation and cytokine assays to determine if and which of the selected peptides that will be recognized specifically by CD4+ T cells from infected cattle. The goal is to combine positive responding peptides with new promising adjuvants in order to develop effective bovine MAP vaccines which do not cross react with traditional skin tests for M. bovis infections.

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Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Adaptive Immunology & Parasitology, Division of Veterinary Diagnostics and Research, National Veterinary Institute
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BFI (2017): BFI-level 1
Web of Science (2017): Indexed yes
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Scopus rating (2016): CiteScore 2.03 SJR 0.951 SNIP 0.646
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.93 SNIP 0.684 CiteScore 1.97
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.898 SNIP 0.666 CiteScore 1.91
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 0.86 SNIP 0.712 CiteScore 2.05
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 0.88 SNIP 0.749 CiteScore 2.16
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 0.854 SNIP 0.66 CiteScore 2.06
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 0.844 SNIP 0.622
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 0.962 SNIP 0.662
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 0.236 SNIP 0.078
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 0.286 SNIP 0.141
Scopus rating (2006): SJR 0.421 SNIP 0.125
Scopus rating (2005): SJR 0.999 SNIP 0.642
Web of Science (2005): Indexed yes
Scopus rating (2004): SJR 0.841 SNIP 0.583
Web of Science (2004): Indexed yes
Scopus rating (2003): SJR 0.807 SNIP 0.626
Scopus rating (2002): SJR 0.775 SNIP 0.591
Web of Science (2002): Indexed yes
Scopus rating (2001): SJR 0.747 SNIP 0.63
Scopus rating (2000): SJR 0.838 SNIP 0.612
Web of Science (2000): Indexed yes
Scopus rating (1999): SJR 0.822 SNIP 0.653
Original language: English
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40th Scandinavian-Society for Immunology Meeting, Geilo, NORWAY, 2011
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Recommendations for Mass Spectrometry Data Quality Metrics for Open Access Data (Corollary to the Amsterdam Principles)

Policies supporting the rapid and open sharing of proteomic data are being implemented by the leading journals in the field. The proteomics community is taking steps to ensure that data are made publicly accessible and are of high quality, a challenging task that requires the development and deployment of methods for measuring and documenting data quality metrics. On September 18, 2010, the United States National Cancer Institute convened the "International Workshop on Proteomic Data Quality Metrics" in Sydney, Australia, to identify and address issues facing the development and use of such methods for open access proteomics data. The stakeholders at the workshop enumerated the key principles underlying a framework for data quality assessment in mass spectrometry data that will meet the needs of the research community, journals, funding agencies, and data repositories. Attendees discussed and agreed up on two primary needs for the wide use of quality metrics: 1) an evolving list of comprehensive quality metrics and 2) standards accompanied by software analytics. Attendees stressed the importance of increased education and training programs to promote reliable protocols in proteomics. This workshop report explores the historic precedents, key discussions, and necessary next steps to enhance the quality of open access data. By agreement, this article is published simultaneously in the Journal of Proteome Research, Molecular and Cellular Proteomics, Proteomics, and Proteomics Clinical Applications as a public service to the research community. The peer review process was a coordinated effort conducted by a panel of referees selected by the journals.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, European Commission, National Cancer Institute, Agilent Research Laboratories, Macquarie University, US National Institute of Health, University of Victoria, University of California, Institute for Systems Biology, Johns Hopkins University, Luxembourg Clinical Proteomics Center, QIMR Berghofer Medical Research Institute, Northeastern University, European Bioinformatics Institute, Thermo Fisher Scientific, AB SCIEX, Wiley-VCH, Weinheim, Hoffmann-La Roche, Cellular and Molecular Logic Unit, University of Michigan, University of Georgia, La Trobe University, Pacific Northwest National Laboratory, National Institute of Standards and Technology, Vanderbilt-Ingram Cancer Center, The Scripps Research Institute, Agilent
**Recommendations for Mass Spectrometry Data Quality Metrics for Open Access Data (Corollary to the Amsterdam Principles)**

Policies supporting the rapid and open sharing of proteomic data are being implemented by the leading journals in the field. The proteomics community is taking steps to ensure that data are made publicly accessible and are of high quality, a challenging task that requires the development and deployment of methods for measuring and documenting data quality.
metrics. On September 18, 2010, the United States National Cancer Institute convened the "International Workshop on Proteomic Data Quality Metrics" in Sydney, Australia, to identify and address issues facing the development and use of such methods for open access proteomics data. The stakeholders at the workshop enumerated the key principles underlying a framework for data quality assessment in mass spectrometry data that will meet the needs of the research community, journals, funding agencies, and data repositories. Attendees discussed and agreed upon two primary needs for the wide use of quality metrics: 1) an evolving list of comprehensive quality metrics and 2) standards accompanied by software analytics. Attendees stressed the importance of increased education and training programs to promote reliable protocols in proteomics. This workshop report explores the historic precedents, key discussions, and necessary next steps to enhance the quality of open access data. By agreement, this article is published simultaneously in the Journal of Proteome Research, Molecular and Cellular Proteomics, Proteomics, and Proteomics Clinical Applications as a public service to the research community. The peer review process was a coordinated effort conducted by a panel of referees selected by the journals.
Response to Comment on "Positive Selection of Tyrosine Loss in Metazoan Evolution"

Su et al. claim guanine-cytosine (GC) content variation can largely explain the observed tyrosine frequency variation, independent of adaptive evolution of cell-signaling complexity. We found that GC content variation, in the absence of selection for amino acid changes, can only maximally account for 38% of the observed tyrosine frequency variation. We also uncovered other mechanisms acting to reduce tyrosine phosphorylation that further support our previous proposal.
Revealing the beneficial effect of protease supplementation to high gravity beer fermentations using “-omics” techniques

Background: Addition of sugar syrups to the basic wort is a popular technique to achieve higher gravity in beer fermentations, but it results in dilution of the free amino nitrogen (FAN) content in the medium. The multicomponent protease enzyme Flavourzyme has beneficial effect on the brewer’s yeast fermentation performance during high gravity fermentations as it increases the initial FAN value and results in higher FAN uptake, higher specific growth rate, higher ethanol yield and improved flavour profile. Results: In the present study, transcriptome and metabolome analysis were used to elucidate the effect on the addition of the multicomponent protease enzyme Flavourzyme and its influence on the metabolism of the brewer’s yeast strain Weihenstephan 34/70. The study underlines the importance of sufficient nitrogen availability during the course of beer fermentation. The applied metabolome and transcriptome analysis allowed mapping the effect of the wort sugar composition on the nitrogen uptake. Conclusion: Both the transcriptome and the metabolome analysis revealed that there is a significantly higher impact of protease addition for maltose syrup supplemented fermentations, while addition of glucose syrup to increase the gravity in the wort resulted in increased glucose repression that lead to inhibition of amino acid uptake and hereby inhibited the effect of the protease addition.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Technical University of Denmark, Novozymes A/S, Chalmers University of Technology
Publication date: 2011
Main Research Area: Technical/natural sciences

Publication information
Journal: Microbial Cell Factories
Role of Natural Killer and Dendritic Cell Crosstalk in Immunomodulation by Commensal Bacteria Probiotics

A cooperative dialogue between natural killer (NK) cells and dendritic cells (DCs) has been elucidated in the last years. They help each other to acquire their complete functions, both in the periphery and in the secondary lymphoid organs. Thus, NK cells' activation by dendritic cells allows the killing of transformed or infected cells in the periphery but may also be important for the generation of adaptive immunity. Indeed, it has been shown that NK cells may play a key role in polarizing a Th1 response upon interaction with DCs exposed to microbial products. This regulatory role of DC/NK cross-talk is of particular importance at mucosal surfaces such as the intestine, where the immune system exists in intimate association with commensal bacteria such as lactic acid bacteria (LAB). We here review NK/DC interactions in the presence of gut-derived commensal bacteria and their role in bacterial strain-dependent immunomodulatory effects. We particularly aim to highlight the ability of distinct species of commensal bacterial probiotics to differently affect the outcome of DC/NK cross-talk and consequently to differently influence the polarization of the adaptive immune response.
SignalP 4.0: discriminating signal peptides from transmembrane regions

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Stockholm University
Authors: Petersen, T. N. (Intern), Brunak, S. (Intern), von Heijne, G. (Ekstern), Nielsen, H. (Intern)
Pages: 785-786
Publication date: 2011
Main Research Area: Technical/natural sciences

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Journal: Nature Methods
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BFI (2018): BFI-level 2
BFI (2017): BFI-level 2
Web of Science (2017): Indexed yes
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Scopus rating (2016): CiteScore 11.58 SJR 19.544 SNIP 5.24
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 20.9 SNIP 6.131 CiteScore 15.62
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 15.179 SNIP 4.815 CiteScore 13.54
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 10.093 SNIP 3.513 CiteScore 12.21
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 8.644 SNIP 2.969 CiteScore 10.1
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 2
Temperature influences the expression profiling of immune response genes in rainbow trout following DNA vaccination and VHS virus infection

A DNA vaccine encoding the glycoprotein (G) genes of the salmonid rhabdovirus viral haemorrhagic septicaemia virus (VHSV) has proven highly efficient against the disease caused by this virus in rainbow trout (Oncorhynchus mykiss). Several studies have demonstrated that this vaccine induces both an early unspecific antiviral response as well as a long-lasting specific protection. However, temperature appears to influence immune response with respect to the nature and duration of the protective mechanisms. In this study, groups of fish were temperature acclimated, vaccinated and challenged at three different temperatures (5, 10 and 15°C). Tissue and organ samples were collected at numerous time points post vaccination (pv) and post viral challenge (pch). Then, gene expression levels of a two immune genes (Vig-1 and Mx3) involved in unspecific antiviral response mechanisms were determined by Q-PCR. The expression profiles appeared similar for the two genes in terms of temperature dependency with a faster induction and shorter duration at the higher temperature. In order to analyze the temperature effect on the relative expression profiles across a larger set of immune genes time points displaying similar Mx3 expression levels post vaccination were identified: 4 days pv (15°C); 7 days pv (10°C); 23 days pv (5°C), respectively. A targeted trout immune gene array including probes for VHSV genes was used for analysis of vaccinated vs control fish per temperature (4-5 replicates). Temperature altered the transcriptome response to the viral challenge, and the number of responsive genes increased at higher temperature: 51 (5°C), 64 (10°C) and 72 (15°C), respectively, indicating that fish kept at higher temperature may have an enhanced immune response. Additional correlation analysis allowed identification of genes that were significantly up- or down regulated synchronous with expression of the vaccine G gene. These findings encompass that for example in fish kept at 5°C, putative CD3, CD4, CD9, CD28, CD53, CD63, CD83, CD84 were up regulated, while CD59, CD83 were down regulated, potentially indicating balancing mechanism of the immune system. An experimental VHSV challenge was performed 7 weeks pv. Similar protection levels of approximately 10% mortality were found for the vaccinated fish, regardless of temperature during immunisation and challenge, whereas the course and level of mortality among the controls were temperature dependent. At day 5 post infection, the number of differentially regulated genes in the livers of vaccinated versus control fish was highest in fish kept at 10°C and lowest in fish at 5°C. This difference presumably reflects the temperature dependent progression of the disease in the controls. Further analysis of the obtained data with respect to gene regulation pathways as a result of DNA vaccination and/or viral infection will be presented.

General information
State: Published
Organisations: Section of Fish Diseases, Division of Poultry, Fish and Fur Animals, National Veterinary Institute, Center for Biological Sequence Analysis, Department of Systems Biology, S.L.U. Bionostra Group, Bionostra Biotechnology Applications, University of Aberdeen, Norwegian School of Veterinary Science
Authors: Einer-Jensen, K. (Intern), Gautier, L. (Intern), Rasmussen, J. S. (Intern), Lorenzen, E. (Intern), Christensen, M. B. (Intern), Villanueva, S. A. (Ekstern), Martin, S. (Ekstern), Evensen, Ø. (Ekstern), Schyth, B. D. (Intern), Lorenzen, N. (Intern)
Publication date: 2011
Event: Abstract from Joint Western Fish Disease Workshop & AFS fish Health Section meeting, Nanaimo, British Columbia, Canada,
Main Research Area: Technical/natural sciences
Electronic versions:
The Effect of Dietary Fish Oil in addition to Lifestyle Counselling on Lipid Oxidation and Body Composition in Slightly Overweight Teenage Boys

Objective. n-3 long-chain polyunsaturated fatty acids (LCPUFAs) have shown potential to increase lipid oxidation and prevent obesity. Subjects. Seventy-eight boys aged 13–15 y with whole-body fat% of 30 ± 9% were randomly assigned to consume bread with fish oil (FO) (1.5 g n-3 LCPUFA/d) or vegetable oil for 16 weeks. All boys were counselled to improve diet and exercise habits. Results. Lifestyle counselling resulted in decreased sugar intake but did not change the physical activity level. Whole-body fat% decreased 0.7 ± 2.5% and 0.6 ± 2.2%, resting metabolic rate after the intervention was 7150 ± 1134 kJ/d versus 7150 ± 1042 kJ/d, and the respiratory quotient was 0.89 ± 0.05 versus 0.88 ± 0.05, in the FO and control group, respectively. No group differences were significant. Conclusion. FO-supple

The Genomic Standards Consortium

A vast and rich body of information has grown up as a result of the world's enthusiasm for 'omics technologies. Finding ways to describe and make available this information that maximise its usefulness has become a major effort across the 'omics world. At the heart of this effort is the Genomic Standards Consortium (GSC), an open-membership organization that drives community-based standardization activities. Here we provide a short history of the GSC, provide an overview of its range of current activities, and make a call for the scientific community to join forces to improve the quality and quantity of contextual information about our public collections of genomes, metagenomes, and marker gene sequences.
The impact of ultraviolet therapy on stratum corneum ceramides and barrier function

The ceramide profile as well as the barrier function is known to be deteriorated in atopic eczema and psoriasis, and ultraviolet (UV) light is known to improve the barrier function. The impact of UV light on ceramides, however, is not clarified. The aim of this study was to examine the effect of UV therapy in dermatological patients on ceramides and skin barrier function. We found that UV light treatment does not change the ratio of important stratum corneum lipids, but we confirm earlier findings of decreased susceptibility to irritants after UV therapy.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Copenhagen University Hospital
Authors: Jungersted, J. M. (Ekstern), Høgh, J. K. (Intern), Hellgren, L. (Intern), Jemec, G. B. E. (Ekstern), Agner, T. (Ekstern)
Pages: 331-333
Publication date: 2011
Main Research Area: Technical/natural sciences

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Journal: Photodermatology, Photoimmunology & Photomedicine
Volume: 27
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BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): SJR 0.631 SNIP 1.148 CiteScore 2.08
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.677 SNIP 0.906 CiteScore 1.61
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.737 SNIP 0.952 CiteScore 1.37
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 0.642 SNIP 0.884 CiteScore 1.56
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 0.773 SNIP 1.052 CiteScore 1.54
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 0.78 SNIP 0.853 CiteScore 1.58
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 0.908 SNIP 1.032
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 0.852 SNIP 1.055
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 0.791 SNIP 0.821
Scopus rating (2007): SJR 0.718 SNIP 0.824
Scopus rating (2006): SJR 0.67 SNIP 1.046
Scopus rating (2005): SJR 0.61 SNIP 0.997
The interplay of descriptor-based computational analysis with pharmacophore modeling builds the basis for a novel classification scheme for feruloyl esterases

One of the most intriguing groups of enzymes, the feruloyl esterases (FAEs), is ubiquitous in both simple and complex organisms. FAEs have gained importance in biofuel, medicine and food industries due to their capability of acting on a large range of substrates for cleaving ester bonds and synthesizing high-added value molecules through esterification and transesterification reactions. During the past two decades extensive studies have been carried out on the production and partial characterization of FAEs from fungi, while much less is known about FAEs of bacterial or plant origin. Initial classification studies on FAEs were restricted on sequence similarity and substrate specificity on just four model substrates and considered only a handful of FAEs belonging to the fungal kingdom. This study centers on the descriptor-based classification and structural analysis of experimentally verified and putative FAEs; nevertheless, the framework presented here is applicable to every poorly characterized enzyme family. 365 FAE-related sequences of fungal, bacterial and plantae origin were collected and they were clustered using Self Organizing Maps followed by k-means clustering into distinct groups based on amino acid composition and physico-chemical composition descriptors derived from the respective amino acid sequence. A Support Vector Machine model was subsequently constructed for the classification of new FAEs into the pre-assigned clusters. The model successfully recognized 98.2% of the training sequences and all the sequences of the blind test. The underlying functionality of the 12 proposed FAE families was validated against a combination of prediction tools and published experimental data. Another important aspect of the present work involves the development of pharmacophore models for the new FAE families, for which sufficient information on known substrates existed. Knowing the pharmacophoric features of a small molecule that are essential for binding to the members of a certain family opens a window of opportunities for tailored applications of FAEs.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Center for Microbial Biotechnology, Chalmers University of Technology
Authors: Udatha, D. G. (Ekstern), Kouskoumvekaki, I. (Intern), Olsson, L. (Intern), Panagiotou, G. (Intern)
Pages: 94-110
Publication date: 2011
Main Research Area: Technical/natural sciences

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BFI (2017): BFI-level 2
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BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 11.05 SJR 2.681 SNIP 3.146
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 2.919 SNIP 3.432 CiteScore 10.56
Web of Science (2015): Indexed yes
The pathogenicity of S. Typhimurium SL1344 is coupled to invasiveness and not the ensuing immune response

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Division of Microbiology and Risk Assessment, National Food Institute
Authors: Brandt, R. (Ekstern), Petersen, A. (Ekstern), Pedersen, S. B. (Intern), Licht, T. R. (Intern), Frøkjær, H. (Ekstern)
Publication date: 2011
Event: Abstract from 15th International Congress of Mucosal Immunology, Paris, France.
Main Research Area: Technical/natural sciences
Source: orbit
Source-ID: 268984
Publication: Research - peer-review › Journal article – Annual report year: 2010

The pathogenicity of S. Typhimurium SL1344 is coupled to invasiveness and not the ensuing immune response

General information
The Salmonella enterica Pan-genome
Salmonella enterica is divided into four subspecies containing a large number of different serovars, several of which are important zoonotic pathogens and some show a high degree of host specificity or host preference. We compare 45 sequenced S. enterica genomes that are publicly available (22 complete and 23 draft genome sequences). Of these, 35 were found to be of sufficiently good quality to allow a detailed analysis, along with two Escherichia coli strains (K-12 substr. DH10B and the avian pathogenic E. coli (APEC O1) strain). All genomes were subjected to standardized gene finding, and the core and pan-genome of Salmonella were estimated to be around 2,800 and 10,000 gene families, respectively. The constructed pan-genomic dendrograms suggest that gene content is often, but not uniformly correlated to serotype. Any given Salmonella strain has a large stable core, whilst there is an abundance of accessory genes, including the Salmonella pathogenicity islands (SPIs), transposable elements, phages, and plasmid DNA. We visualize conservation in the genomes in relation to chromosomal location and DNA structural features and find that variation in gene content is localized in a selection of variable genomic regions or islands. These include the SPIs but also encompass phage insertion sites and transposable elements. The islands were typically well conserved in several, but not all, isolates—a difference which may have implications in, e.g., host specificity.

General information
State: Published
Organisations: Department of Chemical and Biochemical Engineering, Division of Microbiology and Risk Assessment, National Food Institute, Center for Biological Sequence Analysis, Department of Systems Biology
Authors: Jacobsen, A. (Intern), Hendriksen, R. S. (Intern), Aarestrup, F. M. (Intern), Ussery, D. (Intern), Friis, C. (Intern)
Pages: 487-504
Publication date: 2011
Main Research Area: Technical/natural sciences

Publication information
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Ratings:
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.55 SJR 1.295 SNIP 1.116
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 1.334 SNIP 1.021 CiteScore 3.13
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 1.316 SNIP 1.136 CiteScore 3.08
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 1.408 SNIP 1.245 CiteScore 3.7
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 1.417 SNIP 1.279 CiteScore 3.36
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
The strength of intron donor splice sites in human genes displays a bell-shaped pattern

**MOTIVATION:** The gene concept has recently changed from the classical one protein notion into a much more diverse picture, where overlapping or fused transcripts, alternative transcription initiation, and genes within genes, add to the complexity generated by alternative splicing. Increased understanding of the mechanisms controlling pre-mRNA splicing is thus important for a wide range of aspects relating to gene expression. **RESULTS:** We have discovered a convex gene delineating pattern in the strength of 5' intron splice sites. When comparing the strengths of >18 000 intron containing Human genes, we found that when analysing them separately according to the number of introns they contain, initial splice sites were always stronger on average than subsequent ones, and that a similar reversed trend exist towards the terminal gene part. The convex pattern is strongest for genes with up to 10 introns. Interestingly, when analysing the intron containing gene pool from mouse consisting of >15 000 genes, we found the convex pattern to be conserved despite >75 million years of evolutionary divergence between the two organisms. We also analysed an interesting, novel class of chimeric genes which during spliceosome assembly are fused and in tandem are transcribed and spliced into a single mature mRNA sequence. In their splice site patterns, these genes individually seem to deviate from the convex pattern, offering a possible rationale behind their fusion into a single transcript.

**General information**
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology
Authors: Wang, K. (Intern), Wernersson, R. (Intern), Brunak, S. (Intern)
Pages: 3079-3084
Publication date: 2011
Main Research Area: Technical/natural sciences

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Volume: 27
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Supplementary data are available at Bioinformatics online.

Source: orbit
Source-ID: 287072
Publication: Research - peer-review › Journal article – Annual report year: 2011

The testicle, the breast and systems biology

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis
Authors: Belling, K. C. (Intern), Brunak, S. (Intern), Jensen, T. S. (Intern), Nielsen, H. B. (Intern), Gupta, R. (Intern)
Using Electronic Patient Records to Discover Disease Correlations and Stratify Patient Cohorts

Electronic patient records remain a rather unexplored, but potentially rich data source for discovering correlations between diseases. We describe a general approach for gathering phenotypic descriptions of patients from medical records in a systematic and non-cohort dependent manner. By extracting phenotype information from the free-text in such records we demonstrate that we can extend the information contained in the structured record data, and use it for producing fine-grained patient stratification and disease co-occurrence statistics. The approach uses a dictionary based on the International Classification of Disease ontology and is therefore in principle language independent. As a use case we show how records from a Danish psychiatric hospital lead to the identification of disease correlations, which subsequently can be mapped to systems biology frameworks.

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Copenhagen University Hospital, University of Copenhagen
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Main Research Area: Technical/natural sciences

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Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 3.43 SNIP 1.447 CiteScore 4.69
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 3.359 SNIP 1.44 CiteScore 4.74
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 3.295 SNIP 1.457 CiteScore 4.91
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
Scopus rating (2012): SJR 3.329 SNIP 1.642 CiteScore 5.36
ISI indexed (2012): ISI indexed no
Web of Science (2012): Indexed yes
Scopus rating (2011): SJR 3.381 SNIP 1.603 CiteScore 5.25
Verification of systems biology research in the age of collaborative competition.

**General information**

*State:* Published  
*Organisations:* Department of Systems Biology, Center for Biological Sequence Analysis, IBM Computational Biology Center, National Technical University of Athens, Philip Morris International R&D, Columbia University, Merck & Co., Inc., Laboratorio di Bioinformatica, Selventa, Cambridge, Massachusetts, Swiss Federal Institute of Technology, Broad Institute of Harvard University and Massachusetts Institute of Technology, Biobase GmbH, IBM Life Sciences Division, Duke University  
*Pages:* 811-815  
*Publication date:* 2011  
*Main Research Area:* Technical/natural sciences

**Publication information**

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*Ratings:*  
*BFI (2018):* BFI-level 3  
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*Web of Science (2017):* Indexed Yes  
*BFI (2016):* BFI-level 2  
*Scopus rating (2016):* CiteScore 13.16 SJR 20.253 SNIP 6.303  
*Web of Science (2016):* Indexed yes  
*BFI (2015):* BFI-level 2  
*Scopus rating (2015):* SJR 17.892 SNIP 5.505 CiteScore 11.88  
*Web of Science (2015):* Indexed yes  
*BFI (2014):* BFI-level 2  
*Scopus rating (2014):* SJR 16.443 SNIP 5.433 CiteScore 11.4  
*Web of Science (2014):* Indexed yes  
*BFI (2013):* BFI-level 2  
*Scopus rating (2013):* SJR 13.849 SNIP 5.416 CiteScore 10.45
The yeast *Saccharomyces cerevisiae* is a model organism in biology, being widely used in fundamental research, the first eukaryotic organism to be fully sequenced and the platform for the development of many genomics techniques. Therefore, it is not surprising that *S. cerevisiae* has also been widely used in the field of systems biology during the last decade. This thesis investigates *S. cerevisiae* growth physiology and DNA damage response by using a systems biology approach. Elucidation of the relationship between growth rate and gene expression is important to understand the mechanisms regulating cell growth. In order to study this relationship, we have grown *S. cerevisiae* cells in chemostat at defined growth rates and measured the transcriptional response. We have applied a complex experimental design, involving three factors: specific growth rate, oxygen availability and nutrient limitation. We have identified 268 growth rate dependent genes. These genes were used to identify key areas of the metabolism around which expression changes were significantly associated and we found nucleotide synthesis and ATP producing and consuming reactions. Moreover, by scoring the significance of overlap between growth rate dependent genes and known transcription factor (TF) target sets, we identified 13 TFs, involved in stress response, cell cycle and ribosome biogenesis, that appeared to coordinate the response at increasing growth rates. Therefore, in this study we have identified a more conservative set of growth dependent genes by using a multi-factorial experimental design. Moreover, new insights into the metabolic response and transcriptional regulation of these genes have been provided by using systems biology tools (Chapter 3). One of the prerequisite of systems biology should be the standardization and reproducibility of experimental and analytical techniques, in order to allow the comparison of data generated in different laboratories. With the aim of addressing this aspect, we have collaborated in a large study involving ten laboratories, constituting the Yeast Systems Biology Network (YSBN). *S. cerevisiae* cultivations were performed in a single laboratory and samples were sent to the other partners. The experimental design involved two factors: strain (CEN.PK113-7D and YSBN2) and growth condition (batch and
chemostat). Transcriptome was measured with four different platforms (Affymetrix, Agilent, qPCR and TRAC), metabolome was analyzed in seven laboratories, using different protocols, and enzyme activities were determined in two different laboratories. The comparison of the analyses showed that reproducibility of the results was affected by the laboratory and the protocol used. Transcription and enzyme activity analyses gave consistent results, while metabolite level measurements showed some variability. Therefore, even though the source of biomass was unique, the reproducibility of data appeared to be a challenging task. Nevertheless, we were able to perform an integrative analysis and discover that the lower biomass yield of CEN.PK113-7D was due to higher protein turnover than YSBN2; this finding would not be achievable using a single omics dataset. Moreover, the generated datasets are a valuable resource for the yeast systems biology community (Chapter 4). Upon DNA damage, S. cerevisiae cells respond activating the so-called cell cycle checkpoints that promote damage repair and viability. The activation of these checkpoints depends on kinase cascades and regulation of transcription is one of the responses elicited by checkpoint activation. Therefore, we have decided to investigate the transcriptional and phenotypic responses to the alkylation agent methyl methanesulfonate (MMS) of mutant strains carrying deletions of genes encoding protein kinases (Mec1, Tel1, Rad53, Dun1, Chk1, Alk1) and protein phosphatases (Ptc3, Pph3, Oca1) involved in DNA damage response (DDR). We have discovered a prominent role for Rad53, Mec1 and Tel1 in transcriptional response. Moreover, we have shown for the first time the important role of Oca1 at the transcriptional level. We have built a comprehensive network of the central DDR pathway by integrating data from different cellular levels and identified regulatory circuits involving key players of this pathway. Integration of transcriptional and phenotypic data allowed us to discover sets of genes whose expression levels correlate with growth rates upon MMS treatment. Finally, we have also investigated the role of non protein-coding RNAs in DNA damage response (Chapter 5). When DNA damage is repaired, cells restart the cell cycle and resume growth. This process is called damage recovery. In S. cerevisiae, the molecular mechanism of recovery relies on dephosphorylation of Rad53 by protein phosphatases (PPs), that, in case of recovery from MMS-induced damage, are Ptc2, Ptc3 and Pph3. In order to elucidate the relationship between Rad53 and PPs, we have generated strains carrying mutations in Rad53 domains (SCD1 and FHA1) and deletion of genes encoding the PPs. Then, we have investigated the Rad53 phosphorylation status and the phenotype of these mutant strains. This study has allowed us to propose a role for the threonine 8 of Rad53-SCD1 domain and its Ptc2/3-mediated dephosphorylation during MMS recovery (Chapter 6).
Protein Function Prediction in Bacteria

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis
Authors: Kiil, K. (Intern), Ussery, D. (Intern)
Publication date: Sep 2010

Publication information
Place of publication: Kgs. Lyngby, Denmark
Publisher: Technical University of Denmark (DTU)
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Main Research Area: Technical/natural sciences
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Source-ID: 271248
Publication: Research › Ph.D. thesis – Annual report year: 2010

Systems Biology in Industrial Biotechnology and Disease

General information
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Organisations: Center for Biological Sequence Analysis, Department of Systems Biology
Authors: Rasmussen, S. (Intern), Brunak, S. (Intern), Nielsen, H. B. (Intern), Jarmer, H. Ø. (Intern)
Publication date: May 2010

Publication information
Place of publication: Kgs. Lyngby, Denmark
Publisher: Technical University of Denmark (DTU)
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Main Research Area: Technical/natural sciences
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Source-ID: 270898
Publication: Research › Ph.D. thesis – Annual report year: 2010

Computational tools and Interoperability in Comparative Genomics

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A focused, PCR based gene expression signature to refine grade in breast cancer

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Scopus rating (2013): SJR 2.855 SNIP 2.055 CiteScore 5.65
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Scopus rating (2012): SJR 2.962 SNIP 2.155 CiteScore 5.79
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BFI (2010): BFI-level 1
Scopus rating (2010): SJR 2.174 SNIP 1.557
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.948 SNIP 1.527
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Scopus rating (2008): SJR 2.121 SNIP 1.587
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Scopus rating (2003): SJR 1.132 SNIP 1.297
Scopus rating (2002): SJR 1.053 SNIP 1.233
Scopus rating (2001): SJR 1.193 SNIP 1.186
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A human gut microbial gene catalogue established by metagenomic sequencing

To understand the impact of gut microbes on human health and well-being it is crucial to assess their genetic potential. Here we describe the Illumina-based metagenomic sequencing, assembly and characterization of 3.3 million non-redundant microbial genes, derived from 576.7 gigabases of sequence, from faecal samples of 124 European individuals. The gene set, 150 times larger than the human gene complement, contains an overwhelming majority of the prevalent (more frequent) microbial genes of the cohort and probably includes a large proportion of the prevalent human intestinal microbial genes. The genes are largely shared among individuals of the cohort. Over 99% of the genes are bacterial, indicating that the entire cohort harbours between 1,000 and 1,150 prevalent bacterial species and each individual at least 160 such species, which are also largely shared. We define and describe the minimal gut metagenome and the minimal gut bacterial genome in terms of functions present in all individuals and most bacteria, respectively.

