Department of Bio and Health Informatics - DTU Orbit (10/06/2018)

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Organisation profile
Head of Department: Professor Haja Kadarmideen
The department carries out research within bio and health informatics and develops computational methods and machine learning systems as well as systems for artificial intelligence (AI) which uses biological understanding and other scientific background information to expand the biological knowledge and create tools for tomorrow's biotech industry and the health sector. The department is based around the national supercomputer Computerome-a key tool for generating and analysing big data for the department's researchers and partners in Denmark and abroad.
Organisational unit: Department

Publications:
Corrigendum: An analysis of natural T cell responses to predicted tumor neoepitopes [Front Immunol, 8, 1566, (2017)]
An outdated version of Supplementary Table 1 was uploaded to the final version of the paper for publication. This table has not been under peer review and does not include the information described in the paper such as the similarity measurement column. The correct Supplementary Table 1 has now been published in the original article. The authors apologize for this oversight. This error does not change the scientific conclusion of the article in any way. The original article has been updated.

General information
State: Published
Organisations: Department of Bio and Health Informatics, Cancer Genomics, Immunoinformatics and Machine Learning, Technical University of Denmark, National Veterinary Institute, T-cells & Cancer, Universidad Nacional de San Martin
Authors: Bjerregaard, A. M. (Intern), Nielsen, M. (Intern), Jurtz, V. (Intern), Barra, C. M. (Ekstern), Hadrup, S. R. (Intern), Szallasi, Z. (Intern), Eklund, A. C. (Intern)
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BFI (2018): BFI-level 1
Direct acting antiviral treatment of chronic hepatitis C in Denmark: factors associated with and barriers to treatment initiation

Objectives: We describe factors associated with and barriers to initiation of Direct Acting Antiviral (DAA) treatment in patients with chronic hepatitis C, who fulfill national fibrosis treatment guidelines in Denmark. Materials and Methods: In this nationwide cohort study, we included patients with chronic hepatitis C from The Danish Database for Hepatitis B and C (DANHEP) who fulfilled fibrosis treatment criteria. Factors associated with treatment initiation and treatment failure were determined by logistic regression analyses. Medical records were reviewed from patients who fulfilled fibrosis treatment criteria, but did not initiate DAA treatment to determine the cause. Results: In 344 (49%) of 700 patients, who fulfilled treatment criteria, factors associated with DAA treatment initiation were transmission by other routes than injecting drug use odds ratio (OR) 2.13 (CI: 1.38–3.28), previous treatment failure OR 2.58 (CI: 1.84–3.61) and ALT above upper limit of normal OR 1.60 (CI: 1.18–2.17). The most frequent reasons for not starting treatment among 356 (51%) patients were non-adherence to medical appointments (n=107/30%) and ongoing substance use (n=61/17%). Treatment failure with viral relapse occurred in 19 (5.5%) patients, who were more likely to have failed previous treatment OR 4.53 (CI: 1.59–12.91). Conclusions: In this nationwide cohort study, we found non-adherence to medical appointments and active substance use to be major obstacles for DAA treatment initiation. Our findings highlight the need for interventions that can overcome these barriers and increase the number of patients who can initiate and benefit from curative DAA treatment.
Direct whole-genome sequencing of *Plasmodium falciparum* specimens from dried erythrocyte spots

**Background:** *Plasmodium falciparum* malaria remains a major health burden and genomic research represents one of the necessary approaches for continued progress towards malaria control and elimination. Sample acquisition for this purpose is troublesome, with the majority of malaria-infected individuals living in rural areas, away from main infrastructure and the electrical grid. The aim of this study was to describe a low-tech procedure to sample *P. falciparum* specimens for direct whole-genome sequencing.
whole genome sequencing (WGS), without use of electricity and cold-chain. Methods: Venous blood samples were collected from malaria patients in Bandim, Guinea-Bissau and leukocyte-depleted using Plasmodipur filters, the enriched parasite sample was spotted on Whatman paper and dried. The samples were stored at ambient temperatures and subsequently used for DNA-extraction. Ratios of parasite:human content of the extracted DNA was assessed by qPCR, and five samples with varying parasitaemia, were sequenced. Sequencing data were used to analyse the sample content, as well as sample coverage and depth as compared to the 3d7 reference genome. Results: qPCR revealed that 73% of the 199 samples were applicable for WGS, as defined by a minimum ratio of parasite:human DNA of 2:1. WGS revealed an even distribution of sequence data across the 3d7 reference genome, regardless of parasitaemia. The acquired read depths varied from 16 to 99×, and coverage varied from 87.5 to 98.9% of the 3d7 reference genome. SNP-analysis of six genes, for which amplicon sequencing has been performed previously, confirmed the reliability of the WGS-data.

Conclusion: This study describes a simple filter paper based protocol for sampling P. falciparum from malaria patients for subsequent direct WGS, enabling acquisition of samples in remote settings with no access to electricity.

**General information**

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Organisations: Department of Bio and Health Informatics, National Food Institute, Research Group for Genomic Epidemiology, Genomic Epidemiology, University of Copenhagen, University of Southern Denmark, Bandim Health Project, Karolinska Institutet
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Web of Science (2017): Indexed Yes
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Scopus rating (2016): CiteScore 2.89 SJR 1.866 SNIP 1.127
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.087 SNIP 1.16 CiteScore 3.09
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.084 SNIP 1.32 CiteScore 3.07
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 2.18 SNIP 1.294 CiteScore 3.56
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.902 SNIP 1.33 CiteScore 3.61
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.775 SNIP 1.297 CiteScore 3.56
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.838 SNIP 1.259
Web of Science (2010): Indexed yes
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BFI (2008): BFI-level 2
Scopus rating (2008): SJR 1.394 SNIP 1.122
Prevalence and risk factors for CTX-M gram-negative bacteria in hospitalized patients at a tertiary care hospital in Kilimanjaro, Tanzania

Emergence and spread of extended spectrum beta-lactamase (ESBL)-producing gram-negative bacteria, mainly due to CTX-M, is a major global public health problem. Patients infected with ESBL-producing gram-negative bacteria have an increased risk of treatment failure and death. We investigated the prevalence and risk factors for CTX-M gram-negative bacteria isolated from clinical specimens of patients hospitalized at a tertiary care hospital in Kilimanjaro, Tanzania. Isolated gram-negative bacteria from inpatients admitted at Kilimanjaro Christian Medical Centre (KCMC) between August 2013 and August 2015 were fully genome sequenced. The prevalence of ESBL-producing gram-negative bacteria was determined based on the presence of blaCTX-M. The odds ratio (OR) and risk factors for ESBL-producing gram-negative bacteria due to CTX-M were assessed using logistic regression models. The overall CTX-M prevalence (95% CI) was 13.6% (10.1–18.1). Adjusted for other factors, the OR of CTX-M gram-negative bacteria for patients previously hospitalized was 0.26 (0.08–0.88), p = 0.031; the OR for patients currently on antibiotics was 4.02 (1.29–12.58), p = 0.017; the OR for patients currently on ceftriaxone was 0.14 (0.04–0.46), p = 0.001; and the OR for patients with wound infections was 0.24 (0.09–0.61), p = 0.003. The prevalence of ESBL-producing gram-negative bacteria due to CTX-M in this setting is relatively low compared to other previous reports in similar settings. However, to properly stop further spread in the hospital, we recommend setting up a hospital surveillance system that takes full advantage of the available next-generation sequencing facility to routinely screen for all types of bacterial resistance genes.

General information
State: Published
Organisations: Department of Bio and Health Informatics, Genomic Epidemiology, National Food Institute, Research Group for Genomic Epidemiology, Kilimanjaro Christian Medical Centre, Kilimanjaro Christian Medical University College, University of Copenhagen, East African Health Research Commission
Authors: Sonda, T. (Ekstern), Kumburu, H. (Ekstern), van Zwetselaar, M. (Ekstern), Alifrangis, M. (Ekstern), Mmbaga, B. T. (Ekstern), Lund, O. (Intern), Møller Aarestrup, F. (Intern), Kibiki, G. (Ekstern)
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Scopus rating (2017): SNIP 1.179 SJR 1.312
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BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.81 SJR 1.331 SNIP 1.134
Web of Science (2016): Indexed yes
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Accelerated collagen turnover in women with angina pectoris without obstructive coronary artery disease: An iPOWER substudy

Aim: Collagens are major cardiac extracellular matrix components, known to be actively remodelled and accumulated during diffuse myocardial fibrosis. We evaluated whether accelerated collagen turnover described by neo-epitope biomarkers reflecting collagen formation and degradation separates patients with diffuse myocardial fibrosis from asymptomatic controls.

Methods and results: Seventy-one women with angina pectoris without significant coronary artery disease assessed by invasive coronary angiogram were included. Competitive enzyme-linked immunosorbent assays (ELISAs) measuring circulating protein fragments in serum assessed the formation and degradation of collagen type III (Pro-C3, C3M and C3C), IV (P4NP7S and C4M), V (Pro-C5 and C5M) and VI (Pro-C6 and C6M), and degradation of collagen type I (C1M). Serum samples from 32 age-matched asymptomatic women were included as controls. Symptomatic women presented significantly elevated levels of Pro-C6, C3M, C4M and C6M (p<0.0001–0.0058) and significantly decreased levels of Pro-C3, C5M and C6M (p<0.0001–0.041), reflecting accelerated collagen turnover and an imbalanced collagen formation and degradation compared to controls. Cardiac magnetic resonance T1 mapping was performed to determine extracellular volume fraction and thus diffuse myocardial fibrosis. A significant association was identified between C5M and extracellular volume fraction by cardiac magnetic resonance (p=0.01).

Conclusion: Women with angina pectoris, but without significant obstructive coronary artery disease, showed an imbalanced collagen turnover compared to asymptomatic controls. The examined biomarkers are tools to monitor active collagen remodelling in patients with angina pectoris, in risk of developing myocardial fibrosis.
Across academia and industry, text mining has become a popular strategy for keeping up with the rapid growth of the scientific literature. Text mining of the scientific literature has mostly been carried out on collections of abstracts, due to their availability. Here we present an analysis of 15 million English scientific full-text articles published during the period...
1823-2016. We describe the development in article length and publication sub-topics during these nearly 250 years. We showcase the potential of text mining by extracting published protein-protein, disease-gene, and protein subcellular associations using a named entity recognition system, and quantitatively report on their accuracy using gold standard benchmark data sets. We subsequently compare the findings to corresponding results obtained on 16.5 million abstracts included in MEDLINE and show that text mining of full-text articles consistently outperforms using abstracts only.