General information

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BFI (2013): BFI-level 2
Scopus rating (2013): CiteScore 14.96
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Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
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A kit for the investigation of live Escherichia coli cell adhesion to glycosylated surfaces

A combination of microtiter plate functionalization techniques and two facile bacterial adhesion inhibition assays form a flexible toolbox for the investigation of bacterial adhesion mechanisms on glycosylated surfaces.

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Amplification of LAPTM4B and YWHAZ contributes to chemotherapy resistance and recurrence of breast cancer

Adjuvant chemotherapy for breast cancer after surgery has effectively lowered metastatic recurrence rates. However, a considerable proportion of women suffer recurrent cancer at distant metastatic sites despite adjuvant treatment. Identification of the genes crucial for tumor response to specific chemotherapy drugs is a challenge but is necessary to improve outcomes. By using integrated genomics, we identified a small number of overexpressed and amplified genes from chromosome 8q22 that were associated with early disease recurrence despite anthracycline-based adjuvant chemotherapy. We confirmed the association in an analysis of multiple independent cohorts. SiRNA-mediated knockdown of either of two of these genes, the antiapoptotic gene YWHAZ and a lysosomal gene LAPTM4B, sensitized tumor cells to anthracyclines, and overexpression of either of the genes induced anthracycline resistance. Overexpression of LAPTM4B resulted in sequestration of the anthracycline doxorubicin, delaying its appearance in the nucleus. Overexpression of these two genes was associated with poor tumor response to anthracycline treatment in a neoadjuvant chemotherapy trial in women with primary breast cancer. Our results suggest that 8q22 amplification and overexpression of LAPTM4B and YWHAZ contribute to de novo chemotherapy resistance and are permissive for metastatic recurrence. Overexpression of these two genes may predict anthracycline resistance and influence selection of chemotherapy.

General information
Analysis of intra-genomic GC content homogeneity within prokaryotes

Bacterial genomes possess varying GC content (total guanines (Gs) and cytosines (Cs) per total of the four bases within the genome) but within a given genome, GC content can vary locally along the chromosome, with some regions significantly more or less GC rich than on average. We have examined how the GC content varies within microbial genomes to assess whether this property can be associated with certain biological functions related to the organism's environment and phylogeny. We utilize a new quantity GCVAR, the intra-genomic GC content variability with respect to the average GC content of the total genome. A low GCVAR indicates intra-genomic GC homogeneity and high GCVAR heterogeneity.

RESULTS: The regression analyses indicated that GCVAR was significantly associated with domain (i.e. archaea or bacteria), phylum, and oxygen requirement. GCVAR was significantly higher among anaerobes than both aerobic and facultative microbes. Although an association has previously been found between mean genomic GC content and oxygen requirement, our analysis suggests that no such association exists when phylogenetic bias is accounted for. A significant association between GCVAR and mean GC content was also found but appears to be non-linear and varies greatly among phyla.

CONCLUSIONS: Our findings show that GCVAR is linked with oxygen requirement, while mean genomic GC content is not. We therefore suggest that GCVAR should be used as a complement to mean GC content.
Ancient Human Genome Sequence of an Extinct Palaeo-Eskimo

We report here the genome sequence of an ancient human. Obtained from approximately 4,000-year-old permafrost-preserved hair, the genome represents a male individual from the first known culture to settle in Greenland. Sequenced to an average depth of 20x, we recover 79% of the diploid genome, an amount close to the practical limit of current sequencing technologies. We identify 353,151 high-confidence single-nucleotide polymorphisms (SNPs), of which 6.8% have not been reported previously. We estimate raw read contamination to be no higher than 0.8%. We use functional SNP assessment to assign possible phenotypic characteristics of the individual that belonged to a culture whose location has yielded only trace human remains. We compare the high-confidence SNPs to those of contemporary populations to find the populations most closely related to the individual. This provides evidence for a migration from Siberia into the New World some 5,500 years ago, independent of that giving rise to the modern Native Americans and Inuit.
An intuitive Python interface for Bioconductor libraries demonstrates the utility of language translators

Background Computer languages can be domain-related, and in the case of multidisciplinary projects, knowledge of several languages will be needed in order to quickly implements ideas. Moreover, each computer language has relative strong points, making some languages better suited than others for a given task to be implemented. The Bioconductor project, based on the R language, has become a reference for the numerical processing and statistical analysis of data coming from high-throughput biological assays, providing a rich selection of methods and algorithms to the research community. At the same time, Python has matured as a rich and reliable language for the agile development of prototypes or final implementations, as well as for handling large data sets. Results The data structures and functions from Bioconductor can be exposed to Python as a regular library. This allows a fully transparent and native use of Bioconductor
from Python, without one having to know the R language and with only a small community of translators required to know both. To demonstrate this, we have implemented such Python representations for key infrastructure packages in Bioconductor, letting a Python programmer handle annotation data, microarray data, and next-generation sequencing data. Conclusions Bioconductor is now not solely reserved to R users. Building a Python application using Bioconductor functionality can be done just like if Bioconductor was a Python package.
An online survival analysis tool to rapidly assess the effect of 22,277 genes on breast cancer prognosis using microarray data of 1,809 patients

Validating prognostic or predictive candidate genes in appropriately powered breast cancer cohorts are of utmost interest. Our aim was to develop an online tool to draw survival plots, which can be used to assess the relevance of the expression levels of various genes on the clinical outcome both in untreated and treated breast cancer patients. A background database was established using gene expression data and survival information of 1,809 patients downloaded from GEO (Affymetrix HGU133A and HGU133+2 microarrays). The median relapse free survival is 6.43 years, 968/1,231 patients are estrogen-receptor (ER) positive, and 190/1,369 are lymph-node positive. After quality control and normalization only probes present on both Affymetrix platforms were retained (n = 22,277). In order to analyze the prognostic value of a particular gene, the cohorts are divided into two groups according to the median (or upper/lower quartile) expression of the gene. The two groups can be compared in terms of relapse free survival, overall survival, and distant metastasis free survival. A survival curve is displayed, and the hazard ratio with 95% confidence intervals and logrank P value are calculated and displayed. Additionally, three subgroups of patients can be assessed: systematically untreated patients, endocrine-treated ER positive patients, and patients with a distribution of clinical characteristics representative of those seen in general clinical practice in the US. Web address: www.kmplot.com. We used this integrative data analysis tool to confirm the prognostic power of the proliferation-related genes TOP2A and TOP2B, MKI67, CCND2, CCND3, CCNDE2, as well as CDKN1A, and TK2. We also validated the capability of microarrays to determine estrogen receptor status in 1,231 patients. The tool is highly valuable for the preliminary assessment of biomarkers, especially for research groups with limited bioinformatic resources.
Antioxidant properties of modified rutin esters by DPPH, reducing power, iron chelation and human low density lipoprotein assays

Practical limitations exist regarding the effectiveness of flavonoids as antioxidants in many food systems, possibly due to their poor solubility and miscibility in lipidic environments. Current strategies to improve these properties include enzymatically acylating flavonoids with lipophilic moieties. Herein, two derivatives of rutin (possessing C12:0 or C16:0 acyl groups) were assessed for their antioxidant properties, and compared with their parent compound, rutin and with butylated hydroxytoluene (BHT). While all compounds exhibited relatively strong radical scavenging abilities, modified rutin compounds exhibited decreased reducing power and metal chelating abilities as compared to rutin. Conversely, investigations on the oxidation of human low density lipoprotein (LDL) revealed that rutin laurate was most effective in inhibiting oxidation by prolonging LDL lag time for an in vitro system. With regards to in vivo considerations, a pre-treatment step confirmed that the ester bond linking rutin and acyl moieties was most susceptible to hydrolysis by digestive enzymes, while rutin itself was not degraded. Thus, acylation of rutin with medium or long chain fatty acids may result in improved antioxidant abilities in more complex systems, including LDL-oxidation assays. Likely reasons may include improved lipophilic solubility and partitioning properties allowing for better accessibility to the actual site of oxidation. (C) 2010 Elsevier Ltd. All rights reserved.
Assessment of an RNA interference screen-derived mitotic and ceramide pathway metagene as a predictor of response to neoadjuvant paclitaxel for primary triple-negative breast cancer: a retrospective analysis of five clinical trials

Addition of taxanes to preoperative chemotherapy in breast cancer increases the proportion of patients who have a pathological complete response (pCR). However, a substantial proportion of patients do not respond, and the prognosis is particularly poor for patients with oestrogen-receptor (ER)/progesterone-receptor (PR)/human epidermal growth factor receptor 2 (HER2; ERBB2)-negative (triple-negative) disease who do not achieve a pCR. Reliable identification of such patients is the first step in determining who might benefit from alternative treatment regimens in clinical trials. We previously identified genes involved in mitosis or ceramide metabolism that influenced sensitivity to paclitaxel, with an RNA interference (RNAi) screen in three cancer cell lines, including a triple-negative breast-cancer cell line. Here, we assess these genes as a predictor of pCR to paclitaxel combination chemotherapy in triple-negative breast cancer.

METHODS: We derived a paclitaxel response metagene based on mitotic and ceramide genes identified by functional genomics studies. We used area under the curve (AUC) analysis and multivariate logistic regression to retrospectively assess the metagene in six cohorts of patients with triple-negative breast cancer treated with neoadjuvant chemotherapy; two cohorts treated with paclitaxel (n=27, 30) and four treated without paclitaxel (n=88, 28, 48, 39). FINDINGS: The metagene was associated with pCR in paclitaxel-treated cohorts (AUC 0.79 [95% CI 0.53-0.93], 0.72 [0.48-0.90]) but not in non-paclitaxel treated cohorts (0.53 [0.31-0.77], 0.59 [0.22-0.82], 0.53 [0.36-0.71], 0.64 [0.43-0.81]). In multivariate logistic regression, the metagene was associated with pCR (OR 19.92, 2.62-151.57; p=0.0039) with paclitaxel-containing chemotherapy. INTERPRETATION: The paclitaxel response metagene shows promise as a paclitaxel-specific predictor of pCR in patients with triple-negative breast cancer. The metagene is suitable for development into a reverse transcription-PCR assay, for which clinically relevant thresholds could be established in randomised clinical trials. These results highlight the potential for functional genomics to accelerate development of drug-specific predictive biomarkers without the need for training clinical trial cohorts. FUNDING: UK Medical Research Council; Cancer Research UK; the National Institute for Health Research (UK); the Danish Council for Independent Research-Medical Sciences (FSS); Breast Cancer Research Foundation (New York); Fondation Luxembourg pour la Recherche Scientifique; Brussels Region (IRISIB-IP, Life Sciences 2007) and Walloon Region (Biowin-Keymarker); Sally Pearson Breast Cancer Fund; and the European Commission. Copyright © 2010 Elsevier Ltd. All rights reserved.

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Autoimmunity in Arabidopsis acd11 Is Mediated by Epigenetic Regulation of an Immune Receptor

Certain pathogens deliver effectors into plant cells to modify host protein targets and thereby suppress immunity. These target modifications can be detected by intracellular immune receptors, or Resistance (R) proteins, that trigger strong immune responses including localized host cell death. The accelerated cell death 11 (acd11) "lesion mimic" mutant of Arabidopsis thaliana exhibits autoimmune phenotypes such as constitutive defense responses and cell death without pathogen perception. The acd11 phenotype is caused by the accelerated cell death 11 (acd11) gene, which is a putative sphingosine transfer protein. However, the precise role of ACD11 during these processes is unknown.

In a screen for lazarus (laz) mutants that suppress acd11 death we identified two genes, LAZ2 and LAZ5. LAZ2 encodes the histone lysine methyltransferase SDG8, previously shown to epigenetically regulate flowering time via modification of histone 3 (H3). LAZ5 encodes an RPS4-like R-protein, defined by several dominant negative alleles. Microarray and chromatin immunoprecipitation analyses showed that LAZ2/SDG8 is required for LAZ5 expression and H3 lysine 36 trimethylation at LAZ5 chromatin to maintain a transcriptionally active state. We hypothesize that LAZ5 triggers cell death in the absence of ACD11, and that cell death in other lesion mimic mutants may also be caused by inappropriate activation of R genes. Moreover, SDG8 is required for basal and R protein-mediated pathogen resistance in Arabidopsis, revealing the importance of chromatin remodeling as a key process in plant innate immunity.
**Bifidobacterium bifidum Actively Changes the Gene Expression Profile Induced by Lactobacillus acidophilus in Murine Dendritic Cells**

Dendritic cells (DC) play a pivotal regulatory role in activation of both the innate as well as the adaptive immune system by responding to environmental microorganisms. We have previously shown that Lactobacillus acidophilus induces a strong production of the pro-inflammatory and Th1 polarizing cytokine IL-12 in DC, whereas bifidobacteria do not induce IL-12 but inhibit the IL-12 production induced by lactobacilli. In the present study, genome-wide microarrays were used to investigate the gene expression pattern of murine DC stimulated with Lactobacillus acidophilus NCFM and Bifidobacterium bifidum Z9. L. acidophilus NCFM strongly induced expression of interferon (IFN)-beta, other virus defence genes, and cytokine and chemokine genes related to the innate and the adaptive immune response. By contrast, B. bifidum Z9 inhibited the expression of the Th1-promoting genes induced by L. acidophilus NCFM and had an additive effect on genes of the innate immune response and Th2 skewing genes. The gene encoding Jun dimerization protein 2 (JDP2), a transcription factor regulating the activation of JNK, was one of the few genes only induced by B. bifidum Z9. Neutralization of IFN-beta abrogated L. acidophilus NCFM-induced expression of Th1-skewing genes, and blocking of the JNK pathway completely inhibited the expression of IFN-beta. Our results indicate that B. bifidum Z9 actively inhibits the expression of genes related to the adaptive immune system in murine dendritic cells and that JPD2 via blocking of IFN-beta plays a central role in this regulatory mechanism.

**General information**

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Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Center for Biological sequence analysis, Department of Biochemistry and Nutrition  
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Scopus rating (2015): SJR 1.414 SNIP 1.131 CiteScore 3.32  
Web of Science (2015): Indexed yes  
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Web of Science (2014): Indexed yes  
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Scopus rating (2013): SJR 1.74 SNIP 1.147 CiteScore 3.94  
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Bioinformatics Training: A Review of Challenges, Actions and Support Requirements

As bioinformatics becomes increasingly central to research in the molecular life sciences, the need to train non-bioinformaticians to make the most of bioinformatics resources is growing. Here, we review the key challenges and pitfalls to providing effective training for users of bioinformatics services, and discuss successful training strategies shared by a diverse set of bioinformatics trainers. We also identify steps that trainers in bioinformatics could take together to advance the state of the art in current training practices. The ideas presented in this article derive from the first Trainer Networking Session held under the auspices of the EU-funded SLING Integrating Activity, which took place in November 2009.

General information

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BioXSD: the common data-exchange format for everyday bioinformatics web services

Motivation: The world-wide community of life scientists has access to a large number of public bioinformatics databases and tools, which are developed and deployed using diverse technologies and designs. More and more of the resources offer programmatic web-service interface. However, efficient use of the resources is hampered by the lack of widely used, standard data-exchange formats for the basic, everyday bioinformatics data types. Results: BioXSD has been developed as a candidate for standard, canonical exchange format for basic bioinformatics data. BioXSD is represented by a dedicated XML Schema and defines syntax for biological sequences, sequence annotations, alignments and references to resources. We have adapted a set of web services to use BioXSD as the input and output format, and implemented a test-case workflow. This demonstrates that the approach is feasible and provides smooth interoperability. Semantics for BioXSD is provided by annotation with the EDAM ontology. We discuss in a separate section how BioXSD relates to other initiatives and approaches, including existing standards and the Semantic Web.

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CD4+ T-cell activation is differentially modulated by bacteria-primed dendritic cells, but is generally down-regulated by n-3 polyunsaturated fatty acids

Appropriate activation of CD4+ T cells is fundamental for efficient initiation and progression of acquired immune responses. Here, we showed that CD4+ T-cell activation is dependent on changes in membrane n-3 polyunsaturated fatty acids (PUFAs) and is dynamically regulated by the type of signals provided by dendritic cells (DCs). Upon interaction with DCs primed by different concentrations and species of gut bacteria, CD4+ T cells were activated according to the type of DC stimulus. The levels of CD80 were found to correlate to the levels of expression of CD28 and to the proliferation of CD4+ T cells, while the presence of CD40 and CD86 on DCs inversely affected inducible costimulator (ICOS) and cytotoxic T-lymphocyte antigen-4 (CTLA-4) levels in CD4+ T cells. For all DC stimuli, cells high in n-3 PUFAs showed reduced ability to respond to CD28 stimulation, to proliferate, and to express ICOS and CTLA-4. Diminished T-cell receptor (TCR) and CD28 signalling was found to be responsible for n-3 PUFAs effects. Thus, the dietary fatty acid composition influences the overall level of CD4+ T-cell activation induced by DCs, while the priming effect of the DC stimuli modulates CD80, CD86 and CD40 levels, thereby affecting and shaping activation of acquired immunity by differential regulation of proliferation and costimulatory molecule expression in CD4+ T cells.
Ceramides and barrier function in healthy skin

Lipids in the stratum corneum are key components in the barrier function of the skin. Changes in lipid composition related to eczematous diseases are well known, but limited data are available on variations within healthy skin. The objective of the present study was to compare ceramide subgroups and ceramide/cholesterol ratios in young, old, male and female healthy skin. A total of 55 participants with healthy skin was included in the study. Lipid profiles were correlated with transepidermal water loss and with information on dry skin from a questionnaire including 16 people. No statistically significant differences were found between young and old skin for ceramide subgroups or ceramide/cholesterol ratios, and there was no statistically significant correlation between answers about dry skin and ceramide levels. Interestingly, a statistically significant higher ceramide/cholesterol ratio was found for men than for women (p = 0.02).

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Changes in skin barrier during treatment with systemic alitretinoin: focus on skin susceptibility and stratum corneum ceramides

Alitretinoin is a new drug for systemic treatment of chronic hand eczema. Previous functional tests of skin topically treated with retinoids have indicated impaired skin barrier function, but no data are available on barrier parameters after systemic alitretinoin treatment. To investigate the effect of systemic alitretinoin on skin barrier function and response to irritants, a secondary objective was to determine if changes occur in the lipid profile of stratum corneum after treatment with systemic alitretinoin. We conducted an open clinical intervention study on eight people ascribed to systemic alitretinoin treatment. Before initiation and after 2 months of systemic treatment with 30 mg alitretinoin, a challenge with sodium lauryl sulphate (SLS) was performed on the volar forearm and evaluated by trans-epidermal water loss (TEWL), erythema, and a cyanoacrylate skin sample was obtained for lipid analysis. We found no significant changes in response to SLS irritation as evaluated by TEWL and erythema, after treatment with alitretinoin for 2 months. No significant changes in stratum corneum lipids were found after 2 months of treatment. In conclusion, systemic alitretinoin does not influence skin susceptibility to irritants or the ceramide profile of stratum corneum.
Bacterial biofilms are associated with a large number of infections. Biofilm-dwelling bacteria are particularly resistant to antibiotics, making it hard to eradicate biofilm-associated infections. Here, we use a novel cross-disciplinary approach combining microbiology and chemoinformatics to identify new and efficient anti-biofilm drugs. We found that ellagic acid (present in green tea) significantly inhibited biofilm formation of Streptococcus dysgalactiae. Based on ellagic acid, we performed in silico screening of the Chinese Natural Product Database to predict a 2nd-generation list of compounds with similar characteristics. One of these, esculetin, proved to be more efficient in preventing biofilm formation by Staphylococcus aureus. From esculetin a 3rd-generation list of compounds was predicted. One of them, fisetin, was even better to abolish biofilm formation than the two parent compounds. Fisetin dramatically inhibited biofilm formation of both S. aureus and S. dysgalactiae. The compounds did not affect planktonic growth in concentrations where they affected biofilm formation and appeared to be specific antagonists of biofilms. Arguably, since all three compounds are natural ingredients of dietary plants, they should be well-tolerated by humans. Our results indicate that such small plant components, with bacterial lifestyle altering properties are promising candidates for novel generations of antimicrobial drugs. The study underlines the potential in combining chemoinformatics and biofilm research.

**Chemoinformatics-assisted development of new anti-biofilm compounds**

Bacterial biofilms are associated with a large number of infections. Biofilm-dwelling bacteria are particularly resistant to antibiotics, making it hard to eradicate biofilm-associated infections. Here, we use a novel cross-disciplinary approach combining microbiology and chemoinformatics to identify new and efficient anti-biofilm drugs. We found that ellagic acid (present in green tea) significantly inhibited biofilm formation of Streptococcus dysgalactiae. Based on ellagic acid, we performed in silico screening of the Chinese Natural Product Database to predict a 2nd-generation list of compounds with similar characteristics. One of these, esculetin, proved to be more efficient in preventing biofilm formation by Staphylococcus aureus. From esculetin a 3rd-generation list of compounds was predicted. One of them, fisetin, was even better to abolish biofilm formation than the two parent compounds. Fisetin dramatically inhibited biofilm formation of both S. aureus and S. dysgalactiae. The compounds did not affect planktonic growth in concentrations where they affected biofilm formation and appeared to be specific antagonists of biofilms. Arguably, since all three compounds are natural ingredients of dietary plants, they should be well-tolerated by humans. Our results indicate that such small plant components, with bacterial lifestyle altering properties are promising candidates for novel generations of antimicrobial drugs. The study underlines the potential in combining chemoinformatics and biofilm research.

**General information**

State: Published

Organisations: Department of Systems Biology, Center for Biological Sequence Analysis

Authors: Dürig, A. (Intern), Kouskoumvekaki, I. (Intern), Vejborg, R. M. (Intern), Klemm, P. (Ekstern)

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Chronic exposure of adults and embryos of Pandalus borealis to oil causes PAH accumulation, initiation of biomarker responses and an increase in larval mortality

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Authors: Bechmann, R. (Ekstern), Larsen, B. K. (Intern), Taban, I. (Ekstern), Hellgren, L. (Intern), Møller, P. (Intern), Sanni, S. (Ekstern)
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BFI (2011): BFI-level 1
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Scopus rating (2009): SJR 1.302 SNIP 1.202
Combining substrate specificity analysis with support vector classifiers reveals feruloyl esterase as a phylogenetically informative protein group

Background Our understanding of how fungi evolved to develop a variety of ecological niches, is limited but of fundamental biological importance. Specifically, the evolution of enzymes affects how well species can adapt to new environmental conditions. Feruloyl esterases (FAEs) are enzymes able to hydrolyze the ester bonds linking ferulic acid to plant cell wall polysaccharides. The diversity of substrate specificities found in the FAE family shows that this family is old enough to have experienced the emergence and loss of many activities. Methodology/Principal Findings In this study we evaluate the relative activity of FAEs against a variety of model substrates as a novel predictive tool for Ascomycota taxonomic classification. Our approach consists of two analytical steps; (1) an initial unsupervised analysis to cluster the FAEs substrate specificity data which were generated by cultivation of 34 Ascomycota strains and then an analysis of the produced enzyme cocktail against 10 substituted cinnamate and phenylalkanoate methyl esters, (2) a second, supervised analysis for training a predictor built on these substrate activities. By applying both linear and non-linear models we were able to correctly predict the taxonomic Class (~86% correct classification), Order (~88% correct classification) and Family (~88% correct classification) that the 34 Ascomycota belong to, using the activity profiles of the FAEs.