**General information**

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Organisations: Center for Biological Sequence Analysis, Department of Biotechnology and Biomedicine, Office for Innovation & Sector Services, Technical Information Center of Denmark, Department of Bio and Health Informatics, Integrative Systems Biology, Technical University of Denmark
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Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 4.41 SJR 3.243 SNIP 1.363
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 3.476 SNIP 1.442 CiteScore 4.69
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 3.412 SNIP 1.442 CiteScore 4.74
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 3.467 SNIP 1.483 CiteScore 4.91
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
Scopus rating (2012): SJR 3.523 SNIP 1.645 CiteScore 5.36
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
Scopus rating (2011): SJR 3.613 SNIP 1.591 CiteScore 5.25
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
Scopus rating (2010): SJR 3.709 SNIP 1.555
Web of Science (2010): Indexed yes
Scopus rating (2009): SJR 3.428 SNIP 1.428
Web of Science (2009): Indexed yes
Scopus rating (2008): SJR 4.045 SNIP 1.397
Web of Science (2008): Indexed yes
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Scopus rating (2006): SJR 2.419 SNIP 1.082
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Age-related collagen turnover of the interstitial matrix and basement membrane: Implications of age- and sex-dependent remodeling of the extracellular matrix

The extracellular matrix (ECM) plays a vital role in maintaining normal tissue function. Collagens are major components of the ECM and there is a tight equilibrium between degradation and formation of these proteins ensuring tissue health and homeostasis. As a consequence of tissue turnover, small collagen fragments are released into the circulation, which act as important biomarkers in the study of certain tissue-related remodeling factors in health and disease. The aim of this study was to establish an age-related collagen turnover profile of the main collagens of the interstitial matrix (type I and III collagen) and basement membrane (type IV collagen) in healthy men and women. By using well-characterized competitive ELISA-assays, we assessed specific fragments of degraded (C1M, C3M, C4M) and formed (PINP, Pro-C3, P4NP7S) type I, III and IV collagen in serum from 617 healthy men and women ranging in ages from 22 to 86. Subjects were divided into 5-year age groups according to their sex and age. Groups were compared using Kruskal-Wallis adjusted for Dunn’s multiple comparisons test and Mann-Whitney t-test. Age-specific changes in collagen turnover was most profound for type I collagen. PINP levels decreased in men with advancing age, whereas in women, the level decreased in early adulthood followed by an increase around the age of menopause (age 40-60). Sex-specific changes in type I, III and IV collagen turnover was present at the age around menopause (age 40-60) with women having an increased turnover. In summary, collagen turnover is affected by age and sex with the interstitial matrix and the basement membrane being differently regulated. The observed changes needs to be accounted for when measuring ECM related biomarkers in clinical studies.

General information
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Organisations: Department of Biotechnology and Biomedicine, Disease Systems Immunology, Department of Bio and Health Informatics, Nordic Bioscience A/S, Charité-Universitätsmedizin Berlin
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Web of Science (2017): Indexed yes
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Scopus rating (2016): CiteScore 3.11 SJR 1.236 SNIP 1.101
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.427 SNIP 1.136 CiteScore 3.32
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.559 SNIP 1.148 CiteScore 3.54
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Scopus rating (2013): SJR 1.772 SNIP 1.153 CiteScore 3.94
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An adult-based insulin resistance genetic risk score associates with insulin resistance, metabolic traits and altered fat distribution in Danish children and adolescents who are overweight or obese

A genetic risk score (GRS) consisting of 53 insulin resistance variants (GRS53) was recently demonstrated to associate with insulin resistance in adults. We speculated that the GRS53 might already associate with insulin resistance during childhood, and we therefore aimed to investigate this in populations of Danish children and adolescents. Furthermore, we aimed to address whether the GRS associates with components of the metabolic syndrome and altered body composition in children and adolescents. We examined a total of 689 children and adolescents who were overweight or obese and 675 children and adolescents from a population-based study. Anthropometric data, dual-energy x-ray absorptiometry scans, BP, fasting plasma glucose, fasting serum insulin and fasting plasma lipid measurements were obtained, and HOMA-IR was calculated. The GRS53 was examined for association with metabolic traits in children by linear regressions using an additive genetic model. In overweight/obese children and adolescents, the GRS53 associated with higher HOMA-IR (β = 0.109 ± 0.050 (SE); p = 2.73 × 10^{-2}), fasting plasma glucose (β = 0.010 ± 0.005 mmol/l; p = 2.51 × 10^{-2}) and systolic BP SD score (β = 0.026 ± 0.012; p = 3.32 × 10^{-2}) as well as lower HDL-cholesterol (β = -0.008 ± 0.003 mmol/l; p = 1.23 × 10^{-3}), total fat-mass percentage (β = -0.143 ± 0.054%; p = 9.15 × 10^{-3}) and fat-mass percentage in the legs (β = -0.197 ± 0.055%; p = 4.09 × 10^{-4}). In the population-based sample of children, the GRS53 only associated with lower HDL-cholesterol concentrations (β = -0.007 ± 0.003 mmol/l; p = 1.79 × 10^{-2}). An adult-based GRS comprising 53 insulin resistance susceptibility SNPs associates with insulin resistance, markers of the metabolic syndrome and altered fat distribution in a sample of Danish children and adolescents who were overweight or obese.

General information
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Organisations: Department of Bio and Health Informatics, Steno Diabetes Centre, University of Copenhagen
Authors: Graae, A. (Ekstern), Hollensted, M. (Ekstern), Kloppenborg, J. T. (Ekstern), Mahendran, Y. (Ekstern), Schnurr, T. M. (Ekstern), Appel, E. V. R. (Ekstern), Rask, J. (Ekstern), Nielsen, T. R. H. (Ekstern), Johansen, M. Ø. (Ekstern), Linneberg, A. (Ekstern), Jørgensen, M. E. (Ekstern), Granup, N. (Ekstern), Kadarmideen, H. N. (Intern), Holst, B. (Ekstern), Pedersen, O. (Ekstern), Holm, J. (Ekstern), Hansen, T. (Ekstern)
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Colorectal cancer (CRC) is a leading cause of death worldwide. Surgical intervention is a successful treatment for stage I patients, whereas other more advanced cases may require adjuvant chemotherapy. The selection of effective adjuvant treatments remains, however, challenging. Accurate patient stratification is necessary for the identification of the subset of patients likely responding to treatment, while sparing others from pernicious treatment. Targeted sequencing approaches may help in this regard, enabling rapid genetic investigation, and at the same time easily applicable in routine diagnosis.

We propose a set of guidelines for the identification, including variant calling and filtering, of somatic mutations driving tumorigenesis in the absence of matched healthy tissue. We also discuss the inclusion criteria for the generation of our gene panel. Furthermore, we evaluate the prognostic impact of individual genes, using Cox regression models in the context of overall survival and disease-free survival. These analyses confirmed the role of commonly used biomarkers, and shed light on controversial genes such as CYP2C8.

Applying those guidelines, we created a novel gene panel to investigate the onset and progression of CRC in 273 patients. Our comprehensive biomarker set includes 266 genes that may play a role in the progression through the different stages of the disease. Tracing the developmental state of the tumour, and its resistances, is instrumental in patient stratification and reliable decision making in precision clinical practice.

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Scopus rating (2015): SJR 2.26 SNIP 1.116 CiteScore 4.91
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.551 SNIP 1.285 CiteScore 4.96
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 3.061 SNIP 1.261 CiteScore 5.26
ISI indexed (2013): ISI indexed yes
Scopus rating (2012): SJR 2.512 SNIP 1.065 CiteScore 6.54
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Ancient hepatitis B viruses from the Bronze Age to the Medieval period

Hepatitis B virus (HBV) is a major cause of human hepatitis. There is considerable uncertainty about the timescale of its evolution and its association with humans. Here we present 12 full or partial ancient HBV genomes that are between approximately 0.8 and 4.5 thousand years old. The ancient sequences group either within or in a sister relationship with extant human or other ape HBV clades. Generally, the genome properties follow those of modern HBV. The root of the HBV tree is projected to between 8.6 and 20.9 thousand years ago, and we estimate a substitution rate of 8.04 \times 10^{-6} to 1.51 \times 10^{-5} nucleotide substitutions per site per year. In several cases, the geographical locations of the ancient genotypes do not match present-day distributions. Genotypes that today are typical of Africa and Asia, and a subgenotype from India, are shown to have an early Eurasian presence. The geographical and temporal patterns that we observe in ancient and modern HBV genotypes are compatible with well-documented human migrations during the Bronze and Iron Ages. We provide evidence for the creation of HBV genotype A via recombination, and for a long-term association of modern HBV genotypes with humans, including the discovery of a human genotype that is now extinct. These data expose a complexity of HBV evolution that is not evident when considering modern sequences alone.
Ancient pathogen DNA in human teeth and petrous bones

Recent ancient DNA (aDNA) studies of human pathogens have provided invaluable insights into their evolutionary history and prevalence in space and time. Most of these studies were based on DNA extracted from teeth or postcranial bones. In contrast, no pathogen DNA has been reported from the petrous bone which has become the most desired skeletal element in ancient DNA research due to its high endogenous DNA content. To compare the potential for pathogenic aDNA retrieval from teeth and petrous bones, we sampled these elements from five ancient skeletons, previously shown to be carrying Yersinia pestis. Based on shotgun sequencing data, four of these five plague victims showed clearly detectable levels of Y.pestis DNA in the teeth, whereas all the petrous bones failed to produce Y.pestis DNA above baseline levels. A broader comparative metagenomic analysis of teeth and petrous bones from 10 historical skeletons corroborated these results, showing a much higher microbial diversity in teeth than petrous bones, including pathogenic and oral microbial taxa. Our results imply that although petrous bones are highly valuable for ancient genomic analyses as an excellent source of endogenous DNA, the metagenomic potential of these dense skeletal elements is highly limited. This trade-off must be considered when designing the sampling strategy for an aDNA project.

General information

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Organisations: Department of Bio and Health Informatics, Metagenomics, University of Copenhagen, Peter the Great Museum of Anthropology and Ethnography, Samara State University, South Ural State University, National Academy of Sciences of the Republic of Armenia, Tallinn University, University of Tartu
Authors: Margaryan, A. (Ekstern), Hansen, H. B. (Ekstern), Rasmussen, S. (Intern), Sikora, M. (Ekstern), Moiseyev, V. (Ekstern), Khoklov, A. (Ekstern), Epimakhov, A. (Ekstern), Yepiskoposyan, L. (Ekstern), Kriska, A. (Ekstern), Varul, L. (Ekstern), Saag, L. (Ekstern), Lynnerup, N. (Ekstern), Willerslev, E. (Ekstern), Allentoft, M. E. (Ekstern)
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Antibodies to ICAM1-binding PfEMP1-DBLβ are biomarkers of protective immunity to malaria in a cohort of young children from Papua New Guinea

*Plasmodium falciparum* Erythrocyte Membrane Protein 1 (PfEMP1) mediates parasite sequestration to the cerebral microvasculature via binding of DBLβ domains to Intercellular Adhesion Molecule 1 (ICAM1) and is associated with severe cerebral malaria. In a cohort of 187 young children from Papua New Guinea (PNG), we examined baseline antibody levels to the ICAM1-binding PfEMP1 domain, DBLβ3PF11_0521, in comparison to four control antigens including NTS-DBLα and CIDR1 domains from another group A variant and a group B/C variant. Antibody levels for the group A antigens were strongly associated with age and exposure. Antibody responses to DBLβ3PF11_0521 were associated with a 37% reduced risk of high-density clinical malaria in the follow up period (adjusted incidence risk ratio, aIRR = 0.63 [95% CI: 0.45–0.88; p = 0.007]) and a 25% reduction in risk of low-density clinical malaria (aIRR = 0.75 [95% CI: 0.55–1.01; p = 0.06]), whilst there was no such association for other variants. Children who experienced severe malaria also had significantly lower antibody levels to DBLβ3PF11_0521 and the other group A domains than other children. Furthermore, a subset of PNG DBLβ sequences had ICAM1-binding motifs, formed a distinct phylogenetic cluster and were similar to sequences from other endemic areas. PfEMP1 variants associated with these DBLβ were enriched for DC4 and DC13 head-structures implicated in EPCR-binding and severe malaria, suggesting conservation of dual binding specificity.

These results provide further support for the development of specific classes of PfEMP1 as vaccine candidates, and as biomarkers for protective immunity against clinical *P. falciparum* malaria.
Bioinformatics Tools for the Prediction of T-Cell Epitopes

T-cell responses are activated by specific peptides, called epitopes, presented on the cell surface by MHC molecules. Binding of peptides to the MHC is the most selective step in T-cell antigen presentation and therefore an essential factor in the selection of potential epitopes. Several in-vitro methods have been developed for the determination of peptide binding to MHC molecules, but these are all costly and time-consuming. In consequence, significant effort has been dedicated to the development of in-silico methods to model this event. Here, we describe two such tools, NetMHCcons and NetMHCIIpan, for the prediction of peptide binding to MHC class I and class II molecules, respectively, involved in the activation pathways of CD8+ and CD4+ T cells.

Biosynthesis of bioactive diterpenoids in the medicinal plant Vitex agnus-castus

Vitex agnus-castus L. (Lamiaceae) is a medicinal plant historically used throughout the Mediterranean region to treat menstrual cycle disorders and is still used today as a clinically effective treatment for premenstrual syndrome. The pharmaceutical activity of the plant extract is linked to its ability to lower prolactin levels. This feature has been attributed to the presence of dopaminergic diterpenoids that can bind to dopamine receptors in the pituitary gland. Phytochemical analyses of V. agnus-castus show that it contains an enormous array of structurally related diterpenoids and, as such holds potential as a rich source of new dopaminergic drugs. The present work investigated the localisation and biosynthesis of diterpenoids in V. agnus-castus. With the assistance of matrix assisted laser desorption ionization-mass spectrometry imaging (MALDI-MSI), diterpenoids were localised to trichomes on the surface of fruit and leaves. Analysis of a trichome-specific transcriptome database, coupled with expression studies, identified seven candidate genes involved in diterpenoid biosynthesis: three class II diterpene synthases (diTPSs), three class I diTPSs, and a cytochrome P450 (CYP). Combinatorial assays of the diTPSs resulted in the formation of a range of different diterpenes that can account for
several of the backbones of bioactive diterpenoids observed in V. agnus-castus. The identified CYP, VacCYP76BK1, was found to catalyse 16-hydroxylation of the diol-diterpene, peregrinol, to labd-13Z-ene-9,15,16-triol when expressed in Saccharomyces cerevisiae. Notably, this product is a potential intermediate in the biosynthetic pathway towards bioactive furan and lactone containing diterpenoids that are present in this species.

**General information**

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Organisations: Department of Bio and Health Informatics, Metagenomics, University of Copenhagen, University of Melbourne, Evolva Biotech A/S
Authors: Heskes, A. M. (Ekstern), Sundram, T. C. M. (Ekstern), Boughton, B. A. (Ekstern), Jensen, N. B. (Ekstern), Hansen, N. L. (Ekstern), Crocoll, C. (Ekstern), Cozzi, F. (Ekstern), Rasmussen, S. (Intern), Hamberger, B. (Ekstern), Hamberger, B. (Ekstern), Stærk, D. (Ekstern), Møller, B. L. (Ekstern), Pateraki, I. (Ekstern)
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- BFI (2018): BFI-level 2
- Web of Science (2018): Indexed yes
- BFI (2017): BFI-level 2
- Scopus rating (2017): SNIP 1.669 SJR 3.582
- Web of Science (2017): Indexed yes
- BFI (2016): BFI-level 2
- Scopus rating (2016): CiteScore 5.93 SJR 3.462 SNIP 1.467
- BFI (2015): BFI-level 2
- Scopus rating (2015): SJR 3.421 SNIP 1.488 CiteScore 5.94
- BFI (2014): BFI-level 2
- Scopus rating (2014): SJR 3.834 SNIP 1.657 CiteScore 6.42
- Web of Science (2014): Indexed yes
- BFI (2013): BFI-level 2
- Scopus rating (2013): SJR 4.426 SNIP 1.829 CiteScore 7.45
- ISI indexed (2013): ISI indexed yes
- Web of Science (2013): Indexed yes
- BFI (2012): BFI-level 2
- Scopus rating (2012): SJR 4.385 SNIP 1.684 CiteScore 6.69
- ISI indexed (2012): ISI indexed yes
- BFI (2011): BFI-level 2
- Scopus rating (2011): SJR 4.436 SNIP 1.689 CiteScore 6.71
- ISI indexed (2011): ISI indexed yes
- BFI (2010): BFI-level 2
- Scopus rating (2010): SJR 4.55 SNIP 1.727
- Web of Science (2010): Indexed yes
- BFI (2009): BFI-level 2
- Scopus rating (2009): SJR 5.012 SNIP 1.746
- BFI (2008): BFI-level 1
- Scopus rating (2008): SJR 4.738 SNIP 1.494
- Web of Science (2008): Indexed yes
- Scopus rating (2007): SJR 5.32 SNIP 1.679
- Web of Science (2007): Indexed yes
- Scopus rating (2006): SJR 4.68 SNIP 1.572
- Scopus rating (2005): SJR 4.31 SNIP 1.648
- Web of Science (2005): Indexed yes
- Scopus rating (2004): SJR 4.121 SNIP 1.541
- Web of Science (2004): Indexed yes
Characterization of the enhancer and promoter landscape of inflammatory bowel disease from human colon biopsies

Inflammatory bowel disease (IBD) is a chronic intestinal disorder, with two main types: Crohn's disease (CD) and ulcerative colitis (UC), whose molecular pathology is not well understood. The majority of IBD-associated SNPs are located in non-coding regions and are hard to characterize since regulatory regions in IBD are not known. Here we profile transcription start sites (TSSs) and enhancers in the descending colon of 94 IBD patients and controls. IBD-upregulated promoters and enhancers are highly enriched for IBD-associated SNPs and are bound by the same transcription factors. IBD-specific TSSs are associated to genes with roles in both inflammatory cascades and gut epithelia while TSSs distinguishing UC and CD are associated to gut epithelia functions. We find that as few as 35 TSSs can distinguish active CD, UC, and controls with 85% accuracy in an independent cohort. Our data constitute a foundation for understanding the molecular pathology, gene regulation, and genetics of IBD.
Chemotherapy treatment is associated with altered PD-L1 expression in lung cancer patients

Objectives: While the predictive value of programmed cell death ligand-1 (PD-L1) protein expression for immune checkpoint inhibitor therapy of lung cancer has been extensively studied, the impact of standard platinum-based chemotherapy on PD-L1 or programmed cell death-1 (PD-1) expression is unknown. The aim of this study was to determine the changes in PD-L1 expression of tumor cells (TC) and immune cells (IC), in PD-1 expression of IC, and in the amount of stromal mononuclear cell infiltration after platinum-based chemotherapy in patients with lung cancer.

Materials and methods: We determined the amount of stromal mononuclear cells and PD-L1/PD-1 expressions by immunohistochemistry in bronchoscopic biopsy samples including 20 adenocarcinomas (ADC), 15 squamous cell carcinomas (SCC), 2 other types of non-small cell lung cancer, and 4 small cell lung cancers together with their corresponding surgical resection tissues after platinum-based chemotherapy. Results: PD-L1 expression of TC decreased in ten patients (24.4%) and increased in three patients (7.32%) after neoadjuvant chemotherapy (p = 0.051). The decrease in PD-L1 expression, however, was significant only in patients who received cisplatin–gemcitabine combination (p = 0.020), while in the carboplatin–paclitaxel group, no similar tendency could be observed (p = 0.432). There was no difference between ADC and SCC groups. Neither PD-1 expression nor the amount of stromal IC infiltration showed significant changes after chemotherapy. Conclusions: This is the first study, in which both PD-L1 and PD-1 expression were analyzed together with the amount of stromal IC infiltration in different histological subtypes of lung cancer before and after platinum-based chemotherapy. Our results confirm that chemotherapy decreases PD-L1 expression of TC in a subset of patients, therefore, rebiopsy and re-evaluation of PD-L1 expression may be necessary for the indication of immune checkpoint inhibitor therapy.