Conclusion/Significance The good correlation with the FAEs substrate specificities that we have defined via our phylogenetic analysis not only suggests that FAEs are phylogenetically informative proteins but it is also a considerable step towards improved FAEs functional prediction.
Comparative Genomics of Green Sulfur Bacteria

Eleven completely sequenced Chlorobi genomes were compared in oligonucleotide usage, gene contents, and synteny. The green sulfur bacteria (GSB) are equipped with a core genome that sustains their anoxygenic phototrophic lifestyle by photosynthesis, sulfur oxidation, and CO(2) fixation. Whole-genome gene family and single gene sequence comparisons yielded similar phylogenetic trees of the sequenced chromosomes indicating a concerted vertical evolution of large gene sets. Chromosomal synteny of genes is not preserved in the phylum Chlorobi. The accessory genome is characterized by anomalous oligonucleotide usage and endows the strains with individual features for transport, secretion, cell wall, extracellular constituents, and a few elements of the biosynthetic apparatus. Giant genes are a peculiar feature of the genera Chlorobium and Prosthecochloris. The predicted proteins have a huge molecular weight of 10(6), and are probably instrumental for the bacteria to generate their own intimate (micro)environment.
Comparison of 61 Sequenced Escherichia coli Genomes

Escherichia coli is an important component of the biosphere and is an ideal model for studies of processes involved in bacterial genome evolution. Sixty-one publically available E. coli and Shigella spp. sequenced genomes are compared,
using basic methods to produce phylogenetic and proteomics trees, and to identify the pan- and core genomes of this set of sequenced strains. A hierarchical clustering of variable genes allowed clear separation of the strains into clusters, including known pathotypes; clinically relevant serotypes can also be resolved in this way. In contrast, when in silico MLST was performed, many of the various strains appear jumbled and less well resolved. The predicted pan-genome comprises 15,741 gene families, and only 993 (6%) of the families are represented in every genome, comprising the core genome. The variable or ‘accessory’ genes thus make up more than 90% of the pan-genome and about 80% of a typical genome; some of these variable genes tend to be co-localized on genomic islands. The diversity within the species E. coli, and the overlap in gene content between this and related species, suggests a continuum rather than sharp species borders in this group of Enterobacteriaceae.

General information
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Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Technical University of Denmark
Authors: Lukjancenko, O. (Intern), Wassenaar, T. M. (Ekstem), Ussery, D. (Intern)
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Computational Immunology Meets Bioinformatics: The Use of Prediction Tools for Molecular Binding in the Simulation of the Immune System

We present a new approach to the study of the immune system that combines techniques of systems biology with information provided by data-driven prediction methods. To this end, we have extended an agent-based simulator of the immune response, C-IMMSIM, such that it represents pathogens, as well as lymphocytes receptors, by means of their amino acid sequences and makes use of bioinformatics methods for T and B cell epitope prediction. This is a key step for the simulation of the immune response, because it determines immunogenicity. The binding of the epitope, which is the immunogenic part of an invading pathogen, together with activation and cooperation from T helper cells, is required to trigger an immune response in the affected host. To determine a pathogen's epitopes, we use existing prediction methods. In addition, we propose a novel method, which uses Miyazawa and Jernigan protein-protein potential measurements, for assessing molecular binding in the context of immune complexes. We benchmark the resulting model by simulating a classical immunization experiment that reproduces the development of immune memory. We also investigate the role of major histocompatibility complex (MHC) haplotype heterozygosity and homozygosity with respect to the influenza virus and show that there is an advantage to heterozygosity. Finally, we investigate the emergence of one or more dominating clones of lymphocytes in the situation of chronic exposure to the same immunogenic molecule and show that high affinity clones proliferate more than any other. These results show that the simulator produces dynamics that are stable and consistent with basic immunological knowledge. We believe that the combination of genomic information and simulation of the dynamics of the immune system, in one single tool, can offer new perspectives for a better understanding of the immune system.
Country-specific chemical signatures of persistent environmental compounds in breast milk
Recent reports have confirmed a worldwide increasing trend of testicular cancer incidence, and a conspicuously high prevalence of this disease and other male reproductive disorders, including cryptorchidism and hypospadias, in Denmark. In contrast, Finland, a similarly industrialized Nordic country, exhibits much lower incidences of these disorders. The reasons behind the observed trends are unexplained, but environmental endocrine disrupting chemicals (EDCs) that affect foetal testis development are probably involved. Levels of persistent chemicals in breast milk can be considered a proxy for exposure of the foetus to such agents. Therefore, we undertook a comprehensive ecological study of 121 EDCs, including the persistent compounds dioxins, polychlorinated biphenyls (PCBs), pesticides and flame retardants, and non-persistent phthalates, in 68 breast milk samples from Denmark and Finland to compare exposure of mothers to this environmental mixture of EDCs. Using sophisticated, bioinformatic tools in our analysis, we reveal, for the first time, distinct country-specific chemical signatures of EDCs with Danes having generally higher exposure than Finns to persistent bioaccumulative chemicals, whereas there was no country-specific pattern with regard to the non-persistent phthalates. Importantly, EDC levels, including some dioxins, PCBs and some pesticides (hexachlorobenzene and dieldrin) were significantly higher in Denmark than in Finland. As these classes of EDCs have been implicated in testicular cancer or in adversely affecting development of the foetal testis in humans and animals, our findings reinforce the view that environmental exposure to EDCs may explain some of the temporal and between-country differences in incidence of male reproductive disorders.
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**CPHmodels-3.0—remote homology modeling using structure-guided sequence profiles**

CPHmodels-3.0 is a web server predicting protein 3D structure by use of single template homology modeling. The server employs a hybrid of the scoring functions of CPHmodels-2.0 and a novel remote homology-modeling algorithm. A query sequence is first attempted modeled using the fast CPHmodels-2.0 profile-profile scoring function suitable for close homology modeling. The new computational costly remote homology-modeling algorithm is only engaged provided that no suitable PDB template is identified in the initial search. CPHmodels-3.0 was benchmarked in the CASP8 competition and produced models for 94% of the targets (117 out of 128), 74% were predicted as high reliability models (87 out of 117). These achieved an average RMSD of 4.6 Å when superimposed to the 3D structure. The remaining 26% low reliability models (30 out of 117) could superimpose to the true 3D structure with an average RMSD of 9.3 Å. These performance values place the CPHmodels-3.0 method in the group of high performing 3D prediction tools. Beside its accuracy, one of the important features of the method is its speed. For most queries, the response time of the server is

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- **State:** Published
- **Organisations:** Center for Biological Sequence Analysis, Department of Systems Biology
- **Authors:** Nielsen, M. (Intern), Lundegaard, C. (Intern), Lund, O. (Intern), Petersen, T. N. (Intern)
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  - Web of Science (2015): Indexed yes
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  - Web of Science (2014): Indexed yes
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  - Scopus rating (2013): SJR 6.582 SNIP 2.266 CiteScore 8.46
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  - BFI (2012): BFI-level 2
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  - ISI indexed (2012): ISI indexed yes
  - Web of Science (2012): Indexed yes
  - BFI (2011): BFI-level 2
  - Scopus rating (2011): SJR 5.758 SNIP 2.172 CiteScore 7.86
  - ISI indexed (2011): ISI indexed yes
  - Web of Science (2011): Indexed yes
  - BFI (2010): BFI-level 2
  - Scopus rating (2010): SJR 5.24 SNIP 2.034
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  - BFI (2009): BFI-level 2
  - Scopus rating (2009): SJR 5.571 SNIP 1.869
  - BFI (2008): BFI-level 2
  - Scopus rating (2008): SJR 4.641 SNIP 1.557
  - Web of Science (2008): Indexed yes
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CTL epitopes of FMDV determined by NetMHCpan-driven predictions of SLA/peptide binding, confirmed by tetramer complex formation and staining

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Organisations: Adaptive Immunology & Parasitology, Division of Veterinary Diagnostics and Research, National Veterinary Institute, Center for Biological Sequence Analysis, Department of Systems Biology, Department of Acoustic Technology, Agricultural Research Service
Authors: Pedersen, L. E. (Intern), Nielsen, M. (Intern), Patch, J. R. (Ekstern), Jungersen, G. (Intern), Buus, S. (Ekstern), Golde, W. T. (Ekstern)
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Cyclebase.org: version 2.0, an updated comprehensive, multi-species repository of cell cycle experiments and derived analysis results

Cell division involves a complex series of events orchestrated by thousands of molecules. To study this process, researchers have employed mRNA expression profiling of synchronously growing cell cultures progressing through the cell cycle. These experiments, which have been carried out in several organisms, are not easy to access, combine and evaluate. Complicating factors include variation in interdivision time between experiments and differences in relative duration of each cell-cycle phase across organisms. To address these problems, we created Cyclebase, an online resource of cell-cycle-related experiments. This database provides an easy-to-use web interface that facilitates visualization and download of genome-wide cell-cycle data and analysis results. Data from different experiments are normalized to a common timescale and are complimented with key cell-cycle information and derived analysis results. In Cyclebase version 2.0, we have updated the entire database to reflect changes to genome annotations, included information on cyclin-dependent kinase (CDK) substrates, predicted degradation signals and loss-of-function phenotypes from genome-wide screens. The web interface has been improved and provides a single, gene-centric graph summarizing the available cell-cycle experiments. Finally, key information and links to orthologous and paralogous genes are now included to further facilitate comparison of cell-cycle regulation across species. Cyclebase version 2.0 is available at
Deciphering Diseases and Biological Targets for Environmental Chemicals using Toxicogenomics Networks

Exposure to environmental chemicals and drugs may have a negative effect on human health. A better understanding of the molecular mechanism of such compounds is needed to determine the risk. We present a high confidence human protein-protein association network built upon the integration of chemical toxicology and systems biology. This computational systems chemical biology model reveals uncharacterized connections between compounds and diseases, thus predicting which compounds may be risk factors for human health. Additionally, the network can be used to identify unexpected potential associations between chemicals and proteins. Examples are shown for chemicals associated with breast cancer, lung cancer and necrosis, and potential protein targets for di-ethylhexyl-phthalate, 2,3,7,8-tetrachlorodibenzo-p-dioxin, pirinixic acid and permethrine. The chemical-protein associations are supported through recent published studies, which illustrate the power of our approach that integrates toxicogenomics data with other data types.
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Degree of Predicted Minor Histocompatibility Antigen Mismatch Correlates with Poorer Clinical Outcomes of Nonmyeloablative Allogeneic Hematopoietic Cell Transplantation

In fully HLA-matched allogeneic hematopoietic cell transplantations (HCT), the main mechanism of the beneficial graft-versus-tumor (GVT) effect and of the detrimental graft-versus-host disease (GVHD) is believed to be caused by donor cytotoxic T cells directed against disparate recipient minor histocompatibility antigens (miHAs). The most common origin of disparate miHAs is non-synonymous single nucleotide polymorphism (nsSNP) differences between donors and patients. At this time, only some 30 miHAs have been identified and registered, but considering the numerous different HLA-types in the human population as well as all the possible nsSNP differences between any two individuals, it is likely that many miHAs have yet to be discovered. The objective of the current study was to predict novel HLA-A and HLA-B restricted miHAs in a cohort of patients treated with non-myeloablative conditioning allogeneic HCT (matched related donor, n=70; matched unrelated donor, n=56) for hematologic malignancies. Initially, the cohort was genotyped for 53 nsSNPs in 11 known miHA source proteins. Twenty-three nsSNPs within six miHA source proteins showed variation in the graft-versus-host (GVH) direction. No correlation between the number of disparate nsSNPs and clinical outcome could be observed. Next, miHAs in the GVH direction were predicted for each patient-donor pair. Using the NetMHCpan predictor, we identified peptides encompassing a nsSNP variant uniquely expressed by the patient and with predicted binding to any of the HLA-A or -B molecules expressed by the patient and donor. Patients with more than the median of three predicted miHAs had a significantly lower five-year overall survival (42% vs 70%, P=0.0060, adjusted hazard ratio (HR) 2.6, P=0.0047) and significantly higher treatment related mortality (39% vs 10%, P=0.0094, adjusted HR 4.6, P=0.0038). No association between number of predicted miHAs and any other clinical outcome parameters was observed. Collectively, our data suggest that the clinical outcome of HCT is not affected by disparate nsSNPs per se, but rather by the HLA-restricted presentation and recognition of peptides encompassing these. Our data also suggest that 6 of the 11 proteins included in the current study could contain more miHAs yet to be identified, and that the presence of multiple miHAs confers a higher risk of mortality after non-myeloablative conditioning HCT. Furthermore, our data suggest a possible role for in silico based miHA predictions, in donor selection as well as in selecting candidate miHAs for further evaluation in in vitro and in vivo experiments. Copyright © 2010. Published by Elsevier Inc.

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis
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Design of an Enterobacteriaceae Pan-genome Microarray Chip

Abstract. Microarrays are a common method for evaluating genomic content of bacterial species and comparing unsequenced bacterial genomes. This technology allows for quick scans of characteristic genes and chromosomal regions, and to search for indications of horizontal transfer. A high-density microarray chip has been designed, using 116 Enterobacteriaceae genome sequences, taking into account the enteric pan-genome. Probes for the microarray were checked in silico and performance of the chip, based on experimental strains from four different genera, demonstrate a relatively high ability to distinguish those strains on genus, species, and pathotype/serovar levels. Additionally, the microarray performed well when investigating which genes were found in a given strain of interest. The Enterobacteriaceae pan-genome microarray, based on 116 genomes, provides a valuable tool for determination of the genetic makeup of unknown strains within this bacterial family and can introduce insights into phylogenetic relationships.

Dietary fibers as immunoregulatory compounds in health and disease

Many nonstarch polysaccharides (NSPs) classified as dietary fibers have been reported to possess immunoregulatory properties. The fibers reported to activate or by other means modulate immune responses originate from both plant, fungal, and microbial sources and constitute highly distinct structures. In order to enhance our understanding of factors important for the immunoregulatory activities, this article addresses the importance of chemical structure, origin, and purity of fibers for their capacity to interact with key regulatory immune cells. Furthermore, we assess bioavailability, and discuss possible mechanisms involved. The binding of some NSPs to carbohydrate receptors on immune cells is well established and this event leads to activation or other changes. Especially, certain beta-glucans and some mannans have demonstrated immunomodulatory capacity with the specific structure being important for the activity. Within beta-glucans the activity varies according to structure, molecular weight, and solubility. As many of the preparations tested constitute crude extracts or partly purified NSPs, the risk of contaminants holding immunoregulatory activities should not be ignored. To what extent NSPs enter systemic circulation has been difficult to assess, partly due to lack of sensitive analytical methods. The presence of NSPs in blood and Peyer's patches in the gut has been demonstrated, supporting encounter between NSPs and immune cells, but bioavailability studies still constitute a major challenge. Studies demonstrating in
vivo effects of beta-glucans on microbial infections and cancer treatment strongly indicate an immunoregulatory mechanism behind the effects. However, the potential of NSPs as immunoregulatory food ingredients is still far from fully explored.

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**Dietary plant components ellagic acid and tannic acid inhibit Escherichia coli biofilm formation**

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Differences in two-component signal transduction proteins among the genus Brucella: Implications for host preference and pathogenesis

Two-component systems (TCSs) are the predominant bacterial signal transduction mechanisms. Species of the genus Brucella are genetically highly related and differ mainly in mammalian host adaptation and pathogenesis. In this study, TCS proteins encoded in the available genome sequences of Brucella species have been identified using bioinformatic methods. All the Brucella species share an identical set of TCS proteins, and the number of TCS proteins in the closely related opportunistic human pathogen Ochrobactrum anthropi was higher than in Brucella species as expected from its lifestyle. O. anthropi lacks orthologs of the Brucella TCSs NodVW, TceSR and TcfSR, suggesting that these TCS proteins could be necessary for the adaptation of Brucella as an intracellular pathogen. This genomic analysis revealed the presence of a differential distribution of TCS pseudogenes among Brucella species. Moreover, there were also differences in TCS pseudogenes between strains belonging to the same Brucella species, and in particular between B. suis biovars 1 and 2.

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Authors: Binnewies, T. T. (Intern), Ussery, D. (Intern), Lavín, J. (Ekstern), Pisabarro, A. (Ekstern), García-Lobo, J. (Ekstern), Oguiza, J. (Ekstern)
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Differential sensitivity of melanoma cell lines with BRAFV600E mutation to the specific raf inhibitor PLX4032

Blocking oncogenic signaling induced by the BRAFV600E mutation is a promising approach for melanoma treatment. We tested the anti-tumor effects of a specific inhibitor of Raf protein kinases, PLX4032/RG7204, in melanoma cell lines. PLX4032 decreased signaling through the MAPK pathway only in cell lines with the BRAFV600E mutation. Seven out of 10 BRAFV600E mutant cell lines displayed sensitivity based on cell viability assays and three were resistant at concentrations up to 10 μM. Among the sensitive cell lines, four were highly sensitive with IC50 values below 1 μM, and three were moderately sensitive with IC50 values between 1 and 10 μM. There was evidence of MAPK pathway inhibition and cell cycle arrest in both sensitive and resistant cell lines. Genomic analysis by sequencing, genotyping of close to 400 oncogenic mutations by mass spectrometry, and SNP arrays demonstrated no major differences in BRAF locus amplification or in other oncogenic events between sensitive and resistant cell lines. However, metabolic tracer uptake studies demonstrated that sensitive cell lines had a more profound inhibition of FDG uptake upon exposure to PLX4032 than resistant cell lines. In conclusion, BRAFV600E mutant melanoma cell lines displayed a range of sensitivities to PLX4032 and metabolic imaging using PET probes can be used to assess sensitivity.

General information

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Dissecting spatio-temporal protein networks driving human heart development and related disorders

Aberrant organ development is associated with a wide spectrum of disorders, from schizophrenia to congenital heart disease, but systems-level insight into the underlying processes is very limited. Using heart morphogenesis as general model for dissecting the functional architecture of organ development, we combined detailed phenotype information from deleterious mutations in 255 genes with high-confidence experimental interactome data, and coupled the results to thorough experimental validation. Hereby, we made the first systematic analysis of spatio-temporal protein networks driving many stages of a developing organ identifying several novel signaling modules. Our results show that organ development relies on surprisingly few, extensively recycled, protein modules that integrate into complex higher-order networks. This design allows the formation of a complicated organ using simple building blocks, and suggests how mutations in the same genes can lead to diverse phenotypes. We observe a striking temporal correlation between organ complexity and the number of discrete functional modules coordinating morphogenesis. Our analysis elucidates the organization and composition of spatio-temporal protein networks that drive the formation of organs, which in the future may lay the foundation of novel approaches in treatments, diagnostics, and regenerative medicine.
Early adaptive developments of Pseudomonas aeruginosa after the transition from life in the environment to persistent colonization in the airways of human cystic fibrosis hosts

Pseudomonas aeruginosa is an opportunistic pathogen ubiquitous to the natural environment but with the capability of moving to the host environment. Long-term infection of the airways of cystic fibrosis patients is associated with extensive genetic adaptation of P. aeruginosa, and we have studied cases of the initial stages of infection in order to characterize the early adaptive processes in the colonizing bacteria. A combination of global gene expression analysis and phenotypic characterization of longitudinal isolates from cystic fibrosis patients revealed well-known characteristics such as conversion to a mucoid phenotype by mucA mutation and increased antibiotic resistance by nfxB mutation. Additionally, upregulation of the atu operon leading to enhanced growth on leucine provides a possible example of metabolic optimization. A detailed investigation of the mucoid phenotype uncovered profound pleiotropic effects on gene expression including reduction of virulence factors and the Rhl quorum sensing system. Accordingly, mucoid isolates displayed a
general reduction of virulence in the Caenorhabditis elegans infection model, altogether suggesting that the adaptive success of the mucoid variant extends beyond the benefits of alginate overproduction. In the overall perspective the global phenotype of the adapted variants appears to place them on paths in direction of fully adapted strains residing in long-term chronically infected patients.
E Durans Strain M4-5 Isolated From Human Colonic Flora Attenuates Intestinal Inflammation

PURPOSE: The aim of this study was to evaluate in vitro and in vivo effects of a unique high-butyrate-producing bacterial strain from human colonic flora, Enterococcus durans, in prevention and treatment of intestinal inflammation. METHODS: A compartmentalized Caco-2/leukocyte coculture model was used to examine the in vitro effects of E durans and its metabolite butyrate on basal and Escherichia coli–stimulated secretion of proinflammatory immune factors (IL-8, IL-6, and TNF-α) and the anti-inflammatory cytokine IL-10. A murine model of dextran sodium sulfate-induced colitis was used to examine in vivo effects of prevention and therapy with E durans on clinical, biochemical, and histologic parameters of inflammation. RESULTS: In the coculture model, treatment with E durans and with butyrate reduced basal as well as E coli stimulated secretion of IL-8, IL-6, and TNF-α and increased secretion of IL-10. In the in vivo murine model, preventive administration of E durans significantly ameliorated clinical disease activity index (weight loss, fecal bleeding, and stool consistency), reduced myeloperoxidase concentration in colon tissue extracts, improved histologic scores of colonic inflammation, and inhibited colonic transcription of proinflammatory immune factors. The effect of therapeutic treatment alone on these parameters was more moderate but still significant. CONCLUSIONS: We conclude that E durans strain M4 to 5 and its metabolic product butyrate induce significant anti-inflammatory effects, mediated by regulation of pro- and anti-inflammatory immune factors as well as preservation of intestine epithelial integrity, suggesting that this novel anti-inflammatory bacterium may be preferentially a useful prophylactic treatment to avoid inflammatory bowel disease.
Effects of Fish Oil Supplementation on Markers of the Metabolic Syndrome

OBJECTIVE: To investigate whether fish oil affects cardiovascular risk factors during the adolescent growth spurt.

STUDY DESIGN: A total of 78 boys age 13-15 years with a mean body fat percentage of 30% +/- 9% were randomly assigned to consume fish oil (providing 1.5 g of n-3 long-chain polyunsaturated fatty acid/day) or vegetable oil (control) for 16 weeks.

The oils were included in bread. RESULTS: After the intervention, the red blood cell (RBC) content of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) were 1.2% +/- 0.5% and 6.7% +/- 1.6%, respectively, in the those receiving fish oil (FO group), compared with 0.6% +/- 0.3% and 4.1% +/- 0.9% in the control group. Systolic blood pressure (SBP) was 3.8 +/- 1.4 mm Hg lower (P <.006) and diastolic blood pressure (DBP) was 2.6 +/- 1.1 mm Hg lower (P <.01) in the FO group compared with the control group. Plasma triacylglycerol (TAG) concentration and insulin sensitivity were unaffected by either of the treatments. Plasma high-density lipoprotein (HDL) and non-HDL cholesterol were increased by 5% and 7%, respectively, in the FO group, and by 2% and 0% in the control group (P <.01-.02). The changes in RBC EPA content were inversely correlated with the changes in SBP and DBP and directly correlated with the increases in HDL cholesterol and non-HDL cholesterol concentrations. No association was seen between RBC EPA and plasma TAG concentration or insulin sensitivity.

CONCLUSION: Fish oil improves BP in normotensive and normolipidemic slightly overweight adolescent boys. Copyright © 2010 Mosby, Inc. All rights reserved.
Efficacy of Neoadjuvant Cisplatin in Triple-Negative Breast Cancer

PURPOSE Cisplatin is a chemotherapeutic agent not used routinely for breast cancer treatment. As a DNA cross-linking agent, cisplatin may be effective treatment for hereditary BRCA1-mutated breast cancers. Because sporadic triple-negative breast cancer (TNBC) and BRCA1-associated breast cancer share features suggesting common pathogenesis, we conducted a neoadjuvant trial of cisplatin in TNBC and explored specific biomarkers to identify predictors of response.

PATIENTS AND METHODS Twenty-eight women with stage II or III breast cancers lacking estrogen and progesterone receptors and HER2/Neu (TNBC) were enrolled and treated with four cycles of cisplatin at 75 mg/m$^2$ every 21 days. After definitive surgery, patients received standard adjuvant chemotherapy and radiation therapy per their treating physicians. Clinical and pathologic treatment response were assessed, and pretreatment tumor samples were evaluated for selected biomarkers. Results Six (22%) of 28 patients achieved pathologic complete responses, including both patients with BRCA1 germline mutations; 18 (64%) patients had a clinical complete or partial response. Fourteen (50%) patients showed good pathologic responses (Miller-Payne score of 3, 4, or 5), 10 had minor responses (Miller-Payne score of 1 or 2), and four (14%) progressed. All TNBCs clustered with reference basal-like tumors by hierarchical clustering. Factors associated with good cisplatin response include young age ($P = .001$), low BRCA1 mRNA expression ($P = .03$), BRCA1 promoter methylation ($P = .04$), p53 nonsense or frameshift mutations ($P = .01$), and a gene expression signature of E2F3 activation ($P = .03$).

CONCLUSION Single-agent cisplatin induced response in a subset of patients with TNBC. Decreased BRCA1 expression may identify subsets of TNBCs that are cisplatin sensitive. Other biomarkers show promise in
predicting cisplatin response.

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Scopus rating (2006): SJR 5.384 SNIP 3.6
Scopus rating (2005): SJR 5.121 SNIP 4.061
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Equitoxic Doses of 5-Azacytidine and 5-Aza-2’ Deoxycytidine Induce Diverse Immediate and Overlapping Heritable Changes in the Transcriptome

BACKGROUND: The hypomethylating agent 5-Azacytidine (5-Aza-CR) is the first drug to prolong overall survival in patients with myelodysplastic syndrome (MDS). Surprisingly, the deoxyribonucleoside analog 5-Aza-2’deoxycytidine (5-Aza-CdR) did not have a similar effect on survival in a large clinical trial. Both drugs are thought to exert their effects after incorporation into DNA by covalent binding of DNA methyltransferase (DNMT). While 5-Aza-CdR is incorporated into only DNA, 5-Aza-CR is also incorporated into RNA. Here, we have analyzed whether this difference in nucleic acid incorporation may influence the capacities of these drugs to regulate the expression of mRNA and microRNAs (miRNA), which may potentially affect the activities of the drugs in patients. METHODOLOGY/PRINCIPAL FINDINGS: A hematopoietic (HL-60; acute myeloid leukemia) and a solid (T24; transitional cell carcinoma) cancer cell line were treated with equitoxic doses of 5-Aza-CR and 5-Aza-CdR for 24 hrs, and the immediate (day 2) and lasting (day 8) effects on RNA expression examined. There was considerable overlap between the RNAs heritably upregulated by both drugs on day 8 but more RNAs were stably induced by the deoxy analog. Both drugs strongly induced expression of cancer testis antigens. On day 2 more RNAs were downregulated by 5-Aza-CR, particularly at higher doses. A remarkable downregulation of miRNAs and a significant upregulation of tRNA synthetases and other genes involved in amino acid metabolism was observed in T24 cells. CONCLUSIONS/SIGNIFICANCE: Overall, this suggests that significant differences exist in the immediate action of the two drugs, however the dominant pattern of the lasting, and possible heritable changes, is overlapping.