General information
State: Accepted/In press
Organisations: Department of Bio and Health Informatics, Cancer Genomics, Eotvos Lorand University, National Institute of Oncology, Medical University of Vienna, National Korányi Institute of Tuberculosis and Pulmonology, Semmelweis University
Authors: Rojkó, L. (Ekstern), Reiniger, L. (Ekstern), Téglási, V. (Ekstern), Fábián, K. (Ekstern), Pipek, O. (Ekstern), Vágvölgyi, A. (Ekstern), Agócs, L. (Ekstern), Fillinger, J. (Ekstern), Kajdácsi, Z. (Ekstern), Timár, J. (Ekstern), Döme, B. (Ekstern), Szállási, Z. (Intern), Moldvay, J. (Ekstern)
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Journal: Journal of Cancer Research and Clinical Oncology
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Ratings:
CHTyper, a Web Tool for Subtyping of Extraintestinal Pathogenic Escherichia coli based on the fumC and fimH Alleles

Escherichia coli can cause a variety of extra-intestinal infections, such as urinary tract infection, meningitis, peritonitis and septicemia.

General information
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Organisations: Department of Bio and Health Informatics, Genomic Epidemiology, Research Group for Genomic Epidemiology, Statens Seruminstitute, University of Washington
Authors: Roer, L. (Ekstern), Johannesen, T. B. (Ekstern), Hansen, F. (Ekstern), Stegger, M. (Ekstern), Tchesnokova, V. (Ekstern), Sokurenko, E. (Ekstern), Garibay, N. (Ekstern), Allesøe, R. L. (Intern), Thomsen, M. C. F. (Intern), Lund, O. (Intern), Hasman, H. (Ekstern), Hammerum, A. M. (Ekstern)
Number of pages: 7
Comparative genomics sheds light on niche differentiation and the evolutionary history of comammox Nitrospira

The description of comammox Nitrospira spp., performing complete ammonia-to-nitrate oxidation, and their co-occurrence with canonical β-proteobacterial ammonia oxidizing bacteria (β-AOB) in the environment, calls into question the metabolic potential of comammox Nitrospira and the evolutionary history of their ammonia oxidation pathway. We report four new comammox Nitrospira genomes, constituting two novel species, and the first comparative genomic analysis on comammox Nitrospira. Unlike canonical Nitrospira, comammox Nitrospira genomes lack genes for assimilatory nitrite reduction, suggesting that they have lost the potential to use external nitrite nitrogen sources. By contrast, compared to canonical Nitrospira, comammox Nitrospira harbor a higher diversity of urea transporters and copper homeostasis genes and lack cyanate hydratase genes. Additionally, the two comammox clades differ in their ammonium uptake systems. Contrary to β-AOB, comammox Nitrospira genomes have single copies of the two central ammonia oxidation pathway operons. Similar to ammonia oxidizing archaea and some oligotrophic AOB strains, they lack genes involved in nitric oxide reduction. Furthermore, comammox Nitrospira genomes encode genes that might allow efficient growth at low oxygen concentrations. Regarding the evolutionary history of comammox Nitrospira, our analyses indicate that several genes belonging to the ammonia oxidation pathway could have been laterally transferred from β-AOB to comammox Nitrospira. We postulate that the absence of comammox genes in other sublineage II Nitrospira genomes is the result of subsequent loss.
Comparison of CyTOF assays across sites: Results of a six-center pilot study

For more than five years, high-dimensional mass cytometry has been employed to study immunology. However, these studies have typically been performed in one laboratory on one or few instruments. We present the results of a six-center study using healthy control human peripheral blood mononuclear cells (PBMCs) and commercially available reagents to test the intra-site and inter-site variation of mass cytometers and operators. We used prestained controls generated by the primary center as a reference to compare against samples stained at each individual center. Data were analyzed at the primary center, including investigating the effects of two normalization methods. All six sites performed similarly, with CVs for both Frequency of Parent and median signal intensity (MSI) values < 30%. Increased background was seen when using the premixed antibody cocktail aliquots at each site, suggesting that cocktails are best made fresh. Both normalization methods tested performed adequately for normalizing MSI values between centers. Clustering algorithms revealed slight differences between the prestained and the sites-stained samples, due mostly to the increased background of a few antibodies. Therefore, we believe that multicenter mass cytometry assays are feasible.

General information
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Organisations: Department of Bio and Health Informatics, Stanford University, University of Lausanne, Massachusetts Institute of Technology, Fred Hutchinson Cancer Research Center, University of Cape Town
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Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): SNIP 0.715 SJR 1.289
Computational prediction of neoantigens: do we need more data or new approaches?

Personalized cancer immunotherapy may benefit from improved computational algorithms for identifying neoantigens. Recent results demonstrate that machine learning can improve accuracy. Additional improvements may require more genomic data paired with in vitro T cell reactivity measurements, and more sophisticated algorithms that take into account T cell receptor specificity.

General information
Computational Tools for the Identification and Interpretation of Sequence Motifs in Immunopeptidomes

Recent advances in proteomics and mass-spectrometry have widely expanded the detectable peptide repertoire presented by major histocompatibility complex (MHC) molecules on the cell surface, collectively known as the immunopeptidome. Finely characterizing the immunopeptidome brings about important basic insights into the mechanisms of antigen presentation, but can also reveal promising targets for vaccine development and cancer immunotherapy. This report describes a number of practical and efficient approaches to analyze immunopeptidomics data, discussing the identification of meaningful sequence motifs in various scenarios and considering current limitations. Guidelines are provided for the filtering of false hits and contaminants, and to address the problem of motif deconvolution in cell lines expressing multiple MHC alleles, both for the MHC class I and class II systems. Finally, it is demonstrated how machine learning can be readily employed by non-expert users to generate accurate prediction models directly from mass-spectrometry eluted ligand data sets.

General information
State: Accepted/In press
Organisations: Department of Bio and Health Informatics, Immunoinformatics and Machine Learning, Universidad Nacional de San Martin
Authors: Alvarez, B. (Ekstern), Barra, C. (Ekstern), Nielsen, M. (Intern), Andreatta, M. (Ekstern)
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Article number: 1700252
ISSN (Print): 1615-9853
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BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
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Scopus rating (2017): SNIP 0.774 SJR 1.435
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.85 SJR 1.564 SNIP 0.889
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.48 SNIP 0.969 CiteScore 3.7
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.449 SNIP 0.973 CiteScore 3.73
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.488 SNIP 0.978 CiteScore 3.88
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.497 SNIP 1.094 CiteScore 4.1
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.691 SNIP 1.175 CiteScore 4.49
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.514 SNIP 1.123
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Deterministic Evolutionary Trajectories Influence Primary Tumor Growth: TRACERx Renal

The evolutionary features of clear-cell renal cell carcinoma (ccRCC) have not been systematically studied to date. We analyzed 1,206 primary tumor regions from 101 patients recruited into the multi-center prospective study, TRACERx Renal. We observe up to 30 driver events per tumor and show that subclonal diversification is associated with known prognostic parameters. By resolving the patterns of driver event ordering, co-occurrence, and mutual exclusivity at clone level, we show the deterministic nature of clonal evolution. ccRCC can be grouped into seven evolutionary subtypes, ranging from tumors characterized by early fixation of multiple mutational and copy number drivers and rapid metastases to highly branched tumors with >10 subclonal drivers and extensive parallel evolution associated with attenuated progression. We identify genetic diversity and chromosomal complexity as determinants of patient outcome. Our insights reconcile the variable clinical behavior of ccRCC and suggest evolutionary potential as a biomarker for both intervention and surveillance.

General information
State: Published
Organisations: Department of Bio and Health Informatics, Cancer Genomics, The Francis Crick Institute, Guy’s and St Thomas’ National Health Service (NHS) Foundation Trust, University of the Basque Country, The Royal Marsden National Health Service (NHS) Foundation Trust, Wellcome Trust Sanger Institute, MAX DELBRUCK CENTER FOR MOLECULAR MEDICINE, University College London, Eotvos Lorand University, Royal Marsden NHS Foundation Trust
Pages: 595-610
Publication date: 2018
Main Research Area: Technical/natural sciences
Discrepancy between low levels of mTOR activity and high levels of p-S6 in primary central nervous system lymphoma may be explained by PAS domain-containing serine/threonine-protein kinase-mediated phosphorylation

The primary aim of this study was to determine mTOR-pathway activity in primary central nervous system lymphoma (PCNSL), which could be a potential target for therapy. After demonstrating that p-S6 positivity largely exceeded mTOR activity, we aimed to identify other pathways that may lead to S6 phosphorylation. We measured mTOR activity with immunohistochemistry for p-mTOR and its downstream effectors p(T389)-p70S6K1, p-S6, and p-4EBP1 in 31 cases of PCNSL and 51 cases of systemic diffuse large B-cell lymphoma (DLBCL) and evaluated alternative S6 phosphorylation pathways with p-RSK, p(T229)-p70S6K1, and PASK antibodies. Finally, we examined the impact of PASK inhibition on S6 phosphorylation on BHD1 cell line. mTOR-pathway activity was significantly less frequent in PCNSL compared with DLBCL. p-S6 positivity was related to mTOR-pathway in DLBCL, but not in PCNSL. Among the other kinases potentially responsible for S6 phosphorylation, PASK proved to be positive in all cases of PCNSL and DLBCL. Inhibition of PASK resulted in reduced expression of p-S6 in BHD1-cells. This is the first study demonstrating an mTOR independent p-S6 activity in PCNSL and that PASK may contribute to the phosphorylation of S6. Our findings also suggest a potential role of PASK in the pathomechanism of PCNSL and in DLBCL.
Gene co-expression networks in liver and muscle transcriptome reveal sex-specific gene expression in lambs fed with a mix of essential oils

Essential oil (EO) dietary supplementation is a new strategy to improve animal health. EO compounds have antiparasitic, antimicrobial, antiviral, antifungal, antioxidant and anti-inflammatory properties. Nutrigenomics investigations represent innovative approaches in understanding the relationship between diet effect and gene expression related to the animal performance. Few nutrigenomics studies have used a high-throughput RNA-sequencing (RNA-Seq) approach, despite the great potential of RNA-Seq data in gene expression quantification and co-expression network analyses. Our aim is to use the potential of RNA-Seq data in order to evaluate the effect of an EO supplementary diet on gene expression in both lamb liver and muscle. Using a treatment and sex interaction model, 13 and 4 differentially expressed genes were identified in liver and muscle, respectively. Sex-specific differentially expressed (DE) genes were identified in both sexes. Using network-based analysis, different clusters of co-expressed genes that were highly correlated to the diet were detected in males vs. females, in agreement with DE analysis. A total of five regulatory genes in liver tissue associated with EO diet were identified: DNAJB9, MANF, UFM1, CTNNA1 and NFX1. Our study reveals a sex-dependent effect of EO diet in both tissues, and an influence on the expression of genes mainly involved in immune, inflammatory and stress pathway. Our analysis suggests a sex-dependent effect of the EO dietary supplementation on the expression profile of both liver and muscle tissues. We hypothesize that the presence of EOs could have beneficial effects on wellness of male lamb and further analyses are needed to understand the biological mechanisms behind the different effect of EO metabolites based on sex. Using lamb as a model for nutrigenomics studies, it could be interesting to investigate the effects of EO diets in other species and in humans.

General information
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Organisations: Department of Bio and Health Informatics, Administration, University of Perugia, Catholic University of the Sacred Heart
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BFI (2017): BFI-level 1
Scopus rating (2017): SJR 2.11 SNIP 1.151
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 4.05 SJR 2.163 SNIP 1.096
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.348 SNIP 1.159 CiteScore 4.3
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.327 SNIP 1.199 CiteScore 4.18
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 2.195 SNIP 1.188 CiteScore 4.39
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 2.236 SNIP 1.243 CiteScore 4.61
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 2.307 SNIP 1.191 CiteScore 4.38
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 2.142 SNIP 1.037
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 2.21 SNIP 1.012
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 2.287 SNIP 1.007
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 2.12 SNIP 1.039
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 1.878 SNIP 0.927
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 2.287 SNIP 0.915
Web of Science (2005): Indexed yes
Scopus rating (2004): SJR 2.218 SNIP 0.728
Web of Science (2004): Indexed yes
Scopus rating (2003): SJR 1.94 SNIP 0.571
Web of Science (2003): Indexed yes
Scopus rating (2002): SJR 7.349 SNIP 0.529
Scopus rating (2001): SJR 0.132 SNIP 0.016

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Genome-wide analysis yields new loci associating with aortic valve stenosis

Aortic valve stenosis (AS) is the most common valvular heart disease, and valve replacement is the only definitive treatment. Here we report a large genome-wide association (GWA) study of 2,457 Icelandic AS cases and 349,342 controls with a follow-up in up to 4,850 cases and 451,731 controls of European ancestry. We identify two new AS loci, on chromosome 1p21 near PALMD (rs7543130; odds ratio (OR) = 1.20, \( P = 1.2 \times 10^{-22} \)) and on chromosome 2q22 in TEX41 (rs1830321; OR = 1.15, \( P = 1.8 \times 10^{-13} \)). Rs7543130 also associates with bicuspid aortic valve (BAV) (OR = 1.28, \( P = 6.6 \times 10^{-10} \)) and aortic root diameter (\( P = 1.30 \times 10^{-8} \)), and rs1830321 associates with BAV (OR = 1.12, \( P = 5.3 \times 10^{-3} \)) and coronary artery disease (OR = 1.05, \( P = 9.3 \times 10^{-5} \)). The results implicate both cardiac developmental abnormalities and atherosclerosis-like processes in the pathogenesis of AS. We show that several pathways are shared by CAD and AS. Causal analysis suggests that the shared risk factors of Lp(a) and non-high-density lipoprotein cholesterol contribute substantially to the frequent co-occurrence of these diseases.

General information

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BFI (2017): BFI-level 2
Scopus rating (2017): SNIP 2.912 SJR 6.582
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 11.8 SJR 6.414 SNIP 2.855
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 6.287 SNIP 2.86 CiteScore 11.23
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 6.41 SNIP 3.034 CiteScore 10.77
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 6.206 SNIP 2.797 CiteScore 9.85
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
Scopus rating (2012): SJR 5.866 SNIP 2.829 CiteScore 8.32
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
Scopus rating (2011): SJR 3.137 SNIP 1.825 CiteScore 4.44
Hologenomic adaptations underlying the evolution of sanguivory in the common vampire bat

Adaptation to specialized diets often requires modifications at both genomic and microbiome levels. We applied a hologenomic approach to the common vampire bat (Desmodus rotundus), one of the only three obligate blood-feeding (sanguivorous) mammals, to study the evolution of its complex dietary adaptation. Specifically, we assembled its high-quality reference genome (scaffold N50 = 26.9 Mb, contig N50 = 36.6 kb) and gut metagenome, and compared them against those of insectivorous, frugivorous and carnivorous bats. Our analyses showed a particular common vampire bat genomic landscape regarding integrated viral elements, a dietary and phylogenetic influence on gut microbiome taxonomic and functional profiles, and that both genetic elements harbour key traits related to the nutritional (for example, vitamin and lipid shortage) and non-nutritional (for example, nitrogen waste and osmotic homeostasis) challenges of sanguivory. These findings highlight the value of a holistic study of both the host and its microbiota when attempting to decipher adaptations underlying radical dietary lifestyles.

General information
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Organisations: Department of Bio and Health Informatics, University of Copenhagen, Chinese Academy of Sciences, Leibniz Institute for Zoo and Wildlife Research, University of Oxford, University of Glasgow, Stanford University, Animal-INIFAP, BGI-Shenzhen, San Diego Zoo’s Institute for Conservation Research, Universidad Nacional Autonoma de Mexico, National Autonomous University of Mexico, Copenhagen Zoo, Curtin University, Norwegian University of Science and Technology
Pages: 659-668
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Hospital Epidemiology of Methicillin-Resistant Staphylococcus aureus in a Tertiary Care Hospital in Moshi, Tanzania, as Determined by Whole Genome Sequencing

Objective. To determine molecular epidemiology of methicillin-resistant S. aureus in Tanzania using whole genome sequencing. Methods. DNA from 33 Staphylococcus species was recovered from subcultured archived Staphylococcus isolates. Whole genome sequencing was performed on IlluminaMiseq using paired-end 2x250 bp protocol. Raw sequence data were analyzed using online tools. Results. Full susceptibility to vancomycin and chloramphenicol was observed. Thirteen isolates (43.3%) resisted cefoxitin and other antimicrobials tested. Multilocus sequence typing revealed 13 different sequence types among the 30 S. aureus isolates, with ST-8 (n = seven, 23%) being the most common. Gene detection in S. aureus stains were as follows: mecA, 10 (33.3%); pvl, 5 (16.7%); tst, 2 (6.7%). The SNP difference among the six Tanzanian ST-8MRSA isolates ranged from 24 to 196 SNPs and from 16 to 446 SNPs when using the USA300_FPR3757 or the USA500 2395 as a reference, respectively. The mutation rate was 1.38 x 10(-11) SNPs/site/year or 1.4 x 10(-6) SNPs/site/year as estimated by USA300 FPR3757 or the USA500 2395, respectively. Conclusion. S. aureus isolates causing infections in hospitalized patients in Moshi are highly diverse and epidemiologically unrelated. Temporal phylogenetic analysis provided better resolution on transmission and introduction of MRSA and it may be important to include this in future routines.

General information
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Organisations: National Food Institute, Research Group for Genomic Epidemiology, Department of Bio and Health Informatics, Genomic Epidemiology, KCRI Kilimanjaro Clinical Research Institute, University of Copenhagen
Authors: Kumburu, H. H. (Ekstern), Sonda, T. (Ekstern), Leekitcharoenphon, P. (Intern), van Zwetselaar, M. (Ekstern), Lukjancenko, O. (Intern), Alifrangis, M. (Ekstern), Lund, O. (Intern), Mmbaga, B. T. (Ekstern), Kibiki, G. (Ekstern), Aarestrup, F. M. (Intern)
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Main Research Area: Technical/natural sciences

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Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): SJR 0.935 SNIP 0.984
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.32 SJR 0.885 SNIP 0.919
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.854 SNIP 0.799 CiteScore 1.77
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.797 SNIP 0.777 CiteScore 1.29
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.175 SNIP 0.973
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.084 SNIP 0.872
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 0.887 SNIP 0.704
How cancer specific T-cell recognition and functionality is affected by combination of radio- and immunotherapeutic strategies

General information

State: Published
Organisations: National Veterinary Institute, T-cells & Cancer, Cancer Genomics, Immunoinformatics and Machine Learning, Technical University of Denmark
Authors: Meldgaard, T. S. (Intern), Petersen, L. R. (Ekstern), Pedersen, T. K. (Intern), Bjerregaard, A. (Intern), Marquard, A. M. (Intern), Hansen, A. E. (Ekstern), Andresen, T. L. (Ekstern), Hadrup, S. R. (Intern)
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BFI (2017): BFI-level 1
Scopus rating (2017): SNIP 1.987 SJR 2.963
Web of Science (2017): Indexed Yes
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Scopus rating (2016): CiteScore 6.1 SJR 3.105 SNIP 2.196
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Scopus rating (2015): SJR 3.177 SNIP 2.1 CiteScore 5.89
BFI (2014): BFI-level 1
Human MHC-II with Shared Epitope Motifs Are Optimal Epstein-Barr Virus Glycoprotein 42 Ligands—Relation to Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disorder of unknown etiology, which is characterized by inflammation in the synovium and joint damage. Although the pathogenesis of RA remains to be determined, a combination of environmental (e.g., viral infections) and genetic factors influence disease onset. Especially genetic factors play a vital role in the onset of disease, as the heritability of RA is 50–60%, with the human leukocyte antigen (HLA) alleles accounting for at least 30% of the overall genetic risk. Some HLA-DR alleles encode a conserved sequence of amino acids, referred to as the shared epitope (SE) structure. By analyzing the structure of a HLA-DR molecule in complex with Epstein-Barr virus (EBV), the SE motif is suggested to play a vital role in the interaction of MHC II with the viral glycoprotein (gp) 42, an essential entry factor for EBV. EBV has been repeatedly linked to RA by several lines of evidence and, based on several findings, we suggest that EBV is able to induce the onset of RA in predisposed SE-positive individuals, by promoting entry of B-cells through direct contact between SE and gp42 in the entry complex.

General information
State: Published
Organisations: Department of Bio and Health Informatics, Integrative Systems Biology, Immunoinformatics and Machine Learning, Statens Serum Institute, Carlsberg Research Laboratory, Statens Serum Institut
Authors: Trier, N. (Ekstern), Gonzalez-Izarzugaza, J. M. (Intern), Chailyan, A. (Ekstern), Marcatili, P. (Intern), Houen, G. (Ekstern)
Number of pages: 18
Publication date: 2018
Main Research Area: Technical/natural sciences
Ibuprofen alters human testicular physiology to produce a state of compensated hypogonadism

Concern has been raised over increased male reproductive disorders in the Western world, and the disruption of male endocrinology has been suggested to play a central role. Several studies have shown that mild analgesics exposure during fetal life is associated with antiandrogenic effects and congenital malformations, but the effects on the adult man remain largely unknown. Through a clinical trial with young men exposed to ibuprofen, we show that the analgesic resulted in the clinical condition named “compensated hypogonadism,” a condition prevalent among elderly men and associated with reproductive and physical disorders. In the men, luteinizing hormone (LH) and ibuprofen plasma levels were positively correlated, and the testosterone/LH ratio decreased. Using adult testis explants exposed or not exposed to ibuprofen, we demonstrate that the endocrine capabilities from testicular Leydig and Sertoli cells, including testosterone production, were suppressed through transcriptional repression. This effect was also observed in a human steroidogenic cell line. Our data demonstrate that ibuprofen alters the endocrine system via selective transcriptional repression in the human testes, thereby inducing compensated hypogonadism.