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Scopus rating (2014): SJR 1.545 SNIP 1.141 CiteScore 3.54
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Scopus rating (2013): SJR 1.74 SNIP 1.147 CiteScore 3.94
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Web of Science (2013): Indexed yes
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Scopus rating (2012): SJR 1.945 SNIP 1.142 CiteScore 4.15
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Ethnicity and stratum corneum ceramides

BACKGROUND: The barrier function of the skin is dependent on an optimal composition of the stratum corneum lipids, exemplified by the altered lipid profile in patients with atopic eczema (AE). Differences in the global prevalence of AE point to the environment as an important factor in AE. Studies on filaggrin point to a genetic aspect in AE. The influence of environment and genes needs to be explored. OBJECTIVES: To investigate possible differences in stratum corneum lipids between different healthy ethnicities living in the same environment. METHODS: Healthy participants without any major skin diseases were enrolled in the study. Twenty-five participants of Asian origin (Asians), 18 of African origin (Africans) and 28 of Danish origin (white-skinned), all students at universities in the Copenhagen area of Denmark, had the ceramide profile of their stratum corneum examined using the cyanoacrylate method and analysed using high-performance thin layer chromatography. RESULTS: For the ceramide/cholesterol ratio we found statistically significant differences between groups, with Asians having the highest ratio (P <0·001 as compared with both white-skinned individuals and Africans), white-skinned individuals having intermediate values, and Africans having the lowest values. No statistically significant differences were found between any of the ceramide subgroups. CONCLUSIONS: We found different ceramide/cholesterol ratios in comparable groups of different ethnicity, pointing to unknown genetic differences.
Flagellar motility and differential gene expression of Pseudomonas putida KT2440 under partially hydrated conditions: a study with the novel Pressurized Porous Surface Model (PPSM)

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Organisations: Environmental Chemistry, Department of Environmental Engineering, Center for Biological Sequence Analysis, Department of Systems Biology
Authors: Gülez, G. (Intern), Dechesne, A. (Intern), Workman, C. (Intern), Smets, B. F. (Intern)
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Genome update: the 1000th genome - a cautionary tale

There are now more than 1000 sequenced prokaryotic genomes deposited in public databases and available for analysis. Currently, although the sequence databases GenBank, DNA Database of Japan and EMBL are synchronized continually, there are slight differences in content at the genomes level for a variety of logistical reasons, including differences in format and loading errors, such as those caused by file transfer protocol interruptions. This means that the 1000th genome will be different in the various databases. Some of the data on the highly accessed web pages are inaccurate, leading to false conclusions for example about the largest bacterial genome sequenced. Biological diversity is far greater than many have thought. For example, analysis of multiple Escherichia coli genomes has led to an estimate of around 45 000 gene families more genes than are recognized in the human genome. Moreover, of the 1000 genomes available, not a single protein is conserved across all genomes. Excluding the members of the Archaea, only a total of four genes are conserved in all bacteria: two protein genes and two RNA genes.
Genomic Analysis of Two-Component Signal Transduction Proteins in Basidiomycetes

Two-component system (TCS) proteins are components of complex signal transduction pathways in fungi, and play essential roles in the regulation of several cellular functions and responses. Species of basidiomycetes have a marked variation in their specific physiological traits, morphological complexity and lifestyles. In this study, we have used the available complete genomes of basidiomycetes to carry out a thorough identification and an extensive comparative analysis of the TCS proteins in this fungal phylum. In comparison with ascomycetes, basidiomycetes exhibit an intermediate number of TCS proteins. Several TCS proteins are highly conserved among all the basidiomycetes, and other TCS proteins appear to be specific to particular species of basidiomycetes. Moreover, some species appear to have developed a unique histidine kinase group with unusual domain architecture, the Dual-histidine kinases. The presence of differential sets of TCS proteins between basidiomycete species might reflect their adaptation to diverse environmental niches.

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Genomic Characterization of Campylobacter jejuni strain M1
Campylobacter jejuni strain M1 (laboratory designation 99/308) is a rarely documented case of direct transmission of C. jejuni from chicken to a person, resulting in enteritis. We have sequenced the genome of C. jejuni strain M1, and compared this to 12 other C. jejuni sequenced genomes currently publicly available. Compared to these, M1 is closest to strain 81116. Based on the 13 genome sequences, we have identified the C. jejuni pan-genome, as well as the core genome, the auxiliary genes, and genes unique between strains M1 and 81116. The pan-genome contains 2,427 gene families, whilst the core genome comprised 1,295 gene families, or about two-thirds of the gene content of the average of the sequenced C. jejuni genomes. Various comparison and visualization tools were applied to the 13 C. jejuni genome sequences, including a species pan- and core genome plot, a BLAST Matrix and a BLAST Atlas. Trees based on 16S rRNA sequences and on the total gene families in each genome are presented. The findings are discussed in the background of the proven virulence potential of M1.

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Authors: Friis, C. (Intern), Wassenaar, G. M. (Intern), Javed, M. A. (Ekstern), Snipen, L. (Ekstern), Lagesen, K. (Intern), Hallin, P. F. (Intern), Newell, D. G. (Ekstern), Toszeghy, M. (Ekstern), Ridley, A. (Ekstern), Manning, G. (Ekstern), Ussery, D. (Intern)
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Genomic comparisons of Brucella spp. and closely related bacteria using base compositional and proteome based methods

BACKGROUND: Classification of bacteria within the genus Brucella has been difficult due in part to considerable genomic homogeneity between the different species and biovars, in spite of clear differences in phenotypes. Therefore, many different methods have been used to assess Brucella taxonomy. In the current work, we examine 32 sequenced genomes from genus Brucella representing the six classical species, as well as more recently described species, using bioinformatical methods. Comparisons were made at the level of genomic DNA using oligonucleotide based methods (Markov chain based genomic signatures, genomic codon and amino acid frequencies based comparisons) and proteomes (all-against-all BLAST protein comparisons and pan-genomic analyses). RESULTS: We found that the oligonucleotide based methods gave different results compared to that of the proteome based methods. Differences were also found between the oligonucleotide based methods used. Whilst the Markov chain based genomic signatures grouped the different species in genus Brucella according to host preference, the codon and amino acid frequencies based methods reflected small differences between the Brucella species. Only minor differences could be detected between all genera included in this study using the codon and amino acid frequencies based methods. Proteome comparisons were found to be in strong accordance with current Brucella taxonomy indicating a remarkable association between gene gain or loss on one hand and mutations in marker genes on the other. The proteome based methods found greater similarity between Brucella species and Ochrobactrum species than between species within genus Agrobacterium compared to each other. In other words, proteome comparisons of species within genus Agrobacterium were found to be more diverse than proteome comparisons between species in genus Brucella and genus Ochrobactrum. Pan-genomic analyses indicated that uptake of DNA from outside genus Brucella appears to be limited. CONCLUSIONS: While both the proteome based methods and the Markov chain based genomic signatures were able to reflect environmental diversity between the different species and strains of genus Brucella, the genomic codon and amino acid frequencies based comparisons were not found adequate for such comparisons. The proteome comparison based phylogenies of the species in genus Brucella showed a surprising consistency with current Brucella taxonomy.
HLA Class I Binding 9mer Peptides from Influenza A Virus Induce CD4(+) T Cell Responses

Background: Identification of human leukocyte antigen class I (HLA-I) restricted cytotoxic T cell (CTL) epitopes from influenza virus is of importance for the development of new effective peptide-based vaccines. Methodology/Principal Findings: In the present work, bioinformatics was used to predict 9mer peptides derived from available influenza A viral proteins with binding affinity for at least one of the 12 HLA-I supertypes. The predicted peptides were then selected in a way that ensured maximal coverage of the available influenza A strains. One hundred and thirty one peptides were synthesized and their binding affinities for the HLA-I supertypes were measured in a biochemical assay. Influenza-specific T cell responses towards the peptides were quantified using IFN gamma ELISPOT assays with peripheral blood mononuclear cells (PBMC) from adult healthy HLA-I typed donors as responder cells. Of the 131 peptides, 21 were found to induce T cell responses in 19 donors. In the ELISPOT assay, five peptides induced responses that could be totally
blocked by the pan-specific anti-HLA-I antibody W6/32, whereas 15 peptides induced responses that could be completely blocked in the presence of the pan-specific anti-HLA class II (HLA-II) antibody IVA12. Blocking of HLA-II subtype reactivity revealed that 8 and 6 peptide responses were blocked by anti-HLA-DR and -DP antibodies, respectively. Peptide reactivity of PBMC depleted of CD4(+) or CD8(+) T cells prior to the ELISPOT culture revealed that effectors are either CD4(+) (the majority of reactivities) or CD8(+) T cells, never a mixture of these subsets. Three of the peptides, recognized by CD4(+) T cells showed binding to recombinant DRA1*0101/DRB1*0401 or DRA1*0101/DRB5*0101 molecules in a recently developed biochemical assay. Conclusions/Significance: HLA-I binding 9mer influenza virus-derived peptides induce in many cases CD4(+) T cell responses restricted by HLA-II molecules.

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Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 2.473 SNIP 0.985
Web of Science (2009): Indexed yes
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Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 1.289 SNIP 0.525
Homology Modelling of the GABA Transporter and Analysis of Tiagabine Binding

A homology model of the human GABA transporter (GAT-1) based on the recently reported crystal structures of the bacterial leucine transporter from Aquifex aeolicus (LeuT) was developed. The stability of the resulting model embedded in a membrane environment was analyzed by extensive molecular dynamics (MD) simulations. Based on docking studies and subsequent MD simulations of three compounds, the endogenous ligand GABA and two potent inhibitors, (R)-nipecotic acid and the anti-epilepsy drug tiagabine, various binding modes were identified and are discussed. Whereas GABA and (R)-nipecotic acid, which are both substrates, are stabilised with residues located deep inside the occluded state binding pocket (including residues Tyr 60 and Ser 396), tiagabine, which contains a large aliphatic side chain, is stabilised in a binding mode that extends from the substrate binding pocket (i.e., stabilised by Phe 294) to the extracellular vestibule, where the side chain is stabilised by aliphatic residues. The tiagabine binding mode, reaching from the substrate binding site to the extracellular vestibule, forces the side chain of Phe 294 to adopt a distinct conformation from that found in the occluded conformation of the transporter. Hence, in presence of tiagabine, GAT-1 is constrained in an open-to-out conformation. Our results may be of particular interest for the design of new GAT-1 inhibitors.
Identification of CD8(+) T Cell Epitopes in the West Nile Virus Polyprotein by Reverse-Immunology Using NetCTL

Background: West Nile virus (WNV) is a growing threat to public health and a greater understanding of the immune response raised against WNV is important for the development of prophylactic and therapeutic strategies. Methodology/Principal Findings: In a reverse-immunology approach, we used bioinformatics methods to predict WNV-specific CD8(+) T cell epitopes and selected a set of peptides that constitutes maximum coverage of 20 fully-sequenced WNV strains. We then tested these putative epitopes for cellular reactivity in a cohort of WNV-infected patients. We identified 26 new CD8(+) T cell epitopes, which we propose are restricted by 11 different HLA class I alleles. Aiming for optimal coverage of human populations, we suggest that 11 of these new WNV epitopes would be sufficient to cover from 48% to 93% of ethnic populations in various areas of the World. Conclusions/Significance: The 26 identified CD8(+) T cell epitopes contribute to our knowledge of the immune response against WNV infection and greatly extend the list of known WNV CD8(+) T cell epitopes. A polytope incorporating these and other epitopes could possibly serve as the basis for a WNV vaccine.

General information

State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology
Authors: Larsen, M. V. (Intern), Lelic, A. (Ekstern), Parsons, R. (Ekstern), Nielsen, M. (Intern), Hoof, I. (Ekstern), Lamberth, K. (Ekstern), Loeb, M. (Ekstern), Buus, S. (Ekstern), Bramson, J. (Ekstern), Lund, O. (Intern)
Publication date: 2010
Main Research Area: Technical/natural sciences

Publication information

Journal: PLoS One
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BFI (2018): BFI-level 1
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Identification of type 1 diabetes candidate genes by in silico phenome-interactome analysis

General information
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Organisations: Center for Biological Sequence Analysis, Department of Systems Biology
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Journal: Diabetologia
ImmunoGrid: towards agent-based simulations of the human immune system at a natural scale

The ultimate aim of the EU-funded ImmunoGrid project is to develop a natural-scale model of the human immune system—that is, one that reflects both the diversity and the relative proportions of the molecules and cells that comprise it—along with the grid infrastructure necessary to apply this model to specific applications in the field of immunology. These objectives present the ImmunoGrid Consortium with formidable challenges in terms of complexity of the immune system, our partial understanding about how the immune system works, the lack of reliable data and the scale of computational resources required. In this paper, we explain the key challenges and the approaches adopted to overcome them. We also consider wider implications for the present ambitious plans to develop natural-scale, integrated models of the human body.
that can make contributions to personalized health care, such as the European Virtual Physiological Human initiative.

Finally, we ask a key question: How long will it take us to resolve these challenges and when can we expect to have fully functional models that will deliver health-care benefits in the form of personalized care solutions and improved disease prevention?

General information
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Journal: Royal Society of London. Philosophical Transactions. Mathematical, Physical and Engineering Sciences
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BFI (2018): BFI-level 2
BFI (2017): BFI-level 2
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 2.26 SJR 0.874 SNIP 1.024
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 0.78 SNIP 0.985 CiteScore 2.08
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 0.847 SNIP 1.256 CiteScore 2.39
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 1.12 SNIP 1.534 CiteScore 3.12
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 1.068 SNIP 1.387 CiteScore 2.89
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 0.964 SNIP 1.297 CiteScore 2.65
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 1.095 SNIP 1.365
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 1.068 SNIP 1.309
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 0.867 SNIP 1.016
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 0.683 SNIP 0.685
Scopus rating (2006): SJR 0.856 SNIP 0.888
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 0.843 SNIP 0.824
Scopus rating (2004): SJR 0.651 SNIP 0.834
Scopus rating (2003): SJR 0.527 SNIP 0.765
Web of Science (2003): Indexed yes
Scopus rating (2002): SJR 0.368 SNIP 0.631
Scopus rating (2001): SJR 0.296 SNIP 0.4
Scopus rating (2000): SJR 0.315 SNIP 0.393
Scopus rating (1999): SJR 0.436 SNIP 0.297
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Induction of regulatory T cells by probiotics: potential for treatment of allergy?

General information
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Organisations: Center for Biological Sequence Analysis, Department of Systems Biology
Authors: Fink, L. N. (Intern)
Pages: 5-8
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BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): SJR 2.117 SNIP 1.46 CiteScore 4.26
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.193 SNIP 1.454 CiteScore 4.15
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.9 SNIP 1.667 CiteScore 4.1
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.629 SNIP 1.517 CiteScore 3.95
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.908 SNIP 1.498 CiteScore 4.23
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 2.477 SNIP 1.581 CiteScore 4.55
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.713 SNIP 1.366
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Scopus rating (2009): SJR 1.481 SNIP 1.228
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 1.647 SNIP 1.318
Influence of the gut microbiota on transcriptional regulation of genes involved in early life development of the intestinal mucus layer

The interplay between the gut microbiota and the intestinal mucus layer is important both in the maintenance of the epithelial barrier as part of the innate immune defense, and in the conservation of gut homeostasis. Little is known about how the microbiota regulates mucin proteins, which protect the mucosal surfaces of all epithelial linings by physical hindrance or specific binding of pathogenic agents including virus and bacteria. It has been shown that the presence and composition of the microbiota is directly involved in the regulation of gene transcription in the intestinal epithelium. The intestinal mucus layer of germ free mice has been shown to display a distinctly different composition and structure compared to mucus from conventionally bred animals in vitro and in vivo. This points towards an important role of the microbiota in the regulation of mucin production. To which extent expression of all mucin genes are dependent on the presence of microorganisms and whether specific bacteria are capable of regulating mucus production in early life remains, however, to be established. The very first period after birth is believed to be vulnerable for establishment of the gut microbiota and consequently for the health and integrity of the epithelium throughout life. In this period, a development regulated by endogenous factors such as hormones, in parallel with gene regulation caused by the microorganisms present in the gut, takes place. Although the microflora undoubtedly plays a regulatory role in the regulation of production of mucin, the importance of endogenous regulation as opposed to gut microbiota has not been investigated. Four groups of mouse pups (n=8 in each group) from differently colonized dams were analyzed with respect to expression of genes involved in mucin production (muc1-4, tff3) in ileal segments isolated on Day 1 and Day 6 after birth. Additionally, the presence of Lactobacillus and E. coli in the ileal samples was assessed by 16S rRNA gene quantification. The pups in the groups were born from dams that were either: 1) germ free (GF), 2) conventional specific pathogen free (SPF), 3) monocolonized with Lactobacillus acidophilus NCFM (Lb NCFM), or 4) monocolonized with E. coli Nissle (E. coli). All data was found by quantitative real-time PCR (qPCR) on Applied Biosystems platforms. Results from these studies showed interesting differences between the four tested animal groups and the two different days tested, which will be presented at the meeting. This is the first study to examine effects of different colonizing bacteria on mucus related gene expression levels in new born mice. These results may thus improve our understanding of the complex interplay between the gut microbiota and epithelial development in the very early life phases.

General information
State: Published
Organisations: National Food Institute, Division of Microbiology and Risk Assessment, Center for Biological Sequence Analysis, Department of Systems Biology
Authors: Bergström, A. (Intern), Kristensen, M. B. (Intern), Metzdorff, S. B. (Ekstern), Fink, L. N. (Intern), Frøkjær, H. (Ekstern), Licht, T. R. (Intern)
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Gut microbiota, Germ Free animals, Intestinal integrity in the newborn, Mucin genes, Probiotic gut monocolonization

Bibliographical note
Insight into Antigenic Diversity of VAR2CSA-DBL5 epsilion Domain from Multiple Plasmodium falciparum Placental Isolates

Background: Protection against pregnancy associated malaria (PAM) is associated with high levels of anti-VAR2CSA antibodies. This protection is obtained by the parity dependent acquisition of anti-VAR2CSA antibodies. Distinct parity-associated molecular signatures have been identified in VAR2CSA domains. These two observations combined point to the importance of identifying VAR2CSA sequence variation, which facilitate parasitic evasion or subversion of host immune response. Highly conserved domains of VAR2CSA such as DBL5e are likely to contain conserved epitopes, and therefore do constitute attractive targets for vaccine development. Methodology/Principal Findings: VAR2CSA DBL5e-domain sequences obtained from cDNA of 40 placental isolates were analysed by a combination of experimental and in silico methods. Competition ELISA assays on two DBL5e variants, using plasma samples from women from two different areas and specific mice hyperimmune plasma, indicated that DBL5e possess conserved and cross-reactive B cell epitopes. Peptide ELISA identified conserved areas that are recognised by naturally acquired antibodies. Specific antibodies against these peptides labelled the native proteins on the surface of placental parasites. Despite high DBL5e sequence homology among parasite isolates, sequence analyses identified motifs in DBL5e that discriminate parasites according to donor's parity. Moreover, recombinant proteins of two VAR2CSA DBL5e variants displayed diverse recognition patterns by plasma from malaria-exposed women, and diverse proteoglycan binding abilities.

Conclusions/Significance: This study provides insights into conserved and exposed B cell epitopes in DBL5e that might be a focus for cross reactivity. The importance of sequence variation in VAR2CSA as a critical challenge for vaccine development is highlighted. VAR2CSA conformation seems to be essential to its functionality. Therefore, identification of sequence variation sites in distinct locations within VAR2CSA, affecting antigenicity and/or binding properties, is critical to the effort of developing an efficient VAR2CSA-based vaccine. Motifs associated with parasite segregation according to parity constitute one such site.
In Silico Prediction of Human Pathogenicity in the gamma-Proteobacteria

In Background: Although the majority of bacteria are innocuous or even beneficial for their host, others are highly infectious pathogens that can cause widespread and deadly diseases. When investigating the relationships between bacteria and other living organisms, it is therefore essential to be able to separate pathogenic organisms from non-pathogenic ones. Using traditional experimental methods for this purpose can be very costly and time-consuming, and also uncertain since animal models are not always good predictors for pathogenicity in humans. Bioinformatics-based methods are therefore strongly needed to mine the fast growing number of genome sequences and assess in a rapid and reliable way the pathogenicity of novel bacteria. Methodology/Principal Findings: We describe a new in silico method for the prediction of bacterial pathogenicity, based on the identification in microbial genomes of features that appear to correlate with virulence. The method does not rely on identifying genes known to be involved in pathogenicity (for instance virulence factors), but rather it inherently builds families of proteins that, irrespective of their function, are consistently present in only one of the two kinds of organisms, pathogens or non-pathogens. Whether a new bacterium carries proteins contained in these families determines its prediction as pathogenic or non-pathogenic. The application of the method on a set of known genomes correctly classified the virulence potential of 86% of the organisms tested. An additional validation on an independent test-set assigned correctly 22 out of 24 bacteria. Conclusions: The proposed approach was demonstrated to go beyond the species bias imposed by evolutionary relatedness, and performs better than predictors based solely on taxonomy or sequence similarity. A set of protein families that differentiate pathogenic and non-pathogenic strains were identified, including families of yet uncharacterized proteins that are suggested to be involved in bacterial pathogenicity.
Integrated multilaboratory systems biology reveals differences in protein metabolism between two reference yeast strains

The field of systems biology is often held back by difficulties in obtaining comprehensive, high-quality, quantitative data sets. In this paper, we undertook an interlaboratory effort to generate such a data set for a very large number of cellular components in the yeast Saccharomyces cerevisiae, a widely used model organism that is also used in the production of fuels, chemicals, food ingredients and pharmaceuticals. With the current focus on biofuels and sustainability, there is much interest in harnessing this species as a general cell factory. In this study, we characterized two yeast strains, under two standard growth conditions. We ensured the high quality of the experimental data by evaluating a wide range of sampling and analytical techniques. Here we show significant differences in the maximum specific growth rate and
biomass yield between the two strains. On the basis of the integrated analysis of the high-throughput data, we hypothesize that differences in phenotype are due to differences in protein metabolism.

**General information**

State: Published

Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Swiss Federal Institute of Technology, Delft University of Technology, University of Cambridge, Chalmers University of Technology, VTT - Technical Research Centre of Finland, Vrije Universiteit Amsterdam, University of Stuttgart, Bogazici University, Laboratoire Bordelais de Recherche en Informatique


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BFI (2018): BFI-level 2
BFI (2017): BFI-level 2
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 11.8 SJR 6.399 SNIP 2.995
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 6.364 SNIP 3.053 CiteScore 11.23
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 6.331 SNIP 3.091 CiteScore 10.77
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 5.967 SNIP 2.776 CiteScore 9.85
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
Scopus rating (2012): SJR 5.586 SNIP 2.724 CiteScore 8.32
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
Scopus rating (2011): SJR 3.122 SNIP 1.544 CiteScore 4.44
ISI indexed (2011): ISI indexed no
Web of Science (2010): Indexed yes
Original language: English
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http://www.nature.com/ncomms/journal/v1/n9/full/ncomms1150.html

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Publication: Research - peer-review › Journal article – Annual report year: 2011

**Interdisciplinary Analysis of HIV-Specific CD8(+) T Cell Responses against Variant Epitopes Reveals Restricted TCR Promiscuity**

HIV-1 specific CTL responses play a key role in limiting viral replication. CTL responses are sensitive to viral escape mutations, which influence recognition of the virus. Although CTLs have been shown to recognize epitope variants, the
extent of this cross-reactivity has not been quantitatively investigated in a genetically diverse cohort of HIV-1 infected patients. Using a novel bioinformatic binding prediction method, we aimed to explain the pattern of epitope-specific CTL responses based on the patients' HLA genotype and autologous virus sequence quantitatively. Sequences covering predicted and tested HLA class I-restricted epitopes (peptides) within the HIV-Gag, Pol, and Nef regions were obtained from 26 study subjects resulting in 1492 patient-specific peptide pairs. Epitopes that were recognized in ELISPOT assays were found to be significantly more similar to the autologous virus than those that did not elicit a response. A single substitution in the presented epitope decreased the chance of a CTL response by 40%. The impact of sequence similarity on cross-recognition was confirmed by testing immune responses against multiple variants of six selected epitopes. Substitutions at central positions in the epitope were particularly likely to result in abrogation of recognition. In summary, the presented data demonstrate a highly restricted promiscuity of HIV-1 specific CTL in the recognition of variant epitopes. In addition, our results illustrate that bioinformatic prediction methods are useful to study the complex pattern of CTL responses exhibited by an HIV-1 infected patient cohort and for identification of optimal targets for novel therapeutic or vaccine approaches. The Journal of Immunology, 2010, 184: 5383-5391.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology
Authors: Hoof, I. (Intern), Perez, C. (Ekstern), Buggert, M. (Ekstern), Gustafsson, R. (Ekstern), Nielsen, M. (Intern), Lund, O. (Intern), Karlsson, A. (Ekstern)
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BFI (2017): BFI-level 2
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BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 4.79 SJR 3.368 SNIP 1.177
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 3.568 SNIP 1.267 CiteScore 5.05
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 3.716 SNIP 1.279 CiteScore 5.03
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 3.844 SNIP 1.345 CiteScore 5.61
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 3.929 SNIP 1.356 CiteScore 5.82
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 3.947 SNIP 1.341 CiteScore 5.67
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 4.031 SNIP 1.301
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Web of Science (2009): Indexed yes
Lactobacillus acidophilus induces a slow but more sustained chemokine and cytokine response in naive foetal enterocytes compared to commensal Escherichia coli

The first exposure to microorganisms at mucosal surfaces is critical for immune maturation and gut health. Facultative anaerobic bacteria are the first to colonise the infant gut, and the impact of these bacteria on intestinal epithelial cells (IEC) may be determinant for how the immune system subsequently tolerates gut bacteria. RESULTS: To mirror the influence of the very first bacterial stimuli on infant IEC, we isolated IEC from mouse foetuses at gestational day 19 and from germfree neonates. IEC were stimulated with gut-derived bacteria, Gram-negative Escherichia coli Nissle and Gram-positive Lactobacillus acidophilus NCFM, and expression of genes important for immune regulation was measured together with cytokine production. E. coli Nissle and L. acidophilus NCFM strongly induced chemokines and cytokines, but with different kinetics, and only E. coli Nissle induced down-regulation of Toll-like receptor 4 and up-regulation of Toll-like receptor 2. The sensitivity to stimulation was similar before and after birth in germ-free IEC, although Toll-like receptor 2 expression was higher before birth than immediately after. CONCLUSIONS: In conclusion, IEC isolated before gut colonisation occurs at birth, are highly responsive to stimulation with gut commensals, with L. acidophilus NCFM inducing a slower, but more sustained response than E. coli Nissle. E. coli may induce intestinal tolerance through very rapid up-regulation of chemokine and cytokine genes and down-regulation of Toll-like receptor 4, while regulating also responsiveness to Gram-positive bacteria.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Division of Microbiology and Risk Assessment, National Food Institute, Division of Toxicology and Risk Assessment, University of Copenhagen
Authors: Zeuthen, L. (Intern), Fink, L. N. (Intern), Metzdorff, S. B. (Ekstern), Kristensen, M. B. (Intern), Licht, T. R. (Intern), Nellemann, C. L. (Intern), Frekiaer, H. (Intern)
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BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
Lactobacillus acidophilus induces virus immune defence genes in murine dendritic cells by a Toll-like receptor-2-dependent mechanism

Lactobacilli are probiotics that, among other health-promoting effects, have been ascribed immunostimulating and virus-preventive properties. Certain Lactobacillus spp. have been shown to possess strong interleukin-12 (IL-12)-inducing properties. As IL-12 production depends on the up-regulation of type I interferons (IFNs), we hypothesized that the strong IL-12-inducing capacity of Lactobacillus acidophilus NCFM in murine bone-marrow-derived dendritic cells (DCs) is caused by an up-regulation of IFN-beta, which subsequently induces IL-12 and the double-stranded RNA binding Toll-like receptor-3 (TLR-3). The expression of the genes encoding IFN-beta, TLR-3, IL-12 and IL-10 in DCs upon stimulation with L. acidophilus NCFM was determined. Lactobacillus acidophilus NCFM induced a much stronger expression of Ifn-beta, Il-12 and Il-10 compared with the synthetic double-stranded RNA ligand Poly I:C, whereas the levels of expressed Tlr-3 were similar. Whole genome microarray gene expression analysis revealed that other genes related to viral defence were significantly up-regulated and among the strongest induced genes in DCs stimulated with L. acidophilus NCFM. The ability to induce IFN-beta was also detected in another L. acidophilus strain (X37), but was not a property of other probiotic strains tested, i.e. Bifidobacterium bifidum Z9 and Escherichia coli Nissle 1917. The IFN-beta expression was markedly reduced in TLR-2(-/-) DCs, dependent on endocytosis, and the major cause of the induction of IL-12 and Tlr-3 in DCs stimulated with L. acidophilus NCFM. Collectively, our results reveal that certain lactobacilli trigger the expression of viral defence genes in DCs in a TLR-2 manner dependent on IFN-beta.
General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Center for Biological sequence analysis
Authors: Weiss, G. M. (Intern), Rasmussen, S. (Intern), Hjerrild Zeuthen, L. (Ekstern), Nielsen, B. M. N. (Intern), Jarmer, H. Ø. (Intern), Jespersen, H. (Ekstern), Frøkiær, H. (Intern)
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BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.74 SJR 1.888 SNIP 0.937
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.079 SNIP 0.975 CiteScore 3.83
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.029 SNIP 1.05 CiteScore 3.61
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 2.038 SNIP 1.083 CiteScore 3.97
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.902 SNIP 1.047 CiteScore 3.94
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.841 SNIP 0.993 CiteScore 3.75
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 0.121 SNIP 0.897
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 0.122 SNIP 0.928
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 0.111 SNIP 0.921
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 0.122 SNIP 0.964
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 0.122 SNIP 0.887
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 1.64 SNIP 0.921
Web of Science (2005): Indexed yes
Scopus rating (2004): SJR 1.409 SNIP 0.793
Lazarus1, a DUF300 Protein, Contributes to Programmed Cell Death Associated with Arabidopsis acd11 and the Hypersensitive Response