General information
State: Accepted/In press
Organisations: Department of Bio and Health Informatics, Integrative Systems Biology, University of Copenhagen, Copenhagen University Hospital, Université de Rennes 1, Bispebjerg University Hospital, L’Université Nantes Angers Le Mans, Centre Hospitalier Universitaire de Rennes, University of Southern Denmark
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Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 8.56 SJR 6.576 SNIP 2.642
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Scopus rating (2015): SJR 6.814 SNIP 2.691 CiteScore 8.84
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 6.898 SNIP 2.734 CiteScore 8.86
Web of Science (2014): Indexed yes
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Scopus rating (2013): SJR 7.073 SNIP 2.738 CiteScore 9.5
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 6.868 SNIP 2.697 CiteScore 9.49
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 6.864 SNIP 2.646 CiteScore 9.31
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Ibuprofen alters human testicular physiology to produce a state of compensated hypogonadism (vol 115, pg E715, 2018)

General information
State: Published
Organisations: Department of Bio and Health Informatics, Integrative Systems Biology, Bispebjerg University Hospital, University of Southern Denmark, Université de Rennes 1, Rigshospitalet, L’Université Nantes Angers Le Mans, Centre Hospitalier Universitaire de Rennes, University of Copenhagen
Pages: E4143-E4143
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Main Research Area: Technical/natural sciences

Publication information
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Scopus rating (2017): SNIP 2.626 SJR 6.092
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 8.56 SJR 6.576 SNIP 2.642
Web of Science (2016): Indexed yes
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Scopus rating (2015): SJR 6.814 SNIP 2.691 CiteScore 8.84
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 6.898 SNIP 2.734 CiteScore 8.86
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 7.073 SNIP 2.738 CiteScore 9.5
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 6.868 SNIP 2.697 CiteScore 9.49
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 6.864 SNIP 2.646 CiteScore 9.31
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 6.898 SNIP 2.545
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 7.025 SNIP 2.556
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 7.034 SNIP 2.449
Web of Science (2008): Indexed yes
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 6.849 SNIP 2.45
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 6.94 SNIP 2.555
Web of Science (2005): Indexed yes
Scopus rating (2004): SJR 7.197 SNIP 2.629
Web of Science (2004): Indexed yes
Scopus rating (2003): SJR 7.129 SNIP 2.515
Web of Science (2003): Indexed yes
Scopus rating (2002): SJR 6.913 SNIP 2.503
Web of Science (2002): Indexed yes
Scopus rating (2001): SJR 7.189 SNIP 2.47
Web of Science (2001): Indexed yes
Scopus rating (2000): SJR 8.751 SNIP 2.458
Web of Science (2000): Indexed yes
Scopus rating (1999): SJR 8.52 SNIP 2.418
Identification and Characterization of Variant Intolerant Sites across Human Protein 3-Dimensional Structures

General information
State: Published
Organisations: Department of Bio and Health Informatics, Genomic Epidemiology, Broad Institute of Harvard University and Massachusetts Institute of Technology, Massachusetts General Hospital, University of Cologne, University of Luxembourg, Danish Epilepsy Center
Authors: Iqbal, S. (Ekstern), Jespersen, J. B. (Intern), Perez-Palma, E. (Ekstern), May, P. (Ekstern), Heyne, H. (Ekstern), Lage, K. (Ekstern), Steensbjerre Møller, R. (Ekstern), Wagner, F. F. (Ekstern), Daly, M. (Ekstern), Campbell, A. J. (Ekstern), Lal, D. (Ekstern)
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Main Research Area: Technical/natural sciences

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Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): SNIP 0.979 SJR 1.949
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.06 SJR 1.988 SNIP 1.005
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.13 SNIP 1.134 CiteScore 3.3
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.21 SNIP 1.15 CiteScore 3.33
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 2.245 SNIP 1.156 CiteScore 3.64
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 2.361 SNIP 1.143 CiteScore 3.57
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 2.357 SNIP 1.202 CiteScore 3.75
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 2.695 SNIP 1.303
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Identification of the cognate peptide-MHC target of T cell receptors using molecular modeling and force field scoring

Interactions of T cell receptors (TCR) to peptides in complex with MHC (p:MHC) are key features that mediate cellular immune responses. While MHC binding is required for a peptide to be presented to T cells, not all MHC binders are immunogenic. The interaction of a TCR to the p:MHC complex holds a key, but currently poorly comprehended, component for our understanding of this variation in the immunogenicity of MHC binding peptides. Here, we demonstrate that identification of the cognate target of a TCR from a set of p:MHC complexes to a high degree is achievable using simple force-field energy terms. Building a benchmark of TCR:p:MHC complexes where epitopes and non-epitopes are modelled using state-of-the-art molecular modelling tools, scoring p:MHC to a given TCR using force-fields, optimized in a cross-validation setup to evaluate TCR inter atomic interactions involved with each p:MHC, we demonstrate that this approach can successfully be used to distinguish between epitopes and non-epitopes. A detailed analysis of the performance of this force-field-based approach demonstrate that its predictive performance depend on the ability to both accurately predict the binding of the peptide to the MHC and model the TCR:p:MHC complex structure. In summary, we conclude that it is possible to identify the TCR cognate target among different candidate peptides by using a force-field based model, and believe this works could lay the foundation for future work within prediction of TCR:p:MHC interactions.

General information
State: Published
Organisations: Department of Bio and Health Informatics, Immunoinformatics and Machine Learning, Universidad Nacional de San Martin
Authors: Lanzarotti, E. (Ekstern), Marcatili, P. (Intern), Nielsen, M. (Intern)
Number of pages: 7
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Publication date: 2018
Main Research Area: Technical/natural sciences

Publication information
Journal: Molecular Immunology
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ISSN (Print): 0161-5890
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BFI (2018): BFI-level 1
Improved de novo genomic assembly for the domestic donkey

Donkeys and horses share a common ancestor dating back to about 4 million years ago. Although a high-quality genome assembly at the chromosomal level is available for the horse, current assemblies available for the donkey are limited to moderately sized scaffolds. The absence of a better-quality assembly for the donkey has hampered studies involving the characterization of patterns of genetic variation at the genome-wide scale. These range from the application of genomic tools to selective breeding and conservation to the more fundamental characterization of the genomic loci underlying...
speciation and domestication. We present a new high-quality donkey genome assembly obtained using the Chicago HiRise assembly technology, providing scaffolds of subchromosomal size. We make use of this new assembly to obtain more accurate measures of heterozygosity for equine species other than the horse, both genome-wide and locally, and to detect runs of homozygosity potentially pertaining to positive selection in domestic donkeys. Finally, this new assembly allowed us to identify fine-scale chromosomal rearrangements between the horse and the donkey that likely played an active role in their divergence and, ultimately, speciation.

**General information**

State: Published
Organisations: Department of Bio and Health Informatics, Metagenomics, Animal Health Trust, Natural History Museum of Denmark, University of Copenhagen, Centre for Zoo and Wild Animal Health
Authors: Renaud, G. (Forskerdatabase), Petersen, B. (Intern), Seguin-Orlando, A. (Ekstern), Bertelsen, M. F. (Ekstern), Waller, A. (Ekstern), Newton, R. (Ekstern), Paillot, R. (Ekstern), Bryant, N. (Ekstern), Vaudin, M. (Ekstern), Librado, P. (Ekstern), Orlando, L. (Ekstern)
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Publication date: 2018
Main Research Area: Technical/natural sciences

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**Improved methods for predicting peptide binding affinity to MHC class II molecules**

Major histocompatibility complex class II (MHC-II) molecules are expressed on the surface of professional antigen presenting cells where they display peptides to T helper cells, which orchestrate the onset and outcome of many host immune responses. Understanding which peptides will be presented by the MHC-II molecule is therefore important for understanding the activation of T helper cells and can be used to identify T-cell epitopes. We here present updated versions of two MHC class II peptide binding affinity prediction methods, NetMHCII and NetMHCIIpan. These were constructed using an extended data set of quantitative MHC-peptide binding affinity data obtained from the Immune Epitope Database covering HLA-DR, HLA-DQ, HLA-DP and H-2 mouse molecules. We show that training with this extended data set improved the performance for peptide binding predictions for both methods. Both methods are publicly available at www.cbs.dtu.dk/services/NetMHCII-2.3 and www.cbs.dtu.dk/services/NetMHCIIpan-3.2. This article is protected by copyright. All rights reserved.

**General information**

State: Accepted/In press
Organisations: Department of Bio and Health Informatics, Immunoinformatics and Machine Learning, Universidad Nacional de San Martin, University of Copenhagen, La Jolla Institute for Allergy & Immunology
Authors: Jensen, K. K. (Intern), Andreatta, M. (Ekstern), Marcatili, P. (Intern), Buus, S. (Ekstern), Greenbaum, J. A. (Ekstern), Yan, Z. (Ekstern), Sette, A. (Ekstern), Peters, B. (Ekstern), Nielsen, M. (Intern)
Number of pages: 28
Publication date: 2018
Main Research Area: Technical/natural sciences

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Improved Prediction of Bovine Leucocyte Antigens (BoLA) Presented Ligands by Use of Mass-Spectrometry-Determined Ligand and in Vitro Binding Data

Peptide binding to MHC class I molecules is the single most selective step in antigen presentation and the strongest single correlate to peptide cellular immunogenicity. The cost of experimentally characterizing the rules of peptide presentation for a given MHC-I molecule is extensive, and predictors of peptide-MHC interactions constitute an attractive alternative. Recently, an increasing amount of MHC presented peptides identified by mass spectrometry (MS ligands) has been published. Handling and interpretation of MS ligand data is, in general, challenging due to the polyspecificity nature of the data. We here outline a general pipeline for dealing with this challenge and accurately annotate ligands to the relevant MHC-I molecule they were eluted from by use of GibbsClustering and binding motif information inferred from in silico models. We illustrate the approach here in the context of MHC-I molecules (BoLA) of cattle. Next, we demonstrate how such annotated BoLA MS ligand data can readily be integrated with in vitro binding affinity data in a prediction model with very high and unprecedented performance for identification of BoLA-I restricted T-cell epitopes. The prediction model is freely available at http://www.cbs.dtu.dk/services/NetMHCpan/NetBoLApan . The approach has here been applied to the BoLA-I system, but the pipeline is readily applicable to MHC systems in other species.