Background: Programmed cell death (PCD) is a necessary part of the life of multi-cellular organisms. A type of plant PCD is the defensive hypersensitive response (HR) elicited via recognition of a pathogen by host resistance (R) proteins. The lethal, recessive accelerated cell death 11 (acd11) mutant exhibits HR-like accelerated cell death, and cell death execution in acd11 shares genetic requirements for HR execution triggered by one subclass of R proteins. Methodology/Principal Findings: To identify genes required for this PCD pathway, we conducted a genetic screen for suppressors of acd11, here called lazarus (laz) mutants. In addition to known suppressors of R protein-mediated HR, we isolated 13 novel complementation groups of dominant and recessive laz mutants. Here we describe laz1, which encodes a protein with a domain of unknown function (DUF300), and demonstrate that LAZ1 contributes to HR PCD conditioned by the Toll/interleukin-1 (TIR)-type R protein RPS4 and by the coiled-coil (CC)-type R protein RPM1. Using a yeast-based topology assay, we also provide evidence that LAZ1 is a six transmembrane protein with structural similarities to the human tumor suppressor TMEM34. Finally, we demonstrate by transient expression of reporter fusions in protoplasts that localization of LAZ1 is distributed between the cytosol, the plasma membrane and FM4-64 stained vesicles. Conclusions/Significance: Our findings indicate that LAZ1 functions as a regulator or effector of plant PCD associated with the HR, in addition to its role in acd11-related death. Furthermore, the similar topology of a plant and human DUF300 proteins suggests similar functions in PCD across the eukaryotic kingdoms, although a direct role for TMEM34 in cell death control remains to be established. Finally, the subcellular localization pattern of LAZ1 suggests that it may have transport functions for yet unknown, death-related signaling molecules at the plasma membrane and/or endosomal compartments. In summary, our results validate the utility of the large-scale suppressor screen to identify novel components with functions in plant PCD, which may also have implications for deciphering cell death mechanisms in other organisms.
Limitations of Ab Initio Predictions of Peptide Binding to MHC Class II Molecules

Successful predictions of peptide MHC binding typically require a large set of binding data for the specific MHC molecule that is examined. Structure based prediction methods promise to circumvent this requirement by evaluating the physical contacts a peptide can make with an MHC molecule based on the highly conserved 3D structure of peptide:MHC complexes. While several such methods have been described before, most are not publicly available and have not been independently tested for their performance. We here implemented and evaluated three prediction methods for MHC class II molecules: statistical potentials derived from the analysis of known protein structures; energetic evaluation of different peptide snapshots in a molecular dynamics simulation; and direct analysis of contacts made in known 3D structures of peptide:MHC complexes. These methods are ab initio in that they require structural data of the MHC molecule examined, but no specific peptide:MHC binding data. Moreover, these methods retain the ability to make predictions in a sufficiently short time scale to be useful in a real world application, such as screening a whole proteome for candidate binding peptides. A rigorous evaluation of each methods prediction performance showed that these are significantly better than random, but still substantially lower than the best performing sequence based class II prediction methods available. While the approaches presented here were developed independently, we have chosen to present our results together in order to support the notion that generating structure based predictions of peptide:MHC binding without using binding data is unlikely to give satisfactory results.
Lipid asymmetry in plant plasma membranes: phosphate deficiency-induced phospholipid replacement is restricted to the cytosolic leaflet

As in other eukaryotes, plant plasma membranes contain sphingolipids, phospholipids, and free sterols. In addition, plant plasma membranes also contain sterol derivatives and usually 5 mol% DGDG was included. As both the apoplastic plasma membrane leaflet (probably the major water permeability barrier) and rafts both contain only trace amounts of DGDG, we conclude that this lipid class is not compatible with membrane functions requiring a high degree of lipid order. By not replacing phospholipids site specifically with DGDG, negative functional effects of this lipid in the plasma membrane are avoided.-Tjellström, H., Hellgren, L. I., Wieslander, Å., Sandelius, A. S. Lipid asymmetry in plant plasma membranes: phosphate deficiency-induced phospholipid replacement is restricted to the cytosolic leaflet.

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Scopus rating (2007): SJR 2.927 SNIP 1.222
Scopus rating (2006): SJR 3.359 SNIP 2.085
Major histocompatibility complex class I binding predictions as a tool in epitope discovery

Over the last decade, in silico models of the major histocompatibility complex (MHC) class I pathway have developed significantly. Before, peptide binding could only be reliably modelled for a few major human or mouse histocompatibility molecules; now, high-accuracy predictions are available for any human leucocyte antigen (HLA) -A or -B molecule with known protein sequence. Furthermore, peptide binding to MHC molecules from several non-human primates, mouse strains and other mammals can now be predicted. In this review, a number of different prediction methods are briefly explained, highlighting the most useful and historically important. Selected case stories, where these 'reverse immunology' systems have been used in actual epitope discovery, are briefly reviewed. We conclude that this new generation of epitope discovery systems has become a highly efficient tool for epitope discovery, and recommend that the less accurate prediction systems of the past be abandoned, as these are obsolete.

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Malaria vaccine design - Identification of epitopes and characterization of antigenic variation in the PfEMP1 family

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MHC Class II epitope predictive algorithms

Major histocompatibility complex class II (MHC-II) molecules sample peptides from the extracellular space, allowing the immune system to detect the presence of foreign microbes from this compartment. To be able to predict the immune response to given pathogens, a number of methods have been developed to predict peptide-MHC binding. However, few methods other than the pioneering TEPITOPE/ProPred method have been developed for MHC-II. Despite recent progress in method development, the predictive performance for MHC-II remains significantly lower than what can be obtained for MHC-I. One reason for this is that the MHC-II molecule is open at both ends allowing binding of peptides extending out of the groove. The binding core of MHC-II-bound peptides is therefore not known a priori and the binding motif is hence not readily discernible. Recent progress has been obtained by including the flanking residues in the predictions. All attempts to make ab initio predictions based on protein structure have failed to reach predictive performances similar to those that can be obtained by data-driven methods. Thousands of different MHC-II alleles exist in humans. Recently developed pan-specific methods have been able to make reasonably accurate predictions for alleles that were not included in the training data. These methods can be used to define supertypes (clusters) of MHC-II alleles where alleles within each supertype have similar binding specificities. Furthermore, the pan-specific methods have been used to make a graphical atlas such as the MHCMotifviewer, which allows for visual comparison of specificities of different alleles.

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Scopus rating (2009): SJR 0.122 SNIP 0.928
Mice, men and MHC supertypes
Mice are still the most used model organism in initial phases of vaccine design. Bioinformatics is becoming increasingly more important in vaccine development, both for the design of novel simplified epitope-based vaccines and also in order to understand the specific immune response of selected vaccine formulations. Toxoplasma gondii, an intracellular parasite, causes severe neurologic and ocular disease in congenitally infected and immunocompromised individuals. No protective vaccine exists against human toxoplasmosis. However, studies with mice have revealed immunodominant cytotoxic T lymphocyte epitopes originating from type II strains. These verified epitopes might be useful in human vaccines as the peptide binding repertoire of H-2L(d) MHC and MHCs belonging to the HLA-B07 supertype are very similar. Here, the results obtained using these epitopes in BALB/c as well as transgenic HLA-B*0702 mice are discussed. The stunning results obtained from the use of refined computational methods for the prediction of cytotoxic T lymphocyte epitopes are also discussed. The results highlight some important issues regarding both the use of mice but also the choice of bioinformatics methods in vaccine development.
Minimising Immunohistochemical False Negative ER Classification Using a Complementary 23 Gene Expression Signature of ER Status

BACKGROUND: Expression of the oestrogen receptor (ER) in breast cancer predicts benefit from endocrine therapy. Minimising the frequency of false negative ER status classification is essential to identify all patients with ER positive breast cancers who should be offered endocrine therapies in order to improve clinical outcome. In routine oncological practice ER status is determined by semi-quantitative methods such as immunohistochemistry (IHC) or other immunoassays in which the ER expression level is compared to an empirical threshold. The clinical relevance of gene expression-based ER subtypes as compared to IHC-based determination has not been systematically evaluated. Here we attempt to reduce the frequency of false negative ER status classification using two gene expression approaches and compare these methods to IHC based ER status in terms of predictive and prognostic concordance with clinical outcome.

METHODOLOGY/PRINCIPAL FINDINGS: Firstly, ER status was discriminated by fitting the bimodal expression of ESR1 to a mixed Gaussian model. The discriminative power of ESR1 suggested bimodal expression as an efficient way to stratify breast cancer; therefore we identified a set of genes whose expression was both strongly bimodal, mimicking ESR expression status, and highly expressed in breast epithelial cell lines, to derive a 23-gene ER expression signature-based classifier. We assessed our classifiers in seven published breast cancer cohorts by comparing the gene expression-based ER status to IHC-based ER status as a predictor of clinical outcome in both untreated and tamoxifen treated cohorts. In untreated breast cancer cohorts, the 23 gene signature-based ER status provided significantly improved prognostic power compared to IHC-based ER status (P=0.006). In tamoxifen-treated cohorts, the 23 gene ER expression signature predicted clinical outcome (HR=2.20, P=0.00035). These complementary ER signature-based strategies estimated that between 15.1% and 21.8% patients of IHC-based negative ER status would be classified with ER positive breast cancer.

CONCLUSION/SIGNIFICANCE: Expression-based ER status classification may complement IHC to minimise false negative ER status classification and optimise patient stratification for endocrine therapies.
Mutational Mapping and Modeling of the Binding Site for (S)-Citalopram in the Human Serotonin Transporter

The serotonin transporter (SERT) regulates extracellular levels of the neurotransmitter serotonin (5-hydroxytryptamine) in the brain by facilitating uptake of released 5-hydroxytryptamine into neuronal cells. SERT is the target for widely used antidepressant drugs, including imipramine, fluoxetine, and (S)-citalopram, which are competitive inhibitors of the transport function. Knowledge of the molecular details of the antidepressant binding sites in SERT has been limited due to lack of structural data on SERT. Here, we present a characterization of the (S)-citalopram binding pocket in human SERT (hSERT) using mutational and computational approaches. Comparative modeling and ligand docking reveal that (S)-citalopram fits into the hSERT substrate binding pocket, where (S)-citalopram can adopt a number of different binding orientations. We find, however, that only one of these binding modes is functionally relevant from studying the effects of 64 point mutations around the putative substrate binding site. The mutational mapping also identify novel hSERT residues that are crucial for (S)-citalopram binding. The model defines the molecular determinants for (S)-citalopram binding to hSERT and demonstrates that the antidepressant binding site overlaps with the substrate binding site.
Navigating the human metabolome for biomarker identification and design of pharmaceutical molecules

Metabolomics is a rapidly evolving discipline that involves the systematic study of endogenous small molecules that characterize the metabolic pathways of biological systems. The study of metabolism at a global level has the potential to contribute significantly to biomedical research, clinical medical practice, as well as drug discovery. In this paper, we present the most up-to-date metabolite and metabolic pathway resources, and we summarize the statistical, and machine-learning tools used for the analysis of data from clinical metabolomics. Through specific applications on cancer, diabetes, neurological and other diseases, we demonstrate how these tools can facilitate diagnosis and identification of potential biomarkers for use within disease diagnosis. Additionally, we discuss the increasing importance of the integration of metabolomics data in drug discovery. On a case-study based on the Human Metabolome Database (HMDB) and the Chinese Natural Product Database (CNPD), we demonstrate the close relatedness of the two data sets of compounds, and we further illustrate how structural similarity with human metabolites could assist in the design of novel pharmaceuticals and the elucidation of the molecular mechanisms of medicinal plants.

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Reliable predictions of immunogenic peptides are essential in rational vaccine design and can minimize the experimental effort needed to identify epitopes. In this work, we describe a pan-specific major histocompatibility complex (MHC) class I epitope predictor, NetCTLpan. The method integrates predictions of proteasomal cleavage, transporter associated with antigen processing (TAP) transport efficiency, and MHC class I binding affinity into a MHC class I pathway likelihood score and is an improved and extended version of NetCTL. The NetCTLpan method performs predictions for all MHC class I molecules with known protein sequence and allows predictions for 8-, 9-, 10-, and 11-mer peptides. In order to meet the need for a low false positive rate, the method is optimized to achieve high specificity. The method was trained and validated on large datasets of experimentally identified MHC class I ligands and cytotoxic T lymphocyte (CTL) epitopes. It has been reported that MHC molecules are differentially dependent on TAP transport and proteasomal cleavage. Here, we did not find any consistent signs of such MHC dependencies, and the NetCTLpan method is implemented with fixed weights for proteasomal cleavage and TAP transport for all MHC molecules. The predictive performance of the NetCTLpan method was shown to outperform other state-of-the-art CTL epitope prediction methods. Our results further confirm the importance of using full-type human leukocyte antigen restriction information when identifying MHC class I
epitopes. Using the NetCTLpan method, the experimental effort to identify 90% of new epitopes can be reduced by 15% and 40%, respectively, when compared to the NetMHCpan and NetCTL methods. The method and benchmark datasets are available at http://www.cbs.dtu.dk/services/NetCTLpan/

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Scopus rating (2007): SJR 1.254 SNIP 0.74
Scopus rating (2006): SJR 1.224 SNIP 0.762
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NetMHCIIpan-2.0 - Improved pan-specific HLA-DR predictions using a novel concurrent alignment and weight optimization training procedure

BACKGROUND: Binding of peptides to Major Histocompatibility class II (MHC-II) molecules play a central role in governing responses of the adaptive immune system. MHC-II molecules sample peptides from the extracellular space allowing the immune system to detect the presence of foreign microbes from this compartment. Predicting which peptides bind to an MHC-II molecule is therefore of pivotal importance for understanding the immune response and its effect on host-pathogen interactions. The experimental cost associated with characterizing the binding motif of an MHC-II molecule is significant and large efforts have therefore been placed in developing accurate computer methods capable of predicting this binding event. Prediction of peptide binding to MHC-II is complicated by the open binding cleft of the MHC-II molecule, allowing binding of peptides extending out of the binding groove. Moreover, the genes encoding the MHC molecules are immensely diverse leading to a large set of different MHC molecules each potentially binding a unique set of peptides. Characterizing each MHC-II molecule using peptide-screening binding assays is hence not a viable option.

RESULTS: Here, we present an MHC-II binding prediction algorithm aiming at dealing with these challenges. The method is a pan-specific version of the earlier published allele-specific NN-align algorithm and does not require any pre-alignment of the input data. This allows the method to benefit also from information from alleles covered by limited binding data. The method is evaluated on a large and diverse set of benchmark data, and is shown to significantly out-perform state-of-the-art MHC-II prediction methods. In particular, the method is found to boost the performance for alleles characterized by limited binding data where conventional allele-specific methods tend to achieve poor prediction accuracy.

CONCLUSIONS: The method thus shows great potential for efficient boosting the accuracy of MHC-II binding prediction, as accurate predictions can be obtained for novel alleles at highly reduced experimental costs. Pan-specific binding predictions can be obtained for all alleles with known protein sequence and the method can benefit by including data in the training from alleles even where only few binders are known. The method and benchmark data are available at http://www.cbs.dtu.dk/services/NetMHCIIpan-2.0.
β-turns are the most common type of non-repetitive structures, and constitute on average 25% of the amino acids in proteins. The formation of β-turns plays an important role in protein folding, protein stability and molecular recognition processes. In this work we present the neural network method NetTurnP, for prediction of two-class β-turns and prediction of the individual β-turn types, by use of evolutionary information and predicted protein sequence features. It has been evaluated against a commonly used dataset BT426, and achieves a Matthews correlation coefficient of 0.50, which is the highest reported performance on a two-class prediction of β-turn and not-β-turn. Furthermore NetTurnP shows improved performance on some of the specific β-turn types. In the present work, neural network methods have been trained to predict β-turn or not and individual β-turn types from the primary amino acid sequence. The individual β-turn types I, I', II, II', VIII, Via1, Vla2, Vlbα and IV have been predicted based on classifications by PROMOTIF, and the two-class prediction of β-turn or not is a superset comprised of all β-turn types. The performance is evaluated using a golden set of non-homologous sequences known as BT426. Our two-class prediction method achieves a performance of: MCC = 0.50, Qtotal = 82.1%, sensitivity = 75.6%, PPV = 68.8% and AUC = 0.864. We have compared our performance to eleven other prediction methods that obtain Matthews correlation coefficients in the range of 0.17 – 0.47. For the type specific β-turn predictions, only type I and II can be predicted with reasonable Matthews correlation coefficients, where we obtain performance values of 0.36 and 0.31, respectively.

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Networks of High Mutual Information Define the Structural Proximity of Catalytic Sites: Implications for Catalytic Residue Identification

Identification of catalytic residues (CR) is essential for the characterization of enzyme function. CR are, in general, conserved and located in the functional site of a protein in order to attain their function. However, many non-catalytic residues are highly conserved and not all CR are conserved throughout a given protein family making identification of CR a challenging task. Here, we put forward the hypothesis that CR carry a particular signature defined by networks of close proximity residues with high mutual information (MI), and that this signature can be applied to distinguish functional from other non-functional conserved residues. Using a data set of 434 Pfam families included in the catalytic site atlas (CSA) database, we tested this hypothesis and demonstrated that MI can complement amino acid conservation scores to detect CR. The Kullback-Leibler (KL) conservation measurement was shown to significantly outperform both the Shannon entropy and maximal frequency measurements. Residues in the proximity of catalytic sites were shown to be rich in shared MI. A structural proximity MI average score (termed pMI) was demonstrated to be a strong predictor for CR, thus confirming the proposed hypothesis. A structural proximity conservation average score (termed pC) was also calculated and demonstrated to carry distinct information from pMI. A catalytic likeliness score (Cls), combining the KL, pC and pMI measures, was shown to lead to significantly improved prediction accuracy. At a specificity of 0.90, the Cls method was found to have a sensitivity of 0.816. In summary, we demonstrate that networks of residues with high MI provide a distinct signature on CR and propose that such a signature should be present in other classes of functional residues where the requirement to maintain a particular function places limitations on the diversification of the structural environment along the course of evolution.
New human milk fat substitutes from butterfat to improve fat absorption
A new human milk fat substitute (HMFS) was produced from butterfat. A 2-week's feeding experiment was performed using three groups of rats with 10 wt.% fat in their feed; the fat was either (1) butterfat-based HMFS + long-chain polyunsaturated fatty acids (LCPUFA), (2) the reference oil + LCPUFA, or (3) the reference oil without LCPUFA. The apparent fat absorption after intake of butterfat-based HMFS (95.9% +/- 1.8%) was significantly higher than the other two groups, indicating that much less calcium soap was formed after feeding butterfat-based HMFS. Calcium contents in urines and faeces from the two groups fed LCPUFA in their diet were lower than those without supplementation of LCPUFA, suggesting that LCPUFA could improve calcium absorption by reducing the calcium excretion. It can thus be concluded that the butterfat-based HMFS improves fat absorption, and supplementation of LCPUFA in the formula improves calcium absorption.
Novel Insights into the Global Proteome Responses of Insulin-Producing INS-1E Cells To Different Degrees of Endoplasmic Reticulum Stress

Exposure of insulin-secreting beta-cells to inflammatory cytokines or high concentrations of free fatty acids, factors involved in the pathogenesis of type 1 and type 2 diabetes, leads to endoplasmic reticulum (ER) stress, beta-cell dysfunction, and eventually apoptotic beta-cell death. The aim of this study was to investigate the impact of ER stress on beta-cells at the protein level to evaluate the contribution of post-transcriptional and post-translational changes in ER stress-induced beta-cell damage. INS-1E cells were exposed in vitro to the ER-stress inducer cyclopiazonic acid (CPA) at two concentrations, and protein changes were evaluated using 2D-DIGE. CPA, 25 μM, led to massive apoptosis, accompanied by a near complete protein translation shut-down. CPA, 6.25 μM, led to adaptation of the beta-cells to ER stress. Identification of the differentially expressed proteins in the two conditions led to the discovery of a clear pattern of defense pathways, with post-translational modifications playing a crucial role. Key alterations included inhibition of insulin translation and post-translational modifications in ER chaperones HYOU1 and HSPA5. Also, a central role for 14-3-3 proteins is suggested. In conclusion, INS-1E cells are highly sensitive to ER stress, leading to important post-transcriptional and post-translational modifications that may contribute to beta-cell dysfunction and death.

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OCT4 and downstream factors are expressed in human somatic urogenital epithelia and in culture of epididymal spheres

The transcription factor OCT4 plays a crucial role in the earliest differentiation of the mammalian embryo and in self-renewal of embryonic stem cells. However, it remains controversial whether this gene is also expressed in somatic tissues. Here we use a combination of RT-PCR on whole and microdissected tissues, in situ hybridisation, immunohistochemistry, and Western blotting to show that OCT4 and SOX2 together with downstream targets, UTF1 and REX1, are expressed in the human male urogenital tract. We further supported these results by analysis of DNA methylation of a region in the OCT4 promoter. In culture, human primary epididymis cells formed spheres that continued to express the investigated genes for at least 20 days. Transcriptomic analysis of cultured cells showed up-regulation of CD29, CD44, and CD133 that are normally associated with sphere-forming cancer stem cells. Furthermore, stimulation with retinoic acid resulted in down-regulation of OCT4 expression, however, without multilineage differentiation. Our results show that OCT4 and associated genes are expressed in somatic epithelial cells from the urogenital tract and that these cells can form spheres, a general marker of stem cell behaviour.

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On the Origins of a Vibrio species

Thirty-two genome sequences of various Vibrionaceae members are compared, with emphasis on what makes V. cholerae unique. As few as 1,000 gene families are conserved across all the Vibrionaceae genomes analysed; this fraction roughly doubles for gene families conserved within the species V. cholerae. Of these, approximately 200 gene families that cluster on various locations of the genome are not found in other sequenced Vibrionaceae; these are possibly unique to the V. cholerae species. By comparing gene family content of the analysed genomes, the relatedness to a particular species is identified for two unspeciated genomes. Conversely, two genomes presumably belonging to the same species have suspiciously dissimilar gene family content. We are able to identify a number of genes that are conserved in, and unique to, V. cholerae. Some of these genes may be crucial to the niche adaptation of this species.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Norwegian University of Life Sciences
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BFI (2014): BFI-level 2
Scopus rating (2014): SJR 1.316 SNIP 1.136 CiteScore 3.08
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BFI (2013): BFI-level 2
Scopus rating (2013): SJR 1.408 SNIP 1.245 CiteScore 3.7
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 1.417 SNIP 1.279 CiteScore 3.36
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 1.299 SNIP 1.186 CiteScore 3.04
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 1.299 SNIP 1.158
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.464 SNIP 1.168
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 1.253 SNIP 1.058
Scopus rating (2007): SJR 1.283 SNIP 1.157
Web of Science (2007): Indexed yes
Optimization of the BLASTN substitution matrix for prediction of non-specific DNA microarray hybridization

DNA microarray measurements are susceptible to error caused by non-specific hybridization between a probe and a target (cross-hybridization), or between two targets (bulk-hybridization). Search algorithms such as BLASTN can quickly identify potentially hybridizing sequences. We set out to improve BLASTN accuracy by modifying the substitution matrix and gap penalties. We generated gene expression microarray data for samples in which 1 or 10% of the target mass was an exogenous spike of known sequence. We found that the 10% spike induced 2-fold intensity changes in 3% of the probes, two-thirds of which were decreases in intensity likely caused by bulk-hybridization. These changes were correlated with similarity between the spike and probe sequences. Interestingly, even very weak similarities tended to induce a change in probe intensity with the 10% spike. Using this data, we optimized the BLASTN substitution matrix to more accurately identify probes susceptible to non-specific hybridization with the spike. Relative to the default substitution matrix, the optimized matrix features a decreased score for A–T base pairs relative to G–C base pairs, resulting in a 5–15% increase in area under the ROC curve for identifying affected probes. This optimized matrix may be useful in the design of microarray probes, and in other BLASTN-based searches for hybridization partners.

General information
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Organisations: Center for Biological Sequence Analysis, Department of Systems Biology
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BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 9.28 SJR 7.397 SNIP 2.657
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 7.239 SNIP 2.639 CiteScore 9.48
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 6.576 SNIP 2.568 CiteScore 8.74
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 6.582 SNIP 2.266 CiteScore 8.46
DNA supercoiling is the master function that interconnects chromosome structure and global gene transcription. This function has recently been shown to be under strong selection in Escherichia coli. During the evolution of 12 initially identical populations propagated in a defined environment for 20,000 generations, parallel increases in DNA supercoiling were observed in ten populations. The genetic changes associated with the increased supercoiling were examined in one population, and beneficial mutations in the genes topA (encoding topoisomerase I) and fis (encoding a histone-like protein) were identified. To elucidate the molecular basis and impact of these changes, we quantified the level of genetic, phenotypic, and molecular parallelism linked to DNA supercoiling in all 12 evolving populations. First, sequence determination of DNA topology-related loci revealed strong genetic parallelism, with mutations concentrated in three genes (topA, fis, and dusB), although the populations had different alleles at each locus. Statistical analyses of these polymorphisms implied the action of positive selection and, moreover, suggested that fis and dusB, which belong to the
same operon, have related functions. Indeed, we demonstrated that DusB regulates the expression of fis by both experimental and phylogenetic analyses. Second, molecular analyses of five mutations in fis and dusB affecting the transcription, translation, and protein activity of Fis also revealed strong parallelism in the resulting phenotypic effects. Third, artificially increasing DNA supercoiling in one of the two populations that lacked DNA topology changes led to a significant fitness increase. The high levels of molecular and genetic parallelism, targeting a small subset of the many genes involved in DNA supercoiling, indicate that changes in DNA superhelicity have been important in the evolution of these populations. Surprisingly, however, most of the evolved alleles we tested had either no detectable or slightly deleterious effects on fitness, despite these signatures of positive selection.

General information
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Organisations: Center for Biological Sequence Analysis, Department of Systems Biology
Authors: Crozat, E. (Ekstern), Winkworth, C. (Ekstern), Gaffé, J. (Ekstern), Hallin, P. F. (Intern), Riley, M. A. (Ekstern), Lenski, R. E. (Ekstern), Schneider, D. (Ekstern)
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Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 8.142 SNIP 4.662 CiteScore 11.28
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
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Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 6.804 SNIP 5.514 CiteScore 12.36
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 4.901 SNIP 3.176 CiteScore 8.5
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 4.23 SNIP 1.865 CiteScore 6.05
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 6.011 SNIP 3.774
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 5.106 SNIP 2.666
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 4.861 SNIP 1.898
Scopus rating (2007): SJR 4.455 SNIP 1.679
Scopus rating (2006): SJR 4.3 SNIP 1.577
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 4.48 SNIP 1.786
Scopus rating (2004): SJR 4.294 SNIP 1.69
Scopus rating (2003): SJR 4.06 SNIP 1.597
Peptide binding predictions for HLA DR, DP and DQ molecules

BACKGROUND: MHC class II binding predictions are widely used to identify epitope candidates in infectious agents, allergens, cancer and autoantigens. The vast majority of prediction algorithms for human MHC class II to date have targeted HLA molecules encoded in the DR locus. This reflects a significant gap in knowledge as HLA DP and DQ molecules are presumably equally important, and have only been studied less because they are more difficult to handle experimentally. RESULTS: In this study, we aimed to narrow this gap by providing a large scale dataset of over 17,000 HLA-peptide binding affinities for a set of 11 HLA DP and DQ alleles. We also expanded our dataset for HLA DR alleles resulting in a total of 40,000 MHC class II binding affinities covering 26 allelic variants. Utilizing this dataset, we generated prediction tools utilizing several machine learning algorithms and evaluated their performance. CONCLUSION: We found that 1) prediction methodologies developed for HLA DR molecules perform equally well for DP or DQ molecules. 2) Prediction performances were significantly increased compared to previous reports due to the larger amounts of training data available. 3) The presence of homologous peptides between training and testing datasets should be avoided to give real-world estimates of prediction performance metrics, but the relative ranking of different predictors is largely unaffected by the presence of homologous peptides, and predictors intended for end-user applications should include all training data for maximum performance. 4) The recently developed NN-align prediction method significantly outperformed all other algorithms, including a naïve consensus based on all prediction methods. A new consensus method dropping the comparably weak ARB prediction method could outperform the NN-align method, but further research into how to best combine MHC class II binding predictions is required.

General information
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Publication date: 2010
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Web of Science (2016): Indexed yes
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Scopus rating (2015): SJR 1.656 SNIP 1.077 CiteScore 2.77
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.836 SNIP 1.202 CiteScore 2.91
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.932 SNIP 1.335 CiteScore 3.38
Parkinson's disease affects 5 million people worldwide, but the molecular mechanisms underlying its pathogenesis are still unclear. Here, we report a genome-wide meta-analysis of gene sets (groups of genes that encode the same biological pathway or process) in 410 samples from patients with symptomatic Parkinson's and subclinical disease and healthy controls. We analyzed 6.8 million raw data points from nine genome-wide expression studies, and 185 laser-captured human dopaminergic neuron and substantia nigra transcriptomes, followed by two-stage replication on three platforms. We found 10 gene sets with previously unknown associations with Parkinson's disease. These gene sets pinpoint defects in mitochondrial electron transport, glucose utilization, and glucose sensing and reveal that they occur early in disease pathogenesis. Genes controlling cellular bioenergetics that are expressed in response to peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) are underexpressed in Parkinson's disease patients. Activation of PGC-1α results in increased expression of nuclear-encoded subunits of the mitochondrial respiratory chain and blocks the dopaminergic neuron loss induced by mutant α-synuclein or the pesticide rotenone in cellular disease models. Our systems biology analysis of Parkinson's disease identifies PGC-1α as a potential therapeutic target for early intervention.
Phytanic acid—an overlooked bioactive fatty acid in dairy fat?

Phytanic acid is a multibranched fatty acid with reported retinoid X receptor (RXR) and peroxisome proliferator-activated receptor-alpha (PPAR-alpha) agonist activity, which have been suggested to have preventive effects on metabolic dysfunctions. Serum level in man is strongly correlated to the intake of red meat and dairy products and the concentration in these products is strongly correlated to the chlorophyll content in the feed of the cattle. Available data suggest that phytanic acid is a natural agonist for RXR at physiological concentrations, while it is more likely that it is the metabolite pristanic acid, rather than phytanic acid itself, that acts as PPAR-a agonist. Animal studies show increased expression of genes involved in fatty acid oxidation, after intake of phytol, the metabolic precursor of phytanic acid, but it is at present not possible to deduce whether phytanic acid is useful in the prevention of ectopic lipid deposition. Phytanic acid is an efficient inducer of the expression of uncoupler protein 1 (UCP1). UCP1 is expressed in human skeletal muscles, were it might be important for the total energy balance. Therefore, phytanic acid may be able to stimulate energy dissipation in skeletal muscles. Phytanic acid levels in serum are associated with an increased risk of developing prostate cancer, but the available data do not support a general causal link between circulating phytanic acid and prostate cancer risk.
However, certain individuals, with specific single-nucleotide polymorphisms in the gene for the enzyme alpha-methylacyl-CoA racemase, might be susceptible to raised phytanic acid levels.
**Plasmodium falciparum Erythrocyte Membrane Protein 1 Diversity in Seven Genomes – Divide and Conquer**

The var gene encoded hyper-variable Plasmodium falciparum erythrocyte membrane protein 1 (PfEMP1) family mediates cytoadhesion of infected erythrocytes to human endothelium. Antibodies blocking cytoadhesion are important mediators of malaria immunity acquired by endemic populations. The development of a PfEMP1 based vaccine mimicking natural acquired immunity depends on a thorough understanding of the evolved PfEMP1 diversity, balancing antigenic variation against conserved receptor binding affinities. This study redefines and reclassifies the domains of PfEMP1 from seven genomes. Analysis of domains in 399 different PfEMP1 sequences allowed identification of several novel domain classes, and a high degree of PfEMP1 domain compositional order, including conserved domain cassettes not always associated with the established group A–E division of PfEMP1. A novel iterative homology block (HB) detection method was applied, allowing identification of 628 conserved minimal PfEMP1 building blocks, describing on average 83% of a PfEMP1 sequence. Using the HBs, similarities between domain classes were determined, and Duffy binding-like (DBL) domain subclasses were found in many cases to be hybrids of major domain classes. Related to this, a recombination hotspot was uncovered between DBL subdomains S2 and S3. The VarDom server is introduced, from which information on domain classes and homology blocks can be retrieved, and new sequences can be classified. Several conserved sequence elements were found, including: (1) residues conserved in all DBL domains predicted to interact and hold together the three DBL subdomains, (2) potential integrin binding sites in DBLα domains, (3) an acylation motif conserved in group A var genes suggesting N-terminal N-myristoylation, (4) PfEMP1 inter-domain regions proposed to be elastic disordered structures, and (5) several conserved predicted phosphorylation sites. Ideally, this comprehensive categorization of PfEMP1 will provide a platform for future studies on var/PfEMP1 expression and function.

**General information**

State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, University of Copenhagen
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Web of Science (2015): Indexed yes
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ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
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Scopus rating (2011): SJR 3.381 SNIP 1.603 CiteScore 5.25
ISI indexed (2011): ISI indexed no
Web of Science (2011): Indexed yes
Scopus rating (2010): SJR 3.523 SNIP 1.554
Plasmodium falciparum population dynamics in a cohort of pregnant women in Senegal

Background: Pregnant women acquire protective antibodies that cross-react with geographically diverse placental Plasmodium falciparum isolates, suggesting that surface molecules expressed on infected erythrocytes by pregnancy-associated malaria (PAM) parasites have conserved epitopes and, that designing a PAM vaccine may be envisaged. VAR2CSA is the main candidate for a pregnancy malaria vaccine, but vaccine development may be complicated by its sequence polymorphism. Methods: The dynamics of P. falciparum genotypes during pregnancy in 32 women in relation to VAR2CSA polymorphism and immunity was determined. The polymorphism of the msp2 gene and five microsatellites was analysed in consecutive parasite isolates, and the DBL5 epsilon + Interdomain 5 (Id5) part of the var2csa gene of the corresponding samples was cloned and sequenced to measure variation. Results: In primigravidae, the multiplicity of infection in the placenta was associated with occurrence of low birth weight babies. Some parasite genotypes were able to persist over several weeks and, still be present in the placenta at delivery particularly when the host anti-VAR2CSA antibody level was low. Comparison of diversity among genotyping markers confirmed that some PAM parasites may harbour more than one var2csa gene copy in their genome. Conclusions: Host immunity to VAR2CSA influences the parasite dynamics during pregnancy, suggesting that the acquisition of protective immunity requires pre-exposure to a limited number of parasite variants. Presence of highly conserved residues in surface-exposed areas of the VAR2CSA immunodominant DBL5 epsilon domain, suggest its potential in inducing antibodies with broad reactivity.

General information
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Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, University of Copenhagen, Université Paris Descartes
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BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.012 SNIP 1.17 CiteScore 3.09
BFI (2014): BFI-level 1
Predictive biomarker discovery through the parallel integration of clinical trial and functional genomics datasets

The EU multi-disciplinary personalised RNA interference to enhance the delivery of individualised chemotherapeutics and targeted therapies (PREDICT) consortium has recently initiated a framework to accelerate the development of predictive biomarkers of individual patient response to anti-cancer agents. The consortium focuses on the identification of reliable predictive biomarkers to approved agents with anti-angiogenic activity for which no reliable predictive biomarkers exist: sunitinib, a multi-targeted tyrosine kinase inhibitor and everolimus, a mammalian target of rapamycin (mTOR) pathway inhibitor. Through the analysis of tumour tissue derived from pre-operative renal cell carcinoma (RCC) clinical trials, the PREDICT consortium will use established and novel methods to integrate comprehensive tumour-derived genomic data with personalised tumour-derived shRNA and high throughput siRNA screens to identify and validate functionally important genomic or transcriptomic predictive biomarkers of individual drug response in patients. PREDICT’s approach to predictive biomarker discovery differs from conventional associative learning approaches, which can be susceptible to the detection of chance associations that lead to overestimation of true clinical accuracy. These methods will identify molecular pathways important for survival and growth of RCC cells and particular targets suitable for therapeutic development. Importantly, our results may enable individualised treatment of RCC, reducing ineffective therapy in drug resistant disease, leading to improved quality of life and higher cost efficiency, which in turn should broaden patient access to beneficial therapeutics, thereby enhancing clinical outcome and cancer survival. The consortium will also establish and consolidate a European network providing the technological and clinical platform for large-scale functional genomic biomarker discovery. Here we review our current understanding of molecular mechanisms driving resistance to anti-angiogenesis agents, the current limitations of laboratory and clinical trial strategies and how the PREDICT consortium will endeavour to identify a new generation of predictive biomarkers.
Probiotic Escherichia coli strain Nissle 1917 outcompetes intestinal pathogens during biofilm formation

Many bacterial infections are associated with biofilm formation. Bacterial biofilms can develop on essentially all kinds of surfaces, producing chronic and often intractable infections. Escherichia coli is an important pathogen causing a wide range of gastrointestinal infections. E. coli strain Nissle 1917 has been used for many decades as a probiotic against a variety of intestinal disorders and is probably the best field-tested E. coli strain in the world. Here we have investigated the biofilm-forming capacity of Nissle 1917. We found that the strain was a good biofilm former. Not only was it significantly better at biofilm formation than enteropathogenic, enterotoxigenic and enterohaemorrhagic E. coli strains, it was also able to outcompete such strains during biofilm formation. The results support the notion of bacterial prophylaxis employing Nissle 1917 and may partially explain why the strain has a beneficial effect on many intestinal disorders.
Protein and energy metabolism of young male Wistar rats fed conjugated linoleic acid as structured triacylglycerol

Twelve 4-week-old male Wistar rats weighing 100 g were fed diets semi-ad libitum for 22 d containing either 1.5% conjugated linoleic acid (CLA-diet) or high oleic sunflower oil (Control-diet). The CLA was structured triacylglycerol with predominantly cis-9, trans-11 and trans-10, cis-12 fatty acid isomers in the inner position and oleic acid in the other positions of the glycerol molecule. The rats were kept individually in metabolic cages. From days 8-16 energy, nitrogen (N) and carbon
Protein annotation in the era of personal genomics

Protein annotation provides a condensed and systematic view on the function of individual proteins. It has traditionally dealt with sorting proteins into functional categories, which for example has proven to be successful for the comparison of different species. However, if we are to understand the differences between many individuals of the same species—humans in particular—the focus needs be on the functional impact of individual residue variation. To fulfill the promises of personal genomics, we need to start asking not only what is in a genome but also how millions of small differences between individual genomes affect protein function and in turn human health. Copyright © 2010 Elsevier Ltd. All rights reserved.
Proteome analysis of pod and seed development in the model legume Lotus japonicus

Legume pods serve important functions during seed development and are themselves sources of food and feed. Compared to seeds, the metabolism and development of pods are not well-defined. The present characterization of pods from the model legume Lotus japonicus, together with the detailed analyses of the pod and seed proteomes in five developmental stages, paves the way for comparative pathway analysis and provides new metabolic information. Proteins were analyzed by two-dimensional gel electrophoresis and tandem-mass spectrometry. These analyses lead to the identification of 604 pod proteins and 965 seed proteins, including 263 proteins distinguishing the pod. The complete data set is publicly available at http://www.cbs.dtu.dk/cgi-bin/lotus/db.cgi, where spots in a reference map are linked to experimental data, such as matched peptides, quantification values, and gene accessions. Identified pod proteins represented enzymes from 85 different metabolic pathways, including storage globulins and a late embryogenesis abundant protein. In contrast to seed maturation, pod maturation was associated with decreasing total protein content, especially proteins involved in protein biosynthesis and photosynthesis. Proteins detected only in pods included three enzymes participating in the urea cycle and four in nitrogen and amino group metabolism, highlighting the importance of nitrogen metabolism during pod development. Additionally, five legume seed proteins previously unassigned in the glutamate metabolism pathway were identified.

General information

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Division of Microbiology and Risk Assessment, National Food Institute
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Scopus rating (2016): CiteScore 4.34 SJR 1.705 SNIP 1.002
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 1.934 SNIP 1.092 CiteScore 4.45
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 1.945 SNIP 1.185 CiteScore 4.64
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 2.002 SNIP 1.256 CiteScore 5.16
Quantitative phosphoproteomics reveals widespread full phosphorylation site occupancy during mitosis

Eukaryotic cells replicate by a complex series of evolutionarily conserved events that are tightly regulated at defined stages of the cell division cycle. Progression through this cycle involves a large number of dedicated protein complexes and signaling pathways, and deregulation of this process is implicated in tumorigenesis. We applied high-resolution mass spectrometry-based proteomics to investigate the proteome and phosphoproteome of the human cell cycle on a global scale and quantified 6027 proteins and 20,443 unique phosphorylation sites and their dynamics. Co-regulated proteins and phosphorylation sites were grouped according to their cell cycle kinetics and compared to publicly available messenger RNA microarray data. Most detected phosphorylation sites and more than 20% of all quantified proteins showed substantial regulation, mainly in mitotic cells. Kinase-motif analysis revealed global activation during S phase of the DNA damage response network, which was mediated by phosphorylation by ATM or ATR or DNA-dependent protein kinases. We determined site-specific stoichiometry of more than 5000 sites and found that most of the up-regulated sites phosphorylated by cyclin-dependent kinase 1 (CDK1) or CDK2 were almost fully phosphorylated in mitotic cells. In particular, nuclear proteins and proteins involved in regulating metabolic processes have high phosphorylation site occupancy in mitosis. This suggests that these proteins may be inactivated by phosphorylation in mitotic cells.

General information

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Organisations: Center for Biological Sequence Analysis, Department of Systems Biology
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Regulation of immune responses by non—starch polysaccharides: Induction of distinct phenotypes in TLR—triggered dendritic cells and adjuvant properties

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Authors: Wismar, R. (Intern), Pedersen, S. B. (Intern)
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Relating genomic variation to drug response in childhood acute lymphoblastic leukemia by multiplexed targeted sequencing

General information
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis
Authors: Wesolowska, A. (Intern), Dalgaard, M. (Ekstern), Borst, L. (Ekstern), Gautier, L. (Intern), Bak, M. (Ekstern), Weinhold, N. (Intern), Nielsen, B. (Ekstern), Nersting, J. (Ekstern), Tommerup, N. (Ekstern), Brunak, S. (Intern), Sicheritz-Pontén, T. (Intern), Løffers, H. (Ekstern), Schmiegelow, K. (Ekstern), Gupta, R. (Intern)
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Web of Science (2013): Indexed yes
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Scopus rating (2011): SJR 5.989 SNIP 1.973 CiteScore 6.69
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 5.012 SNIP 1.819
BFI (2009): BFI-level 1
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 3.713 SNIP 1.154
Scopus rating (2007): SJR 3.218 SNIP 0.721
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 2.523 SNIP 0.331
Skin barrier response to occlusion of healthy and irritated skin: Differences in trans-epidermal water loss, erythema and stratum corneum lipids

Background: Occlusion of the skin is a risk factor for development of irritant contact dermatitis. Occlusion may, however, have a positive effect on skin healing. No consensus on the effect of occlusion has been reached. Objectives: To investigate skin barrier response to occlusion on intact and damaged skin. Methods: In study A, the response to occlusion (nitrile glove material) for either 8 hr daily for 7 days or for 72 consecutive hours, respectively, was determined and compared with that of non-occluded skin. In study B, the response to occlusion of for 72 consecutive hours of skin that had been damaged by either sodium lauryl sulfate (SLS) or tape stripping, respectively, was determined and compared with that of non-occluded pre-damaged skin. Skin barrier function was assessed by measurements of trans-epidermal water loss (TEWL) and erythema. In study A, stratum corneum lipids were analysed. Results: Occlusion of healthy skin did not significantly influence skin barrier function, ceramide profile or the ceramide/cholesterol ratio. Occlusion of the skin after SLS irritation resulted in higher TEWL than in the control (P = 0.049). Occlusion of the skin after tape stripping resulted in lower TEWL than in control skin (P = 0.007). Conclusions: A week of occlusion did not significantly affect healthy skin, but was found to decrease healing of SLS-damaged skin, and to improve healing of tape-stripped skin.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis
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Scopus rating (2016): CiteScore 2.47 SJR 0.829 SNIP 1.59
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 1 SNIP 1.468 CiteScore 2.85
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 0.874 SNIP 1.677 CiteScore 2.02
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 0.796 SNIP 1.409 CiteScore 1.87
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 0.87 SNIP 1.361 CiteScore 1.98
ISI indexed (2012): ISI indexed yes
Standard operating procedure for computing pangenome trees

We present the pan-genome tree as a tool for visualizing similarities and differences between closely related microbial genomes within a species or genus. Distance between genomes is computed as a weighted relative Manhattan distance based on gene family presence/absence. The weights can be chosen with emphasis on groups of gene families conserved to various degrees inside the pan-genome. The software is available for free as an R-package.
State of the art and challenges in sequence based T-cell epitope prediction

Sequence based T-cell epitope predictions have improved immensely in the last decade. From predictions of peptide binding to major histocompatibility complex molecules with moderate accuracy, limited allele coverage, and no good estimates of the other events in the antigen-processing pathway, the field has evolved significantly. Methods have now been developed that produce highly accurate binding predictions for many alleles and integrate both proteosomal cleavage and transport events. Moreover have so-called pan-specific methods been developed, which allow for prediction of peptide binding to MHC alleles characterized by limited or no peptide binding data. Most of the developed methods are publicly available, and have proven to be very useful as a shortcut in epitope discovery. Here, we will go through some of the history of sequence-based predictions of helper as well as cytotoxic T cell epitopes. We will focus on some of the most accurate methods and their basic background.
Stratum corneum lipids, skin barrier function and filaggrin mutations in patients with atopic eczema

Background: Prior to the discovery of filaggrin (FLG) mutations, evidence for an impaired skin barrier in atopic dermatitis (AD) has been documented, and changes in ceramide profile, altered skin pH and increased trans-epidermal water loss (TEWL) in patients with AD have been reported. Until now, no studies have analysed stratum corneum (SC) lipids combined with skin barrier parameters in subjects of known FLG genotype.

Methods: A cohort of 49 German individuals genotyped for the most common FLG mutations (R501X, 2282del4) had SC samples taken for lipid analysis by high-performance thin layer chromatography. In addition, TEWL, erythema, skin hydration and pH were measured. In 27 of the 49 individuals, a 24-h irritation patch test with sodium lauryl sulphate was performed. For the analysis, both the AD group and the control group were stratified by FLG mutation status (FLGmut/FLGwt).

Results: In the FLGmut AD group, significantly lower levels of ceramide 4 and significantly higher levels of ceramide 7 were observed when compared to both healthy control groups. However, ceramide 7 levels also significantly differed between FLGwt AD and FLGwt controls, as did ceramide 1 levels. No significant differences were observed for ceramide 2, 3, 5 and 6. FLGmut individuals had significantly higher skin pH values than individuals not carrying FLG mutations. Patients with AD with FLG mutations had significantly higher erythema compared to patients with AD without FLG mutations.

Conclusion: Our results confirm previous observations of altered ceramide levels in AD, which however appear to show no clear relationship with FLG mutations.
Structural Properties of MHC Class II Ligands, Implications for the Prediction of MHC Class II Epitopes

Major Histocompatibility class II (MHC-II) molecules sample peptides from the extracellular space allowing the immune system to detect the presence of foreign microbes from this compartment. Prediction of MHC class II ligands is complicated by the open binding cleft of the MHC class II molecule, allowing binding of peptides extending out of the binding groove. Furthermore, only a few HLA-DR alleles have been characterized with a sufficient number of peptides (100–200 peptides per allele) to derive accurate description of their binding motif. Little work has been performed characterizing structural properties of MHC class II ligands. Here, we perform one such large-scale analysis. A large set of SYFPEITHI MHC class II ligands covering more than 20 different HLA-DR molecules was analyzed in terms of their secondary structure and surface exposure characteristics in the context of the native structure of the corresponding source protein. We demonstrated that MHC class II ligands are significantly more exposed and have significantly more coil content than other peptides in the same protein with similar predicted binding affinity. We next exploited this observation to derive an improved prediction method for MHC class II ligands by integrating prediction of MHC-peptide binding with prediction of surface exposure and protein secondary structure. This combined prediction method was shown to significantly outperform the state-of-the-art MHC class II peptide binding prediction method when used to identify MHC class II ligands. We also tried to integrate N- and O-glycosylation in our prediction methods but this additional information was found not to improve prediction performance. In summary, these findings strongly suggest that local structural properties influence antigen processing and/or the accessibility of peptides to the MHC class II molecule.
Chromosomal instability (CIN) is a common cause of tumour heterogeneity and poor prognosis in solid tumours and describes cell-cell variation in chromosome structure or number across a tumour population. In this article we consider
evidence suggesting that CIN may be targeted and may influence response to distinct chemotherapy regimens, using HER2-positive breast cancer as an example. Pre-clinical models have indicated a role for HER2 signalling in initiating CIN and defective cell-cycle control, and evidence suggests that HER2-targeting may attenuate this process. Anthracyclines and platinum agents may target tumours with distinct patterns of karyotypic complexity, whereas taxanes may have preferential activity in tumours with relative chromosomal stability. A greater understanding of karyotypic complexity and identification of methods to directly examine and target CIN may support novel strategies to improve outcome in cancer. J. Cell. Biochem. 111: 782-790, 2010.

**General information**

State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Cancer Research UK, London Research Institute, Royal Marsden Hospital, The Breakthrough Breast Cancer Research Centre, Institute of Cancer Research
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- Scopus rating (2014): SJR 1.52 SNIP 1.066 CiteScore 3.31
- BFI (2013): BFI-level 1
- Scopus rating (2013): SJR 1.574 SNIP 1.004 CiteScore 3.34
- ISI indexed (2013): ISI indexed yes
- BFI (2012): BFI-level 1
- Scopus rating (2012): SJR 1.536 SNIP 1.022 CiteScore 3.42
- ISI indexed (2012): ISI indexed yes
- BFI (2011): BFI-level 1
- Scopus rating (2011): SJR 1.519 SNIP 0.853 CiteScore 3.03
- ISI indexed (2011): ISI indexed yes
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- Scopus rating (2010): SJR 1.734 SNIP 0.971
- Web of Science (2010): Indexed yes
- BFI (2009): BFI-level 1
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- BFI (2008): BFI-level 1
- Scopus rating (2008): SJR 1.976 SNIP 0.908
- Scopus rating (2007): SJR 2.062 SNIP 0.876
- Web of Science (2007): Indexed yes
- Scopus rating (2006): SJR 1.92 SNIP 0.967
- Scopus rating (2005): SJR 0.31 SNIP 0.932
- Scopus rating (2004): SJR 0.338 SNIP 0.788
- Scopus rating (2003): SJR 0.406 SNIP 0.726
- Scopus rating (2002): SJR 0.442 SNIP 0.674
- Scopus rating (2001): SJR 1.183 SNIP 0.709
The EMBRACE web service collection

The EMBRACE (European Model for Bioinformatics Research and Community Education) web service collection is the culmination of a 5-year project that set out to investigate issues involved in developing and deploying web services for use in the life sciences. The project concluded that in order for web services to achieve widespread adoption, standards must be defined for the choice of web service technology, for semantically annotating both service function and the data exchanged, and a mechanism for discovering services must be provided. Building on this, the project developed: EDAM, an ontology for describing life science web services; BioXSD, a schema for exchanging data between services; and a centralized registry (http://www.embraceregistry.net) that collects together around 1000 services developed by the consortium partners. This article presents the current status of the collection and its associated recommendations and standards definitions.

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Scopus rating (2012): SJR 6.13 SNIP 2.392 CiteScore 8.62
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Abstract. The Genome Atlas is a resource for addressing the challenges of synchronising prokaryotic genomic sequence data from multiple public repositories. This resource can integrate bioinformatic analyses in various data format and quality. Existing open source tools have been used together with scripts and algorithms developed in a variety of programming languages at the Centre for Biological Sequence Analysis in order to create a three-tier software application for genome analysis. The results are made available via a web interface developed in Java, PHP and Perl CGI. User-configurable and dynamic views of Chromosomal maps are made possible through an updated GeneWiz browser (version 0.94) which uses Java to allow rapid zooming in and out of the atlases.
The Genome of Trichomonas vaginalis

General information
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Organisations: Center for Biological Sequence Analysis, Department of Systems Biology
Authors: Carlton, J. M. (Ekstern), Malik, S. (Ekstern), Sullivan, S. A. (Ekstern), Sicheritz-Pontén, T. (Intern), Tang, P. (Ekstern), Hirt, R. P. (Ekstern)
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The Immune Epitope Database 2.0

The Immune Epitope Database (IEDB, www.iedb.org) provides a catalog of experimentally characterized B and T cell epitopes, as well as data on Major Histocompatibility Complex (MHC) binding and MHC ligand elution experiments. The database represents the molecular structures recognized by adaptive immune receptors and the experimental contexts in which these molecules were determined to be immune epitopes. Epitopes recognized in humans, nonhuman primates, rodents, pigs, cats and all other tested species are included. Both positive and negative experimental results are captured. Over the course of 4 years, the data from 180,978 experiments were curated manually from the literature, which covers approximately 99% of all publicly available information on peptide epitopes mapped in infectious agents (excluding HIV) and 93% of those mapped in allergens. In addition, data that would otherwise be unavailable to the public from 129,186 experiments were submitted directly by investigators. The curation of epitopes related to autoimmunity is expected to be completed by the end of 2010. The database can be queried by epitope structure, source organism, MHC restriction, assay type or host organism, among other criteria. The database structure, as well as its querying, browsing and reporting interfaces, was completely redesigned for the IEDB 2.0 release, which became publicly available in early 2009.