General information
State: Published
Organisations: Department of Bio and Health Informatics, Immunoinformatics and Machine Learning, The Roslin Institute, Target Discovery Institute Mass Spectrometry Laboratory
Authors: Nielsen, M. (Intern), Connelley, T. (Ekstern), Ternette, N. (Ekstern)
Pages: 559-567
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Main Research Area: Technical/natural sciences

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BFI (2017): BFI-level 2
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Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 4.34 SJR 1.76 SNIP 1.018
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 1.933 SNIP 1.08 CiteScore 4.45
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 1.959 SNIP 1.174 CiteScore 4.64
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 2.012 SNIP 1.248 CiteScore 5.16
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 2.04 SNIP 1.323 CiteScore 5.12
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 2.137 SNIP 1.261 CiteScore 5.12
ISI indexed (2011): ISI indexed yes
Integrative network analysis highlights biological processes underlying GLP-1 stimulated insulin secretion: A DIRECT study

Glucagon-like peptide 1 (GLP-1) stimulated insulin secretion has a considerable heritable component as estimated from twin studies, yet few genetic variants influencing this phenotype have been identified. We performed the first genome-wide association study (GWAS) of GLP-1 stimulated insulin secretion in non-diabetic individuals from the Netherlands Twin register (n = 126). This GWAS was enhanced using a tissue-specific protein-protein interaction network approach. We identified a beta-cell protein-protein interaction module that was significantly enriched for low gene scores based on the GWAS P-values and found support at the network level in an independent cohort from Tübingen, Germany (n = 100). Additionally, a polygenic risk score based on SNPs prioritized from the network was associated (P <0.05) with glucose-stimulated insulin secretion phenotypes in up to 5,318 individuals in MAGIC cohorts. The network contains both known and novel genes in the context of insulin secretion and is enriched for members of the focal adhesion, extracellular-matrix receptor interaction, actin cytoskeleton regulation, Rap1 and PI3K-Akt signaling pathways. Adipose tissue is, like the beta-cell, one of the target tissues of GLP-1 and we thus hypothesized that similar networks might be functional in both tissues. In order to verify peripheral effects of GLP-1 stimulation, we compared the transcriptome profiling of ob/ob mice treated with liraglutide, a clinically used GLP-1 receptor agonist, versus baseline controls. Some of the upstream regulators of differentially expressed genes in the white adipose tissue of ob/ob mice were also detected in the human beta-cell network of genes associated with GLP-1 stimulated insulin secretion. The findings provide biological insight into the mechanisms through which the effects of GLP-1 may be modulated and highlight a potential role of the beta-cell expressed genes RYR2, G6D2, KIAA0232, COL4A1 and COL4A2 in GLP-1 stimulated insulin secretion.

General information
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Organisations: Department of Bio and Health Informatics, Integrative Systems Biology, Disease Intelligence and Molecular Evolution, Vrije Universiteit Amsterdam, Sanofi Aventis Deutschland GmbH, University of Copenhagen, NIHR Oxford Biomedical Research Centre, University of Oxford, University of Dundee, Eberhard-Karls-Universität Tübingen, VU University Medical Centre, Leiden University Medical Center, Vrije Universiteit Amsterdam, Imperial College London
Number of pages: 12
Publication date: 2018
Main Research Area: Technical/natural sciences
Isolation and characterization of bacteriophages with therapeutic potential

The concerning spread of antibiotic resistant bacteria has directed the spotlight upon bacteriophages, in short phages, as potential candidates for therapeutic purposes. Far for being a novelty, phage therapy has been widely used in the 20s and 30s in western countries until the discovery of antibiotics, which, coupled with a lack of knowledge of phage biology at that
Bone mineral density (BMD) assessed by DXA is used to evaluate bone health. In children, total body (TB) measurements are commonly used; in older individuals, BMD at the lumbar spine (LS) and femoral neck (FN) is used to diagnose osteoporosis. To date, genetic variants in more than 60 loci have been identified as associated with BMD. To investigate the genetic determinants of TB-BMD variation along the life course and test for age-specific effects, we performed a meta-analysis of 30 genome-wide association studies (GWASs) of TB-BMD including 66,628 individuals overall and divided across five age strata, each spanning 15 years. We identified variants associated with TB-BMD at 80 loci, of which 36 have not been previously identified; overall, they explain approximately 10% of the TB-BMD variance when combining all age groups and influence the risk of fracture. Pathway and enrichment analysis of the association signals showed clustering within gene sets implicated in the regulation of cell growth and SMAD proteins, overexpressed in the musculoskeletal system, and enriched in enhancer and promoter regions. These findings reveal TB-BMD as a relevant trait for genetic studies of osteoporosis, enabling the identification of variants and pathways influencing different bone compartments. Only variants in ESR1 and close proximity to RANKL showed a clear effect dependency on age. This most likely indicates that the majority of genetic variants identified influence BMD early in life and that their effect can be captured throughout the life course.

Life-Course Genome-wide Association Study Meta-analysis of Total Body BMD and Assessment of Age-Specific Effects

Bone mineral density (BMD) assessed by DXA is used to evaluate bone health. In children, total body (TB) measurements are commonly used; in older individuals, BMD at the lumbar spine (LS) and femoral neck (FN) is used to diagnose osteoporosis. To date, genetic variants in more than 60 loci have been identified as associated with BMD. To investigate the genetic determinants of TB-BMD variation along the life course and test for age-specific effects, we performed a meta-analysis of 30 genome-wide association studies (GWASs) of TB-BMD including 66,628 individuals overall and divided across five age strata, each spanning 15 years. We identified variants associated with TB-BMD at 80 loci, of which 36 have not been previously identified; overall, they explain approximately 10% of the TB-BMD variance when combining all age groups and influence the risk of fracture. Pathway and enrichment analysis of the association signals showed clustering within gene sets implicated in the regulation of cell growth and SMAD proteins, overexpressed in the musculoskeletal system, and enriched in enhancer and promoter regions. These findings reveal TB-BMD as a relevant trait for genetic studies of osteoporosis, enabling the identification of variants and pathways influencing different bone compartments. Only variants in ESR1 and close proximity to RANKL showed a clear effect dependency on age. This most likely indicates that the majority of genetic variants identified influence BMD early in life and that their effect can be captured throughout the life course.
Metabolite ratios as potential biomarkers for type 2 diabetes: a DIRECT study

Aims/hypothesis: Circulating metabolites have been shown to reflect metabolic changes during the development of type 2 diabetes. In this study we examined the association of metabolite levels and pairwise metabolite ratios with insulin responses after glucose, glucagon-like peptide-1 (GLP-1) and arginine stimulation. We then investigated if the identified metabolite ratios were associated with measures of OGTT-derived beta cell function and with prevalent and incident type 2 diabetes.

Methods: We measured the levels of 188 metabolites in plasma samples from 130 healthy members of twin families (from the Netherlands Twin Register) at five time points during a modified 3 h hyperglycaemic clamp with glucose, GLP-1 and arginine stimulation. We validated our results in cohorts with OGTT data (n = 340) and epidemiological case-control studies of prevalent (n = 4925) and incident (n = 4277) diabetes. The data were analysed using regression models with adjustment for potential confounders.

Results: There were dynamic changes in metabolite levels in response to the different secretagogues. Furthermore, several fasting pairwise metabolite ratios were associated with one or multiple clamp-derived measures of insulin secretion (all p <9.2 × 10^-7). These associations were significantly stronger compared with the individual metabolite components. One of the ratios, valine to phosphatidylcholine acyl-alkyl C32:2 (PC ae C32:2), in addition showed a directionally consistent positive association with OGTT-derived beta cell function and with prevalent and incident type 2 diabetes. Methods: We measured the levels of 188 metabolites in plasma samples from 130 healthy members of twin families (from the Netherlands Twin Register) at five time points during a modified 3 h hyperglycaemic clamp with glucose, GLP-1 and arginine stimulation. We validated our results in cohorts with OGTT data (n = 340) and epidemiological case-control studies of prevalent (n = 4925) and incident (n = 4277) diabetes. The data were analysed using regression models with adjustment for potential confounders.

Results: There were dynamic changes in metabolite levels in response to the different secretagogues. Furthermore, several fasting pairwise metabolite ratios were associated with one or multiple clamp-derived measures of insulin secretion (all p <9.2 × 10^-7). These associations were significantly stronger compared with the individual metabolite components. One of the ratios, valine to phosphatidylcholine acyl-alkyl C32:2 (PC ae C32:2), in addition showed a directionally consistent positive association with OGTT-derived beta cell function and with prevalent and incident type 2 diabetes.

Conclusions/interpretation: In this study we have shown that the Val_PC ae C32:2 metabolite ratio is associated with an increased risk of type 2 diabetes and measures of insulin secretion and resistance. The observed effects were stronger than that of the individual metabolites and independent of known risk factors.