General information
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Organisations: Center for Biological Sequence Analysis, Department of Systems Biology
Authors: Hoof, I. (Intern), Vita, R. (Ekstern), Zarebski, L. (Ekstern), Greenbaum, J. (Ekstern), Emami, H. (Ekstern), Salimi, N. (Ekstern), Damle, R. (Ekstern), Sette, A. (Ekstern), Peters, B. (Ekstern)
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The MHC motif viewer: a visualization tool for MHC binding motifs

In vertebrates, the onset of cellular immune reactions is controlled by presentation of peptides in complex with major histocompatibility complex (MHC) molecules to T cell receptors. In humans, MHCs are called human leukocyte antigens (HLAs). Different MHC molecules present different subsets of peptides, and knowledge of their binding specificities is important for understanding differences in the immune response between individuals. Algorithms predicting which peptides bind a given MHC molecule have recently been developed with high prediction accuracy. The utility of these algorithms is hampered by the lack of tools for browsing and comparing specificity of these molecules. We have developed a Web server, MHC Motif Viewer, which allows the display of the binding motif for MHC class I proteins for human, chimpanzee, rhesus monkey, mouse, and swine, as well as HLA-DR protein sequences. The binding motif for each MHC molecule is predicted using state-of-the-art, pan-specific peptide-MHC binding-prediction methods, and is visualized as a sequence logo, in a format that allows for a comprehensive interpretation of binding motif anchor positions and amino acid preferences.

The most common Chinese rhesus macaque MHC class I molecule shares peptide binding repertoire with the HLA-B7 supertype

Of the two rhesus macaque subspecies used for AIDS studies, the Simian immunodeficiency virus-infected Indian rhesus macaque (Macaca mulatta) is the most established model of HIV infection, providing both insight into pathogenesis and a system for testing novel vaccines. Despite the Chinese rhesus macaque potentially being a more relevant model for AIDS outcomes than the Indian rhesus macaque, the Chinese-origin rhesus macaques have not been well-characterized for their major histocompatibility complex (MHC) composition and function, reducing their greater utilization. In this study, we characterized a total of 50 unique Chinese rhesus macaques from several varying origins for their entire MHC class I allele composition and identified a total of 58 unique complete MHC class I sequences. Only nine of the sequences had been associated with Indian rhesus macaques, and 28/58 (48.3%) of the sequences identified were novel. From all MHC alleles detected, we prioritized Mamu-A1*02201 for functional characterization based on its higher frequency of expression. Upon
the development of MHC/peptide binding assays and definition of its associated motif, we revealed that this allele shares peptide binding characteristics with the HLA-B7 supertype, the most frequent supertype in human populations. These studies provide the first functional characterization of an MHC class I molecule in the context of Chinese rhesus macaques and the first instance of HLA-B7 analogy for rhesus macaques.

**General information**

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**Organisations:** Center for Biological Sequence Analysis, Department of Systems Biology  
**Authors:** Solomon, C. (Ekstern), Southwood, S. (Ekstern), Hoof, I. (Intern), Rudersdorf, R. (Ekstern), Peters, B. (Ekstern), Sidney, J. (Ekstern), Pinilla, C. (Ekstern), Marcondes, M. (Ekstern), Ling, B. (Ekstern), Marx, P. (Ekstern), Sette, A. (Ekstern), Mothe, B. (Ekstern)  
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Scopus rating (2015): SJR 1.551 SNIP 0.819 CiteScore 2.47  
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BFI (2014): BFI-level 1  
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Web of Science (2014): Indexed yes  
BFI (2013): BFI-level 1  
Scopus rating (2013): SJR 1.231 SNIP 0.763 CiteScore 2.48  
ISI indexed (2013): ISI indexed yes  
Web of Science (2013): Indexed yes  
BFI (2012): BFI-level 1  
Scopus rating (2012): SJR 1.365 SNIP 0.943 CiteScore 2.91  
ISI indexed (2012): ISI indexed yes  
Web of Science (2012): Indexed yes  
BFI (2011): BFI-level 1  
Scopus rating (2011): SJR 1.304 SNIP 0.888 CiteScore 2.83  
ISI indexed (2011): ISI indexed yes  
Web of Science (2011): Indexed yes  
BFI (2010): BFI-level 1  
Scopus rating (2010): SJR 1.186 SNIP 0.847  
Web of Science (2010): Indexed yes  
BFI (2009): BFI-level 1  
Scopus rating (2009): SJR 1.486 SNIP 0.847  
Web of Science (2009): Indexed yes  
BFI (2008): BFI-level 1  
Scopus rating (2008): SJR 1.386 SNIP 0.774  
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Web of Science (2006): Indexed yes
The phosphorylation specificity of B-RAF(WT), B-RAF(D594V), B-RAF(V600E) and B-RAF(K601E) kinases: An in silico study

Phosphorylation of the B-RAF kinase is an essential process in tumour induction and maintenance in several cancers. Herein the phosphorylation specificity of the activation segment of the wild type B-RAF kinase and the B-RAF(D594V), B-RAF(V600E) and B-RAF(K601E) mutants was examined by molecular dynamics (MD) simulations and GRID molecular interaction field analysis. According to our analysis, Thr599 and Ser602 were the only residues in the activation segment in B-RAF(WT) that were well exposed to ATP binding, which is in agreement with the experimental results, and provide a molecular basis of the observed phosphorylation. The phosphorylation specificity was altered significantly for each of the three different mutants studied due to the large conformational changes and subsequent alterations in the electrostatic forces between several residues for each of these mutants. Thus the analysis revealed limited phosphorylation potential of the non-active B-RAF(D594V) mutant and several potential ATP binding sites were identified for the highly active B-RAF(V600E) mutant. The Lys601 residue, which is specific to RAF and not present in the activation segment of other similar kinases, was identified to potentially be of major importance to the observed differences in the phosphorylation specificity of the mutants. Our results indicate that Lys601 might be a specific ATP coordinating residue, contributing to the B-RAF phosphorylation specificity. The overall results can be helpful for the understanding of the B-RAF phosphorylation processes on a molecular level. (c) 2009 Elsevier Inc. All rights reserved.
The protease inhibitors ritonavir and saquinavir influence lipid metabolism: a pig model for the rapid evaluation of new drugs

Background: Studies of the effects of antiretroviral drugs on lipid metabolism are limited by the availability of suitable models. We have thus developed an animal model utilising Gottingen mini-pigs. The normal lipid metabolism of mini-pigs closely reflects that of humans and they are expected to have similar reactions to antiretroviral drugs. Methods: The pigs were treated orally with high doses of the protease inhibitors ritonavir and saquinavir for 4 weeks. The model allows repeated concomitant biopsies from liver, muscle, adipose tissue and plasma samples. Results: The study showed a general decrease in polyunsaturated fatty acids; changes in both saturated and monounsaturated fatty acids were also apparent after antiretroviral treatment. The changes were observed after 4 weeks of treatment. At 4 weeks post-treatment, the levels of all fatty acids were lower compared with pretreatment levels, suggesting a prolonged effect of the antiretroviral drug treatment lasting beyond the 4 week post-treatment observation period. Conclusions: The Gottingen mini-pig model is a promising animal model for rapid screening of the metabolic effects induced by antiretroviral drugs.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Department of Biochemistry and Nutrition
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Volume: 15
Issue number: 2
The Thousandth Genome – A Cautionary Tale

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology
Authors: Lagesen, K. (Intern), Ussery, D. (Intern), Wassenaar, G. M. (Intern)
Pages: 603-609
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The Type 1 Diabetes - HLA Susceptibility Interactome - Identification of HLA Genotype-Specific Disease Genes for Type 1 Diabetes

Background: The individual contribution of genes in the HLA region to the risk of developing type 1 diabetes (T1D) is confounded by the high linkage disequilibrium (LD) in this region. Using a novel approach we have combined genetic association data with information on functional protein-protein interactions to elucidate risk independent of LD and to place the genetic association into a functional context. Methodology/Principal Findings: Genetic association data from 2300 single nucleotide polymorphisms (SNPs) in the HLA region was analysed in 2200 T1D family trios divided into six risk groups based on HLA-DRB1 genotypes. The best SNP signal in each gene was mapped to proteins in a human protein interaction network and their significance of clustering in functional network modules was evaluated. The significant network modules identified through this approach differed between the six HLA risk groups, which could be divided into two groups based on carrying the DRB1*0301 or the DRB1*0401 allele. Proteins identified in networks specific for DRB1*0301 carriers were involved in stress response and inflammation whereas in DRB1*0401 carriers the proteins were involved in antigen processing and presentation. Conclusions/Significance: In this study we were able to hypothesise functional differences between individuals with T1D carrying specific DRB1 alleles. The results point at candidate proteins involved in distinct cellular processes that could not only help the understanding of the pathogenesis of T1D, but also the distinction between individuals at different genetic risk for developing T1D.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis
Authors: Brorsson, C. (Ekstern), Hansen, N. T. (Intern), Bergholdt, R. (Ekstern), Brunak, S. (Intern), Pociot, F. (Ekstern)
Pages: e9576
Publication date: 2010
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Scopus rating (2015): SJR 1.414 SNIP 1.131 CiteScore 3.32
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.545 SNIP 1.141 CiteScore 3.54
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Scopus rating (2013): SJR 1.74 SNIP 1.147 CiteScore 3.94
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
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Scopus rating (2011): SJR 2.369 SNIP 1.23 CiteScore 4.58
ISI indexed (2011): ISI indexed no
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 2.631 SNIP 1.161
Web of Science (2010): Indexed yes
Several findings suggest a functional and anatomical differentiation along the dorso-ventral axis of the hippocampus. Lesion studies in rats have indicated that the dorsal hippocampus preferentially plays a role in spatial learning and memory, while the ventral hippocampus is involved in anxiety-related behaviors. Based on such findings our aim was to investigate the molecular differentiation along the dorso-ventral axis of the hippocampal granular cell layer of the rat dentate gyrus. Homogeneous isolation of this specific area was performed by laser-capture microdissection and Illumina microarray chips were used to identify genes differentially expressed in dorsal and ventral granular cell layer, respectively. Selected genes were confirmed by quantitative polymerase chain reaction analyses. From the total amount of 22518 probes 229 genes were found to be differentially expressed between dorsal and ventral granular cell layer with a false discovery rate below 5% and with a relative change in gene expression level of 20% or more. From this pool of genes 45 genes were more than two-fold regulated, 13 genes being dorsally enriched and 32 genes being ventrally enriched.

Moreover, cluster analysis based on all genes represented on the microarray chip showed a clear differentiation between dorsal and ventral subgroups. Our findings demonstrate a dorso-ventral differentiation in gene expression even at the subregional level of the rat hippocampus, more specifically in the granular cell layer, substantiating the existence of functional heterogeneity along the dorso-ventral axis of the hippocampus.
Projects:

**Extracellular matrix remodeling in cardiovascular and renal fibrosis**

Department of Systems Biology

Center for Biological Sequence Analysis

**Period:** 01/03/2015 → 28/02/2018

**Number of participants:** 2

**Project participant:**

Nielsen, Signe Holm (Intern)

Main Supervisor:

Pedersen, Susanne Brix (Intern)

**Whole genome based diagnostics and investigations**

The advancement of genome technologies holds great promise for improving the quality and speed of public health laboratory investigations, and for decreasing their cost. The latest genome DNA sequencers are now suitable for routine use in public health laboratories and may replace conventional culture-based and molecular bacterial methods for laboratory diagnosis. Especially in low income areas this might create new options, and enable laboratories in developing countries to “leapfrog”, avoiding the development of very costly and often insufficient laboratory systems similar to those that are implemented in OECD countries where separate specialist testing capacities exist for each of the many microbiological families. The problem is the need of very specialized knowledge, computation and tools to analyze the data generated in a standardized and comparable way and provide plain language reports to the primary care users. Such tools are developed or under development in a web-accessible format at DTU. In the project the latest sequencing technology is made available in a diagnostic laboratory in Tanzania and combined with analytic facilities at one of the world’s largest bioinformatic centers at DTU. Two PhD-students from Tanzania are being educated in sequencing technology and use this on routine diagnostic samples. To ensure dissemination to other countries in the region and provide capacity Building, Kilimanjaro Clinical Research Institute (KCRI) at the Kilimanjaro Christian Medical Centre is used as a focal point for WHO GFN training courses.

National Food Institute

Research Group for Genomic Epidemiology

Department of Systems Biology

Center for Biological Sequence Analysis

University of Copenhagen

Kilimanjaro Christian Medical Centre

**Period:** 01/01/2013 → 31/12/2016

**Number of participants:** 5

**Epidemiology, Health, Infections, Vaccines, Research**

Contact person:
Can the use of dairy phospholipids as emulgators protect against a pro-obesogenic intestinal microbiota?

The results from a pilot-study in our labs, indicates that it possible to modulate the composition of the intestinal microbiota by emulsifying fat in milk phospholipids (MPL), instead of using soy-lecithin that is normally used e.g. in infant formulas. In the study, we mimicked the intestinal colonization occurring at birth, by transferring germ-free mice out of the sterile environment and into cages containing faeces from a normal mouse, while they were given the emulsions for three week. The results show that the numbers of bacteria from the phylum Firmicutes decreased in the colon lumen in mice that were given the MPL-based emulsions (fig. 1 below) while Bacteriodetes was not affected. Since obesity-development have been linked to increased ratio between Firmicutes and Bacteriodetes in the colon, the result indicates that it could be possible to reduce the risk of developing obesity later in life by exchanging soy-lecithin with MPL in infant formulas. To elucidate this possibility, we want to perform three studies in which we will validate the results from the pilot-study in a bigger study, determine the mechanism that is explaining the effect on microbial composition and determine whether this effect is persistent also after intake of the emulsion have stopped and whether it actually reduce the risk of developing obesity and metabolic diseases later in life.

National Food Institute

Division of Food Microbiology

Department of Systems Biology

Center for Biological Sequence Analysis

Period: 02/01/2012 → 31/12/2015

Number of participants: 3

Project participant:

Licht, Tine Rask (Intern)

Bennike, Rikke Mette Guldhammer (Intern)

Project Manager, organisational:

Hellgren, Lars (Intern)

Financing sources

Source: Public research council

Name of research programme: Mejerbrugets ForskningsFond

Amount: 360,000.00 Danish Kroner

Project

Selection of protective antigens in Lawsonia intracellularis by reverse vaccinology

National Veterinary Institute

Division of Veterinary Diagnostics and Research

Adaptive Immunology & Parasitology

Center for Biological Sequence Analysis

Period: 01/10/2011 → 30/09/2014

Number of participants: 5

Lawsonia

Acronym: Lawsonia antigens
Predicting individual response and resistance to VEGFR/mTOR pathway therapeutic intervention using biomarkers discovered through tumour functional genomics

Center for Biological Sequence Analysis
Period: 01/01/2011 → 31/12/2013
Number of participants: 1
Acronym: PREDICT
Project participant:
Johansen, Ulla (Intern)

CGE: Center for Genomic Epidemiology
The cost of sequencing a bacterial genome is $50 and is expected to decrease further in the near future and the equipment needed cost less than $150 000. Thus, within a few years all clinical microbiological laboratories will have a sequencer in use on a daily basis. The price of genome sequencing is already so low that whole genome sequencing will also find worldwide application in human and veterinary practices as well as many other places where bacteria are handled. In Denmark alone this equals more than 1 million isolates annually in 15-20 laboratories and globally up to 1-2 billion isolates per year. The limiting factor will therefore in the future not be the cost of the sequencing, but how to assemble, process and handle the large amount of data in a standardized way that will make the information useful, especially for diagnostic and surveillance.

The aim of this center is to provide the scientific foundation for future internet-based solutions where a central database will enable simplification of total genome sequence information and comparison to all other sequenced including spatial-temporal analysis. We will develop algorithms for rapid analyses of whole genome DNA-sequences, tools for analyses and extraction of information from the sequence data and internet/web-interfaces for using the tools in the global scientific and medical community. The activity is being expanded to also include other microorganisms, such as vira and parasites as well as metagenomic samples.

National Food Institute
Research Group for Genomic Epidemiology

Department of Systems Biology
Center for Biological Sequence Analysis
Period: 01/04/2010 → 30/09/2016
Number of participants: 5
Genomic Epidemiology, genome, CGE
Project participant:
Hasman, Henrik (Intern)
Hendriksen, Rene S. (Intern)
Lund, Ole (Intern)
Other:
Carlsson, Susanne (Intern)
Project Manager, academic:
Aarestrup, Frank Møller (Intern)

Financing sources
Source: Public research programme (public)
Name of research programme: Innovationsfonden
Web address: http://innovationsfonden.dk/da
Amount: 11,246,579.00 Danish Kroner
T Cell Reactive Tetramers for Virus Infections in Pigs

Virus infections in livestock are constant threats to animal welfare and productivity all over the world. In this project we will deliver new advanced technological reagents for measurement of the cytotoxic cells of the immune system with activity against virus infected cells in pigs. This will be an extremely important tool in the development of new efficacious vaccines against diseases like foot- and mouth disease and influenza. All cells of the body exhibit small fragments of their contents on the cell surface. A virus-infected cell will therefore display fragments of virus proteins which, like a key in a lock on the cytotoxic cell, will activate killing of the infected cell. This will stop replication of the virus and this cell-mediated immunity is therefore a crucial part of the host defence against virus infections. The virus-key is made up of host tissue-type molecules displaying a small virus peptide (a chain of 8 to 11 amino acids). We will produce luminescent recombinant virus-keys, MHC class I tetramers, for pigs, which will enable us to directly stain and identify host cell with cytotoxic activity against virus. With these tetramers we can determine exactly which peptides in the virus proteins that mediate the desired immune response, and thereby which virus components that can be used in new targeted vaccines. Furthermore, we will be able to measure if vaccines have induced the desired cytotoxic effector cells, and we can develop computer models to predict peptide antigens of new viruses. The project group consists of scientists from Technical University of Denmark, Copenhagen University and leading American scientists in virus infections and MHC molecules in pigs.

Adaptive Immunology & Parasitology
Division of Veterinary Diagnostics and Research
National Veterinary Institute
Center for Biological Sequence Analysis
Department of Systems Biology
University of Copenhagen
United States Department of Agriculture
Period: 01/07/2009 → 31/12/2012
Number of participants: 5
Project ID: 22380 X-1
Project participant:
Pedersen, Lasse Eggers (Intern)
Nielsen, Morten (Intern)
Project Manager, organisational:
Jungersen, Gregers (Intern)
Buus, Søren (Ekstern)
Golde, William T. (Ekstern)

Financing sources
Source: Forskningsrådene - Andre
Name of research programme: Forskningsrådene - Andre
Amount: 4,657,800.00 Danish Kroner

Development of plant sink organs : Novel genes for science, agronomy and industrial use

Center for Biological Sequence Analysis
Department of Systems Biology
Period: 01/06/2004 → 31/05/2008
Number of participants: 1
Project ID: 45669
Project Manager, organisational:
Brunak, Søren (Intern)

Financing sources
Source: Forskningsrådene - STVF
Name of research programme: Forskningsrådene - STVF
Amount: 1,788,000.00 Danish Kroner
Advanced microarray data analysis
Center for Biological Sequence Analysis
Department of Systems Biology
Period: 20/01/2004 → 30/06/2004
Number of participants: 1
Project Manager, organisational:
Boesen, Lone (Intern)

Financing sources
Source: Uddannelse, udenlandske offentlige og private
Name of research programme: Uddannelse, udenlandske offentlige og private
Amount: 224,799.21 Danish Kroner

A European Network for Integrated Genome Annotation
The objective of the BIOSAPIENS Network of Excellence is to provide an infrastructure to support a large scale, concerted effort to annotate genome data by laboratories distributed around Europe. This will use both informatics tools and input from experimentalists. Experimental validation of a statistically significant subset of the predictions will be an integral part of the process, leading to an iterative improvement in methods. The Network will bring together many of the best laboratories to create a European Virtual Institute for Genome Annotation, divided into nodes, each focussed on one aspect of genome annotation. Through integration the institute will help to improve bioinformatics research in Europe, by providing a focus for annotation and by the organisation of European meetings and workshops to encourage cooperation, rather than duplication of effort. It will also be pro-active in forging closer integration between the experimentalists and bioinformaticians, through a directed programme of genome analysis, focused on specific biological problems. The annotations generated by the Institute will be available in the public domain and easily accessible through a single portal on the web. This will be achieved through a distributed annotation system (DAS), which will evolve to take advantage of new developments in the GRID. The BIOSAPIENS NoE will increase European competitiveness, especially for SME's, by new discoveries, increased integration, expert training and improved tools and services. The Institute will establish a permanent European School of Bioinformatics, to train bioinformaticians and to encourage best practice in the exploitation of genome annotation data for biologists throughout Europe. In summary the Institute will further a European Research area for Bioinformatics, enhancing Europe's role in the academic and industrial exploitation of genomics.

Center for Biological Sequence Analysis
Department of Systems Biology
Period: 01/01/2004 → 31/12/2008
Number of participants: 1
Acronym: BIOSAPIENS
Project ID: 45664
Project Manager, organisational:
Brunak, Søren (Intern)

Financing sources
Source: Forsk. EU - Rammeprogram
Name of research programme: Forsk. EU - Rammeprogram
Amount: 1,350,000.00 Danish Kroner

A software platform for sequence analysis of repertoires of antibody sequences
Center for Biological Sequence Analysis
Department of Systems Biology
Period: 01/01/2004 → 31/12/2004
Number of participants: 1
Project ID: 45645
Project Manager, organisational:
Lund, Ole (Intern)

Financing sources
Source: Sam.arb.aftaler, Private danske - Andre virksomheder
Name of research programme: Sam.arb.aftaler, Private danske - Andre virksomheder
Amount: 246,834.00 Danish Kroner
Computer resources for a new Danish platform for integrative biology with focus on systemic proteomics

Center for Biological Sequence Analysis

Department of Systems Biology
Period: 01/01/2004 → 31/12/2004
Number of participants: 1
Project ID: 45661
Project Manager, organisational:
Brunak, Søren (Intern)

Financing sources
Source: Forskningsprojekter - Andre ministerier og styrelser
Name of research programme: Forskningsprojekter - Andre ministerier og styrelser
Amount: 3,500,000.00 Danish Kroner

Interaction proteome

Center for Biological Sequence Analysis

Department of Systems Biology
Period: 01/01/2004 → 31/12/2008
Number of participants: 1
Project Manager, organisational:
Brunak, Søren (Intern)

Financing sources
Source: Forsk. EU - Rammeprogram
Name of research programme: Forsk. EU - Rammeprogram
Amount: 5,380,000.00 Danish Kroner

Systemic transcriptomics in biotechnology

Center for Biological Sequence Analysis

Department of Systems Biology
Period: 01/01/2004 → 30/06/2007
Number of participants: 1
Project Manager, organisational:
Brunak, Søren (Intern)

Financing sources
Source: Forskningsrådene - STVF
Name of research programme: Forskningsrådene - STVF
Amount: 12,000,000.00 Danish Kroner

Translating genome and proteome information into immune recognition

Recent advances in immunology prompt us to suggest an immediate, highly significant application of genomics information. The immune system considers peptides as key targets and has devoted an entire arm - one that essentially controls specific immune responsiveness - to peptide recognitions. Thus if one could predict how the immune system handles proteins, and how it generates, selects and recognises peptides, then one should be able to translate genomes/proteomes to immunogens, and thereby forecast immune recognition. Although many of the mechanisms involved in antigen presentation have been described in general terms, only few have been described in sufficient details to allow for accurate prediction of their outcome. We propose to integrate cell biology with bioinformatics to create a European databank of immune epitope and the accompanying data mining tools, which should allow scientists and clinicians to screen whole genomes and proteomes for the presence of immunogenic epitopes. The ability to identify immune targets will be of considerable practical utility. With computational prediction tool, whole genomes can be searched and the amount of time and resources spent in vaccine-relevant discovery can be significantly reduced. Capacity is an important issue when searching several pathogen genomes for conserved vaccine candidates. Time is also an issue when searching for patient-specific immunotherapy targets (e.g. cancer).
Center for Biological Sequence Analysis

Department of Systems Biology
Period: 01/01/2004 → 31/12/2007
Number of participants: 1
Project ID: 45646
Project Manager, organisational: Brunak, Søren (Intern)

Financing sources
Source: Forsk. EU - Rammeprogram
Name of research programme: Forsk. EU - Rammeprogram
Amount: 2,900,000.00 Danish Kroner
Project

Systems biology - integrating data at multiple levels of biological information and understanding complex biochemical pathways

Center for Biological Sequence Analysis

Department of Systems Biology
Period: 01/11/2003 → 31/05/2005
Number of participants: 1
Project Manager, organisational: Brunak, Søren (Intern)

Financing sources
Source: Forsk. Private danske - Andre
Name of research programme: Forsk. Private danske - Andre
Amount: 1,472,386.00 Danish Kroner
Project

Muskelbiopsier under insulinstimulering

Center for Biological Sequence Analysis

Department of Systems Biology
Period: 27/06/2003 → 30/06/2004
Number of participants: 1
Project Manager, organisational: Boesen, Lone (Intern)

Financing sources
Source: Forsk. Private danske - Andre
Name of research programme: Forsk. Private danske - Andre
Amount: 208,500.00 Danish Kroner
Project

DNA microarray core facility

Center for Biological Sequence Analysis

Department of Systems Biology
Period: 16/06/2003 → 31/12/2004
Number of participants: 1
Project Manager, organisational: Boesen, Lone (Intern)

Financing sources
Source: Forskningsrådene - SNF
Name of research programme: Forskningsrådene - STVF
Amount: 1,500,000.00 Danish Kroner
Project
SIGA
Center for Biological Sequence Analysis
Department of Systems Biology
Period: 12/06/2003 → 30/04/2005
Number of participants: 1
Project Manager, organisational: Boesen, Lone (Intern)
Financing sources
Source: Forsk. Andre offentlige og private - Udenlandske
Name of research programme: Forsk. Andre offentlige og private - Udenlandske
Amount: 5,400,000.00 Danish Kroner

A danish platform for integrative biology
Center for Biological Sequence Analysis
Department of Systems Biology
Period: 01/06/2003 → 30/06/2006
Number of participants: 1
Project Manager, organisational: Brunak, Søren (Intern)
Financing sources
Source: Forsk. Andre statslige danske - Grundforskn.fonden
Name of research programme: Forsk. Andre statslige danske - Grundforskn.fonden
Amount: 8,256,000.00 Danish Kroner

DNA Array
Center for Biological Sequence Analysis
Department of Systems Biology
Period: 13/02/2003 → 13/02/2003
Number of participants: 1
Project Manager, organisational: Boesen, Lone (Intern)
Financing sources
Source: Indtægtsdækket virksomhed UK 90
Name of research programme: Indtægtsdækket virksomhed UK 90
Amount: 10,000.00 Danish Kroner

Activities:

10th European Mucosal Immunology Group meeting
Carsten Eriksen (Participant)
Department of Systems Biology
Center for Biological Sequence Analysis

Related event
10th European Mucosal Immunology Group meeting
19/10/2016 → 21/10/2016
Copenhagen, Denmark
The 12th Congress of the Pan-American Section of the International Society on Toxinology
Period: 18 Sep 2016
Mikael Engmark (Participant)
Department of Bio and Health Informatics
Department of Systems Biology
Center for Biological Sequence Analysis
Network Engineering of Eukaryotic Cell Factories

Description
Poster presentation
Documents:
PosterIST2016_ver2

Related event
The 12th Congress of the Pan-American Section of the International Society on Toxinology: Toxins by the Beach
18/09/2016 → 23/09/2016
Miami Beach, United States
Activity: Attending an event › Participating in or organising workshops, courses, seminars etc.

The Oxford Venoms Symposium 2016
Period: 6 Sep 2016
Mikael Engmark (Invited speaker)
Department of Bio and Health Informatics
Department of Systems Biology
Center for Biological Sequence Analysis
Network Engineering of Eukaryotic Cell Factories

Related event
The Oxford Venoms Symposium 2016: Making sense of venoms in health and disease
05/09/2016 → 06/09/2016
Oxford, United Kingdom
Activity: Attending an event › Participating in or organising workshops, courses, seminars etc.

2nd International Conference on Clinical Sciences and Drug Discovery
Period: 29 Jul 2016
Lasse Westergaard Folkersen (Invited speaker)
Department of Systems Biology
Center for Biological Sequence Analysis
Integrative Systems Biology

Description
Dundee, Scotland

"Novel drug-discovery strategies using multi-omics patient-centric biobanks"

Related external organisation
Unknown external organisation
Activity: Talks and presentations › Conference presentations
Hack-MCFC
Period: 29 Jul 2016
Lasse Westergaard Folkesen (Participant)
Department of Systems Biology
Center for Biological Sequence Analysis
Integrative Systems Biology

**Description**
Big data Analytics Hackaton - first price for best prediction of football matches

HackMCFC Big Data Hackaton event with Manchester City
Links:

**Related event**

**Hack-MCFC: Manchester City Player Performance Hack**
29/07/2016 → 31/07/2016
Manchester, United Kingdom
Activity: Attending an event › Participating in or organising workshops, courses, seminars etc.

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**University of Mississippi Medical Center**
Period: 18 Apr 2016 → 29 May 2016
Signe Holm Nielsen (Visiting researcher)
Department of Systems Biology
Center for Biological Sequence Analysis

**Description**
PhD Researcher
Exchange student at Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, Mississippi.
Research area: Myocardial Infarction
Internal supervisor: Dr. Merry L. Lindsey
Activity: Visiting an external institution › Visiting another research institution

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**Keystone Symposia - Fibrosis: From Basic Mechanisms to Targeted Therapies**
Period: 9 Feb 2016
Signe Holm Nielsen (Participant)
Department of Systems Biology
Center for Biological Sequence Analysis

**Description**
Presenter of one poster at Keystone Symposia, Fibrosis: From Basic Mechanisms to Targeted Therapies. Poster Title:
Neo-epitope biomarkers of extracellular matrix remodeling as a diagnostic tool for Hepatocellular Carcinoma Authors: S.H. Nielsen; M Karsdal; D van der Poorten; D Leeming; J George; R Vongsuvanh; D Guldager Kring Rasmussen; F Genovesi

**Related event**

**Keystone Symposia - Fibrosis: From Basic Mechanisms to Targeted Therapies**
07/02/2016 → 11/02/2016
Keystone, Colorado, United States
Activity: Attending an event › Participating in or organising workshops, courses, seminars etc.

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**NIASC eSCIENCE Seminar 2016**
Period: 13 Jan 2016
Lasse Westergaard Folkersen (Invited speaker)
Department of Systems Biology
Center for Biological Sequence Analysis
Integrative Systems Biology

**Description**
http://www.conferencemanager.dk/NIASC-eSCIENCE-seminar-2016

Novel drug-discovery strategies using multi-omics patient-centric biobanks

**Related external organisation**

**Unknown external organisation**
Activity: Talks and presentations › Conference presentations

**B M C Bioinformatics (Journal)**
Period: 2015 → …
Jose Maria Gonzalez-Izarzugaza (Editor)
Department of Systems Biology
Center for Biological Sequence Analysis
Integrative Systems Biology

**Description**
https://bmcbioinformatics.biomedcentral.com/about/editorial-board

**Related journal**

**B M C Bioinformatics**
1471-2105
BFI (2018): BFI-level 1, Scopus rating (2016): CiteScore 2.54 SJR 1.467 SNIP 0.946, ISI indexed (2013): ISI indexed yes,
Web of Science (2017): Indexed yes
Indexed in DOAJ
Central database
Activity: Research › Journal editor

**PeerJ (Journal)**
Period: 2015 → …
Jose Maria Gonzalez-Izarzugaza (Reviewer)
Department of Systems Biology
Center for Biological Sequence Analysis
Integrative Systems Biology

**Description**
https://peerj.com/JMGIzarzugaza/

**Related journal**

**PeerJ**
2167-8359
BFI (2018): BFI-level 1, Scopus rating (2016): CiteScore 2.36 SJR 1.109 SNIP 0.865, ISI indexed (2013): ISI indexed no,
Web of Science (2017): Indexed yes
Indexed in DOAJ
Central database
Activity: Research › Journal editor

**Member of the Danish reference group for the EU-IMI program (External organisation)**
Period: 15 Dec 2015 → …
Susanne Brix Pedersen (Participant)
Department of Systems Biology
Center for Biological Sequence Analysis

**Description**
Body type: EU-IMI

**Related external organisation**

**Member of the Danish reference group for the EU-IMI program**
Activity: Membership › Membership of committees, commissions, boards, councils, associations, organisations, or similar

**Panel member of Medical and Health Sciences under the National Research Council in Portugal (External organisation)**
Period: 15 Nov 2015 → …
Susanne Brix Pedersen (Participant)
Department of Systems Biology
Center for Biological Sequence Analysis

**Description**
Body type: FCT (National Research Council)
Degree of recognition: International

**Related external organisation**

**Panel member of Medical and Health Sciences under the National Research Council in Portugal**
Activity: Membership › Membership in review committee

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**American Society of Nephrology**
Period: 4 Nov 2015 → 9 Nov 2015
Signe Holm Nielsen (Speaker)
Department of Systems Biology
Center for Biological Sequence Analysis

**Description**
Presenting two posters as first author. This conference was supported by Otto Mønsted Fonden.

**Links:**
https://www.asn-online.org/education/kidneyweek/archives/

**Related event**

**American Society of Nephrology: Kidney Week**
04/11/2015 → 08/11/2015
San Diego, CA, United States
Activity: Talks and presentations › Conference presentations

**High-throughput epitope profiling for mamba neurotoxins**
Period: 2 Oct 2015
Mikael Engmark (Invited speaker)
Department of Systems Biology
Center for Biological Sequence Analysis

**Description**
30 min talk.
Drug Research Academy symposium. Invited speaker at Drug Research Academy.

**Documents:**
DRA symposium UCPH Programme 2015

**Related event**
Snake Summit Copenhagen 2015: From Fangs to Pharmacology
02/10/2015 → …
København, Denmark
Activity: Talks and presentations › Conference presentations

**18th World Congress of the International Society on Toxinology**
Period: 25 Sep 2015 → 30 Sep 2015
Mikael Engmark (Participant)
Department of Systems Biology
Center for Biological Sequence Analysis

**Description**
Presented the poster High-throughput epitope identification for snakebite antivenom
Documents:
IST2015_poster_ver2
Links:
http://lpmhealthcare.com/ist2015/

**Related event**

**18th World Congress of the International Society on Toxinology**
25/09/2015 → 30/09/2015
Oxford, United Kingdom
Activity: Attending an event › Participating in or organising workshops, courses, seminars etc.

**First Annual Danish Bioinformatics Conference**
Maria Maddalena Sperotto (Organizer)
Department of Systems Biology
Center for Biological Sequence Analysis

**Description**
Member of the Management Committee
Documents:
DKBiC-2015
Links:

**Related event**

**First Annual Danish Bioinformatics Conference**
27/08/2015 → 27/11/2015
Odense, Denmark
Activity: Attending an event › Participating in or organising a conference

**InFLAME (External organisation)**
Period: 12 Apr 2015 → …
Susanne Brix Pedersen (Participant)
Department of Systems Biology
Center for Biological Sequence Analysis

**Description**
Body type: WUN
Degree of recognition: International

**Related external organisation**

**InFLAME**
Activity: Membership › Membership of research networks or expert groups

**Pregnancy and Programming and Later Risk of Obesity and Related Disease, Frederiksberg, Denmark, 1-5 December 2014**
Period: 1 Dec 2014 → 5 Dec 2014
Amalie Ribel-Madsen (Participant)
Department of Systems Biology
Center for Biological Sequence Analysis

**Description**
Participant

**Related event**

**Pregnancy and Programming and Later Risk of Obesity and Related Disease, Frederiksberg, Denmark, 1-5 December 2014**
01/12/2014 → 05/12/2014
Frederiksberg, Denmark
Activity: Attending an event › Participating in or organising workshops, courses, seminars etc.

**Novel Targets for Enhancing Functional Beta-Cell Mass, Copenhagen, Denmark, 8 September 2014**
Period: 8 Sep 2014
Amalie Ribel-Madsen (Participant)
Department of Systems Biology
Center for Biological Sequence Analysis

**Description**
Participant

**Related event**

**Novel Targets for Enhancing Functional Beta-Cell Mass, Copenhagen, Denmark, 8 September 2014**
08/09/2014 → 08/09/2014
Copenhagen, Denmark
Activity: Attending an event › Participating in or organising workshops, courses, seminars etc.

**Diabetes and Obesity in a Global Life Perspective, Copenhagen, Denmark, 4-5 September 2014**
Period: 4 Sep 2014 → 5 Sep 2014
Amalie Ribel-Madsen (Participant)
Department of Systems Biology
Center for Biological Sequence Analysis

**Description**
Participant

**Related event**

**Diabetes and Obesity in a Global Life Perspective, Copenhagen, Denmark, 4-5 September 2014**
04/09/2014 → 05/09/2014
Copenhagen, Denmark
Activity: Attending an event › Participating in or organising a conference

Amalie Ribel-Madsen (Participant)
Department of Systems Biology
Center for Biological Sequence Analysis

Description
Presenter of poster

Links:
http://www.issfal.org/conferences/2014-stockholm (ISSFAL 2014)

Related event

28/06/2014 → 02/07/2014
Stockholm, Sweden
Activity: Attending an event › Participating in or organising a conference

Early Nutritional Programming of Later Life Health Symposium, Utrecht, Netherlands, 15 May 2014
Period: 15 May 2014
Amalie Ribel-Madsen (Participant)
Center for Biological Sequence Analysis

Related event

Early Nutritional Programming of Later Life Health Symposium, Utrecht, Netherlands, 15 May 2014
15/05/2014 → 15/05/2014
Utrecht, Netherlands
Activity: Attending an event › Participating in or organising a conference

53rd Annual Meeting of Society of Toxicology and ToxExpo
Period: 24 Mar 2014 → 27 Mar 2014
Kristine Grønning Kongsbak (Participant)
Center for Biological Sequence Analysis
Integrative Systems Biology
National Food Institute
Division of Toxicology and Risk Assessment

Related event

53rd Annual Meeting of Society of Toxicology and ToxExpo
24/03/2014 → 27/03/2014
Phoenix, AZ, United States
Activity: Attending an event › Participating in or organising a conference

Amalie Ribel-Madsen (Speaker)
Department of Systems Biology
Center for Biological Sequence Analysis

Description
Presenter of poster

Links:
Related event

13/03/2014 → 15/03/2014
Munich, Germany
Activity: Talks and presentations › Conference presentations

Statistical Genetics
Period: 2 Sep 2013 → 10 Dec 2013
Anders Stockmarr (Lecturer)
Department of Applied Mathematics and Computer Science
Statistics and Data Analysis
Center for Biological Sequence Analysis

Description
13 week course.

Related event

Statistical Genetics
02/09/2013 → 10/12/2013
Lyngby, Denmark
Activity: Talks and presentations › Conference presentations

International School and Conference on Network Science
Period: 3 Jun 2013 → 7 Jun 2013
Janne Marie Laursen (Participant)
Department of Systems Biology
Center for Biological Sequence Analysis

Related event

International School and Conference on Network Science
03/06/2013 → 07/06/2013
Copenhagen, Denmark
Activity: Attending an event › Participating in or organising a conference

15th European Congress of Endocrinology 2013
Period: 26 Apr 2013 → 1 May 2013
Camilla Ingvorsen (Participant)
Department of Systems Biology
Center for Biological Sequence Analysis

Related event

15th European Congress of Endocrinology 2013
27/04/2013 → 01/05/2013
Copenhagen, Denmark
Activity: Attending an event › Participating in or organising a conference

Identification of a novel immunoregulatory signaling pathway exploited by M. tuberculosis in dendritic cells
Period: 15 Apr 2013
Janne Marie Laursen (Lecturer)
Department of Systems Biology
Center for Biological Sequence Analysis

**Related event**

**41st Scandinavian Society of Immunology Meeting**

14/04/2013 → 17/04/2013  
København, Denmark  
Activity: Talks and presentations › Conference presentations

**Abcam Symposium: Programming Obesity**

Period: 14 Apr 2013 → 16 Apr 2013  
Camilla Ingvorsen (Participant)  
Department of Systems Biology  
Center for Biological Sequence Analysis

**Related event**

**Abcam Symposium: Programming Obesity: Central and peripheral contributors**

14/04/2013 → 16/04/2013  
Cambridge, United Kingdom  
Activity: Attending an event › Participating in or organising a conference

**Joint Symposium of Centre for Fetal programming and Early Nutrition Consortium**

Period: 13 Mar 2013  
Camilla Ingvorsen (Participant)  
Department of Systems Biology  
Center for Biological Sequence Analysis

**Related event**

**Joint Symposium of Centre for Fetal programming and Early Nutrition Consortium: Fetal and childhood programming, Preventing type 2 generations in the next generation**

13/03/2013 → …  
Hellerup, Denmark  
Activity: Attending an event › Participating in or organising a conference

**Society of Toxicology**

Period: 10 Mar 2013 → 14 Mar 2013  
Kristine Grønning Kongsbak (Participant)  
Department of Systems Biology  
Center for Biological Sequence Analysis  
Integrative Systems Biology  
National Food Institute  
Division of Toxicology and Risk Assessment

**Description**

Præsentation af en videnskabelig poster med titlen "A Systems Chemical Biology Approach to Predict Effects From Chemical Cocktail Exposure"

**Society of Toxicology Annual Meeting 2013**

**Related event**

**Society of Toxicology: Annual Meeting 2013**

10/03/2013 → 14/03/2013  
San Antonio, Texas, United States  
Activity: Attending an event › Participating in or organising workshops, courses, seminars etc.
27th Nordic Lipid Symposium
Period: Jan 2013
Rikke Mette Guldhammer Bennike (Speaker)
Department of Systems Biology
Center for Biological Sequence Analysis
National Food Institute
Division of Food Microbiology

Related event
27th Nordic Lipid Symposium
17/06/2013 → 19/06/2013
Helsinki, Finland
Activity: Talks and presentations › Conference presentations

Symposium for Biotech Research
Period: 14 Nov 2012
Camilla Ingvorsen (Participant)
Department of Systems Biology
Center for Biological Sequence Analysis

Related event
Symposium for Biotech Research
13/11/2008 → …
Lyngby, Denmark
Activity: Attending an event › Participating in or organising a conference

7th Conference of the Hellenic Society for Computational Biology & Bioinformatics
Eirini Kouskoumvekaki (Speaker)
Department of Systems Biology
Center for Biological Sequence Analysis

Description
Disclosing the medicinal value of the vegetarian diet by global characterization of the plant metabolic space.

Related event
7th Conference of the Hellenic Society for Computational Biology & Bioinformatics
04/10/2012 → 06/10/2012
Heraklion, Greece
Activity: Talks and presentations › Conference presentations

Bliver vores krop programmeret til overvægt?
Period: 24 Sep 2012 → 28 Sep 2012
Camilla Ingvorsen (Lecturer)
Department of Systems Biology
Center for Biological Sequence Analysis

Related event
Naturvidenskabsfestival 2012
24/09/2012 → 28/09/2012
Denmark
Benzon Symposium No. 58 Adipose Tissue in Health and Disease
Camilla Ingvorsen (Participant)
Department of Systems Biology
Center for Biological Sequence Analysis

Related event

Benzon Symposium No. 58 Adipose Tissue in Health and Disease
27/08/2012 → 30/08/2012
Copenhagen, Denmark
Activity: Attending an event › Participating in or organising a conference

243rd ACS National Meeting
Eirini Kouskoumvekaki (Speaker)
Department of Systems Biology
Center for Biological Sequence Analysis

Description
Development of a human diet interactome map

Related event

243rd ACS National Meeting
25/03/2012 → 29/03/2012
San Diego, CA, United States
Activity: Talks and presentations › Conference presentations

Annual Plant Biotech Denmark Meeting 2012
Period: 2 Feb 2012 → 3 Feb 2012
Eirini Kouskoumvekaki (Invited speaker)
Department of Systems Biology
Center for Biological Sequence Analysis

Description
Use of Chemoinformatics for the Elucidation of Phytochemicals’ Role in Health and Disease

Related event

Annual Plant Biotech Denmark Meeting 2012
02/02/2012 → 03/02/2012
Copenhagen, Denmark
Activity: Talks and presentations › Conference presentations

Fetal programming of metabolic syndrome in rat offspring exposed to maternal overnutrition
Period: 23 Nov 2011
Camilla Ingvorsen (Lecturer)
Department of Systems Biology
Center for Biological Sequence Analysis

Related event

Academic Open Mic
23/11/2011 → …
Kgs. Lyngby, Denmark
Activity: Talks and presentations › Conference presentations

**Symposium for Biotech Research**
Period: 9 Nov 2011
Camilla Ingvorsen (Participant)
Department of Systems Biology
Center for Biological Sequence Analysis

**Related event**
**Symposium for Biotech Research**
13/11/2008 → …
Lyngby, Denmark
Activity: Attending an event › Participating in or organising a conference

**7th World Congress on Developmental Origins of Health and Disease**
Period: 18 Sep 2011 → 20 Sep 2011
Camilla Ingvorsen (Participant)
Department of Systems Biology
Center for Biological Sequence Analysis
Links:
http://www.dohad2011.org/

**Related event**
**7th World Congress on Developmental Origins of Health and Disease**
18/09/2011 → 21/09/2011
Portland, OR, United States
Activity: Attending an event › Participating in or organising a conference

**Programmering af metabolisk syndrom i fosterlivet**
Period: 28 Apr 2011
Camilla Ingvorsen (Speaker)
Department of Systems Biology
Center for Biological Sequence Analysis
Links:
http://www.midi.dtu.dk/Nyheder/Nyt_fra_Institutterne.aspx?guid={09E4D9DF-817C-424B-9BA2-799EF689188D} (Link to presentation.)

**Related event**
**Forskningens Døgn 2011**
28/04/2011 → …
København, Denmark
Activity: Talks and presentations › Conference presentations

**Editor for British Journal of Nutrition (External organisation)**
Period: 1 Jan 2011 → 31 Jan 2012
Susanne Brix Pedersen (Participant)
Department of Systems Biology
Center for Biological Sequence Analysis

**Description**
Body type: Journal
Degree of recognition: International
Related external organisation

**Editor for British Journal of Nutrition**
Activity: Membership › Membership in review committee

**En spændende dag på DTU: DNT i tid & rum samt Planck projektet - evigt som pyramidene**
Period: 17 Nov 2010
Rasmus Wernersson (Speaker)
Department of Systems Biology
Center for Biological Sequence Analysis

Description
Place: Bioteket. Bygn. nr. 221. lok. 021
Documents:
InvitationNov2010MEver3.JPG

Related external organisation

**Unknown external organisation**
Activity: Talks and presentations › Conference presentations

**The role of endotoxemia in adipose tissue inflammation**
Period: 5 Nov 2010
Camilla Ingvorsen (Speaker)
Department of Systems Biology
Center for Biological Sequence Analysis

Related event

**DanORC Young Investigators network**
05/11/2010 → …
Copenhagen, Denmark
Activity: Talks and presentations › Conference presentations

18th European Symposium on Quantitative Structure-Activity Relationships
Period: 19 Sep 2010 → 24 Sep 2010
Eirini Kouskoumvekaki (Speaker)
Department of Systems Biology
Center for Biological Sequence Analysis

Description
Back to the roots – Benefits and limitations concerning the in silico integration of natural products in drug discovery

Related event

**18th European Symposium on Quantitative Structure-Activity Relationships**
19/09/2010 → 24/09/2010
Rhodes, Greece
Activity: Talks and presentations › Conference presentations

4th Danish Conference on Biotechnology and Molecular Biology
Eirini Kouskoumvekaki (Invited speaker)
Department of Systems Biology
Center for Biological Sequence Analysis

Description
Related event

4th Danish Conference on Biotechnology and Molecular Biology
28/05/2009 → 29/05/2009
Vejle, Denmark
Activity: Talks and presentations › Conference presentations

International Drug Discovery Science and Technology
Eirini Kouskoumvekaki (Speaker)
Department of Systems Biology
Center for Biological Sequence Analysis

Description
Mapping the Chemogenomics Space of Natural Compounds

Related event

International Drug Discovery Science and Technology
18/10/2008 → 22/10/2008
Beijing, China
Activity: Talks and presentations › Conference presentations

EUROFUNG Meeting
Period: 2 Apr 2008 → 3 Apr 2008
Eirini Kouskoumvekaki (Invited speaker)
Department of Systems Biology
Center for Biological Sequence Analysis

Description
Exploitation of Metabolite Profiling for Genotyping Aspergilli

Related event

EUROFUNG Meeting 2008
02/04/2008 → 03/04/2008
Edinburgh, United Kingdom
Activity: Talks and presentations › Conference presentations

1st Annual Symposium for Biotechnological Research
Period: 8 Nov 2007
Eirini Kouskoumvekaki (Invited speaker)
Department of Systems Biology
Center for Biological Sequence Analysis

Description
Similarity Analysis of Human Nuclear Receptors based on Ligand-binding Information'

Related event

1st Annual Symposium for Biotechnological Research
08/11/2007 → …
Kgs. Lyngby, Denmark
Activity: Talks and presentations › Conference presentations

4th International Symposium on Computational Methods in Toxicology and Pharmacology Integrating Internet Resources
Period: 1 Sep 2007 → 5 Sep 2007
Eirini Kouskoumvekaki (Speaker)
Department of Systems Biology
Center for Biological Sequence Analysis

Description
Prediction of pH-dependent Aqueous Solubility of Drug-like molecules and Drug Candidates with Chemoinformatics Tools

Related event

4th International Symposium on Computational Methods in Toxicology and Pharmacology Integrating Internet Resources
01/09/2007 → 05/09/2007
Moscow, Russian Federation
Activity: Talks and presentations › Conference presentations

Prizes:

IUSS VIC Keystone rejse legat
Simon Welner (Recipient)
National Veterinary Institute, Center for Biological Sequence Analysis, Section for Immunology and Vaccinology, Section for Virology

Description
Fondsmidler til at hjælpe PhD/DVM studerende med at deltage i Keystone symposiet ad 20.-25.01.2015: "Immunity to veterinary pathogens: Informing vaccine development"

Modtog et legat på 1000 USD. Dog skal jeg betale nogle af pengene tilbage, da jeg også modtog et andet legat udbudt af Keystone, så jeg i alt har modtaget flere penge end mine rejsemidler er budgetteret til.

Details
Awarded date: 20 Jan 2015
Granting Organisations: IUSS VIC: International Union of Immunological Societies - Veterinary Immunology Committee
Prize: Prizes, scholarships, distinctions

Keystone symposia future of science fund scholarship
Simon Welner (Recipient)
National Veterinary Institute, Center for Biological Sequence Analysis, Section for Immunology and Vaccinology, Section for Virology

Description
Fik bevilget 1200 USD

Details
Awarded date: 20 Jan 2015
Prize: Prizes, scholarships, distinctions

Press clippings:

Bedre smittesporing med supercomputer
Emma Elisabeth Hagberg
17/09/2016

Subject
gener og genoer; husdyrsgdomme; produktionsdyr; dataanalyse
Molecular Evolution, Department of Bio and Health Informatics, Disease Intelligence and Molecular Evolution

Media contribution (1)

Bedre smittesporing med supercomputer
17/09/2016
Dynamo, Print
Julie Iben Schmidt
The birth season influences your unborn child's immune response
Susanne Brix Pedersen
12/11/2015
Department of Systems Biology, Center for Biological Sequence Analysis

Media contribution (1)

The birth season influences your unborn child's immune response
12/11/2015
Politiken, Print
Susanne Brix Pedersen
Department of Systems Biology, Center for Biological Sequence Analysis
Press / Media

Mendelian Randomization studies: The use of a new study type to deduce causality in humans
Lasse Westergaard Folkersen
20/10/2015
Department of Systems Biology, Center for Biological Sequence Analysis, Integrative Systems Biology

Media contribution (1)

Mendelian Randomization studies: The use of a new study type to deduce causality in humans
20/10/2015
Videnskab.dk, Print
Jonas Salomonsen
http://videnskab.dk/krop-sundhed/mendelsk-randomisering-ny-metode-er-forskernes-vises-sten
Lasse Westergaard Folkersen
Department of Systems Biology, Center for Biological Sequence Analysis, Integrative Systems Biology
Press / Media

Mendelian Randomization and Alcohol
Lasse Westergaard Folkersen
19/10/2015

Description
Interview about Mendelian Randomization and Alcohol

Subject
http://www.dr.dk/radio/ondemand/p1-radioavis/radioavisen-2015-10-19-12-00-2#!/
Department of Systems Biology, Center for Biological Sequence Analysis, Integrative Systems Biology

Media contribution (1)

Mendelian Randomization and Alcohol
19/10/2015
DR1, Radio
5 minutes
http://www.dr.dk/radio/ondemand/p1-radioavis/radioavisen-2015-10-19-12-00-2#!/
Lasse Westergaard Folkersen
Department of Systems Biology, Center for Biological Sequence Analysis, Integrative Systems Biology
Press / Media

Large study investigates the beneficial effect of alcohol, by using genetics
Lasse Westergaard Folkersen
19/10/2015
Department of Systems Biology, Center for Biological Sequence Analysis, Integrative Systems Biology

Media contribution (1)

Large study investigates the beneficial effect of alcohol, by using genetics
19/10/2015
Videnskab.dk, Print
Jonas Salomonsen
http://videnskab.dk/krop-sundhed/kaempestudie-sar-tvivl-om-alkohols-gavnlige-virkning
Lasse Westergaard Folkersen
Department of Systems Biology, Center for Biological Sequence Analysis, Integrative Systems Biology
Press / Media

Dit immunforsvar slapper af om sommeren
Susanne Brix Pedersen
13/05/2015
Department of Systems Biology, Center for Biological Sequence Analysis

Media contribution (1)

Dit immunforsvar slapper af om sommeren
13/05/2015
P4 København, Radio
http://www.dr.dk/radio/ondemand/p4kbh/p4-ettermiddag-2015-05-13#!
Susanne Brix Pedersen
Department of Systems Biology, Center for Biological Sequence Analysis
Press / Media

Dit immunforsvar slapper af om sommeren
Susanne Brix Pedersen
12/05/2015
Department of Systems Biology, Center for Biological Sequence Analysis

Media contribution (1)

Forsøg med ny online eksamensform i "Introduktion til Bioinformatik"
Rasmus Wernersson
01/11/2007
Description
English summary: short article to the internal DTU newspaper detailing my experience with the new online exam, I have introduced to the "Introduction to Bioinformatics" course.
Subject
Undervisning
Department of Systems Biology, Center for Biological Sequence Analysis

Media contribution (1)

Forsøg med ny online eksamensform i "Introduktion til Bioinformatik"
01/11/2007
DTU Avisen, Print
Rasmus Wernersson
Department of Systems Biology, Center for Biological Sequence Analysis

Relations
Research outputs:
Forsøg med ny online eksamensform i "Introduktion til Bioinformatik".
Press / Media