General information

State: Published

Organisations: Department of Bio and Health Informatics, Integrative Systems Biology, Disease Intelligence and Molecular Evolution, Helmholtz Zentrum München, VU University Medical Centre, Vrije Universiteit Amsterdam, German Institute of Human Nutrition, Leiden University Medical Center, German Center for Diabetes Research, Vrije Universiteit Amsterdam, MAX DELBRUCK CENTER FOR MOLECULAR MEDICINE, University of Oxford, University of Dundee, Københavns Universitet


Pages: 117-129

Publication date: 2018

Main Research Area: Technical/natural sciences
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: Published
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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Scopus rating (2014): SJR 6.64 SNIP 2.552 CiteScore 8.74
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Scopus rating (2011): SJR 5.976 SNIP 2.19 CiteScore 7.86
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Molecular profiling of short-term and long-term surviving patients identifies CD34 mRNA level as prognostic for glioblastoma survival

Despite extensive treatment, overall survival (OS) for glioblastoma (GBM) remains poor. A small proportion of patients present long survival over 3 years, but the underlying molecular background separating these long-term survivors (LTS) from short-term survivors (STS) are insufficiently understood. Accordingly, study aim was to identify independent prognostic biomarkers for survival. Study cohort consisted of 93 primary GBM patients treated with radiation-, chemo- and bevacizumab therapy, among which 14 STS (OS ≤ 12 months) and 6 LTS (OS ≥ 36 months) were identified, all confirmed being IDH wild-type. RNA expression levels in diagnostic tumor specimen for 792 genes were analyzed by NanoString technology. While no differences were found with regard to GBM subtype between LTS versus STS, comparative analysis of individual genes identified 14 significantly differently expressed candidate genes. Univariate analysis in the whole patient cohort found that 12 of these were significantly associated with OS, of which increased IFNG, CXCL9, LGALS4, CD34 and decreased MGMT levels remained significant associated with prolonged OS in multivariate analysis correcting for known prognostic variables. Validation analyses in an independent dataset from the AVAglio study confirmed CD34 as significant in comparative analysis between STS and LTS patients and as an independent prognostic factor. Analysis of this dataset further supported CD34 expression to be associated with improved bevacizumab efficacy, while CD34 immunohistochemistry indicated variation in CD34 expression to result primarily from varying tumor vascularization. Collectively, CD34 expression candidates as a prognostic biomarker in GBM able to identify survival outliers and could also be predictive for efficacy of bevacizumab.
With the advancement of personalized cancer immunotherapies, new tools are needed to identify tumor antigens and evaluate T-cell responses in model systems, specifically those that exhibit clinically relevant tumor progression. Key transgenic mouse models of breast cancer are generated and maintained on the FVB genetic background, and one such model is the mouse mammary tumor virus-polyomavirus middle T antigen (MMTV-PyMT) mouse - an immunocompetent transgenic mouse that exhibits spontaneous mammary tumor development and metastasis with high penetrance. Backcrossing the MMTV-PyMT mouse from the FVB strain onto a C57BL/6 genetic background, in order to leverage well-developed C57BL/6 immunological tools, results in delayed tumor development and variable metastatic phenotypes.
Therefore, we initiated characterization of the FVB MHC Class I H-2^q haplotype to establish useful immunological tools for evaluating antigen specificity in the murine FVB strain. Our study provides the first detailed molecular and immunoproteomic characterization of the FVB H-2^q MHC Class I alleles, including >8500 unique peptide ligands, a multi-allele murine MHC peptide prediction tool, and in vivo validation of these data using MMTV-PyMT primary tumors. This work allows researchers to rapidly predict H-2 peptide ligands for immune testing, including, but not limited to, the MMTV-PyMT model for metastatic breast cancer.

**General information**

**State:** Accepted/In press  
**Organisations:** Department of Bio and Health Informatics, Immunoinformatics and Machine Learning, University of Oklahoma Health Sciences Center, Universidad Nacional de San Martin, Utah State University  
**Authors:** Devette, C. I. (Ekstern), Andreatta, M. (Ekstern), Bardet, W. (Ekstern), Cate, S. J. (Ekstern), Jurtz, V. I. (Intern), Jackson, K. W. (Ekstern), Welm, A. L. (Ekstern), Nielsen, M. (Intern), Hildebrand, W. H. (Ekstern)  
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**Origins and genetic legacies of the Caribbean Taino**

The Caribbean was one of the last parts of the Americas to be settled by humans, but how and when the islands were first occupied remains a matter of debate. Ancient DNA can help answering these questions, but the work has been hampered by poor DNA preservation. We report the genome sequence of a 1,000-year-old Lucayan Taino individual recovered from the site of Preacher's Cave in the Bahamas. We sequenced her genome to 12.4-fold coverage and show that she is genetically most closely related to present-day Arawakan speakers from northern South America, suggesting that the ancestors of the Lucayans originated there. Further, we find no evidence for recent inbreeding or isolation in the ancient genome, suggesting that the Lucayans had a relatively large effective population size. Finally, we show that the native American components in some present-day Caribbean genomes are closely related to the ancient Taino, demonstrating an element of continuity between precontact populations and present-day Latino populations in the Caribbean.

**General information**

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**Organisations:** Department of Bio and Health Informatics, Metagenomics, University of Copenhagen, Trinity College Dublin, Temple University, Stanford University, National Autonomous University of Mexico, Universidad de Santiago de Compostela, University of Oxford, Archaeological and Historical Conservancy Inc., Arizona State University, Research Atlantica Inc., Universiteit Leiden, Leiden University  
**Authors:** Schroeder, H. (Ekstern), Sikora, M. (Ekstern), Gopalakrishnan, S. (Ekstern), Cassidy, L. M. (Ekstern), Delserc, P. M. (Ekstern), Velasco, M. S. (Ekstern), Schraiber, J. G. (Ekstern), Rasmussen, S. (Intern), Homburger, J. R. (Ekstern), Avila-Arcos, M. C. (Ekstern), Allentoft, M. E. (Ekstern), Moreno-Mayar, J. V. (Ekstern), Renaud, G. (Ekstern), Gomez-Carballa, A. (Ekstern), Laffoon, J. E. (Ekstern), Hopkins, R. J. A. (Ekstern), Higham, T. F. G. (Ekstern), Carr, R. S. (Ekstern), Schaffer, W. C. (Ekstern), Day, J. S. (Ekstern), Hoogland, M. (Ekstern), Salas, A. (Ekstern), Bustamante, C. D. (Ekstern), Nielsen, R. (Ekstern), Bradley, D. G. (Ekstern), Hofman, C. L. (Ekstern), Willerslev, E. (Ekstern)  
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Scopus rating (2015): SJR 6.814 SNIP 2.691 CiteScore 8.84
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Scopus rating (2014): SJR 6.898 SNIP 2.734 CiteScore 8.86
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Scopus rating (2013): SJR 7.073 SNIP 2.738 CiteScore 9.5
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Scopus rating (2012): SJR 6.868 SNIP 2.697 CiteScore 9.49
ISI indexed (2012): ISI indexed yes
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Scopus rating (2011): SJR 6.864 SNIP 2.646 CiteScore 9.31
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 6.898 SNIP 2.545
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 7.025 SNIP 2.556
Web of Science (2009): Indexed yes
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Scopus rating (2008): SJR 7.034 SNIP 2.449
Web of Science (2008): Indexed yes
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Web of Science (2004): Indexed yes
Scopus rating (2003): SJR 7.129 SNIP 2.515
Web of Science (2003): Indexed yes
Scopus rating (2002): SJR 6.913 SNIP 2.503
Web of Science (2002): Indexed yes
Scopus rating (2001): SJR 7.189 SNIP 2.47
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Overexpression of BLM promotes DNA damage and increased sensitivity to platinum salts in triple negative breast and serous ovarian cancers

Platinum based therapy is an effective treatment for a subset of triple negative breast cancer and ovarian cancer patients. In order to increase response rate and decrease unnecessary use, robust biomarkers that predict response to therapy are needed. We performed an integrated genomic approach combining differential analysis of gene expression and DNA copy number in sensitive compared to resistant triple negative breast cancers in two independent neoadjuvant cisplatin treated cohorts. Functional relevance of significant hits was investigated in vitro by overexpression, knockdown and targeted inhibitor treatment. We identified two genes, the Bloom helicase (BLM) and Fanconi anemia complementation group I (FANCI), that have both increased DNA copy number and gene expression in the platinum sensitive cases. Increased level of expression of these two genes was also associated with platinum but not with taxane response in ovarian cancer. As a functional validation, we found that overexpression of BLM promotes DNA damage and induces sensitivity to cisplatin, but has no effect on paclitaxel sensitivity. A biomarker based on the expression levels of the BLM and FANCI genes is a potential predictor of platinum sensitivity in triple negative breast cancer and ovarian cancer. Through integrated analysis of gene expression and copy number data from two independent clinical trials in triple negative breast cancer, we identify two genes, BLM and FANCI, involved in double-strand DNA repair where increased expression is related to sensitivity to platinum induced DNA damage. Further functional validation reveals that overexpression of BLM alone promotes DNA damage.
Physiological and Genetic Adaptations to Diving in Sea Nomads

Understanding the physiology and genetics of human hypoxia tolerance has important medical implications, but this phenomenon has thus far only been investigated in high-altitude human populations. Another system, yet to be explored, is humans who engage in breath-hold diving. The indigenous Bajau people ("Sea Nomads") of Southeast Asia live a subsistence lifestyle based on breath-hold diving and are renowned for their extraordinary breath-holding abilities. However, it is unknown whether this has a genetic basis. Using a comparative genomic study, we show that natural selection on genetic variants in the PDE10A gene have increased spleen size in the Bajau, providing them with a larger reservoir of oxygenated red blood cells. We also find evidence of strong selection specific to the Bajau on BDKRB2, a gene affecting the human diving reflex. Thus, the Bajau, and possibly other diving populations, provide a new opportunity to study human adaptation to hypoxia tolerance.

General information
Predicted MHC peptide binding promiscuity explains MHC class I 'hotspots' of antigen presentation defined by mass spectrometry eluted ligand data

Peptides that bind to and are presented by MHC class I and class II molecules collectively make up the immunopeptidome. In the context of vaccine development, an understanding of the immunopeptidome is essential, and much effort has been dedicated to its accurate and cost-effective identification. Current state-of-the-art methods mainly comprise in silico tools for predicting MHC binding, which is strongly correlated with peptide immunogenicity. However, only a small proportion of the peptides that bind to MHC molecules are, in fact, immunogenic, and substantial work has been dedicated to uncovering additional determinants of peptide immunogenicity. In this context, and in light of recent advancements in mass spectrometry (MS), the existence of immunological hotspots has been given new life, inciting the hypothesis that hotspots are associated with MHC class I peptide immunogenicity. We here introduce a precise terminology for defining these hotspots and carry out a systematic analysis of MS and in silico predicted hotspots. We find that hotspots defined from MS data are largely captured by peptide binding predictions, enabling their replication in silico. This leads us to conclude that hotspots, to a great degree, are simply a result of promiscuous HLA binding, which disproves the hypothesis that the identification of hotspots provides novel information in the context of immunogenic peptide prediction. Furthermore, our analyses demonstrate that the signal of ligand processing, although present in the MS data, has very low predictive power to discriminate between MS and in silico defined hotspots.
Pros and cons of different therapeutic antibody formats for recombinant antivenom development
Antibody technologies are being increasingly applied in the field of toxinology. Fuelled by the many advances in immunology, synthetic biology, and antibody research, different approaches and antibody formats are being investigated for the ability to neutralize animal toxins. These different molecular formats each have their own therapeutic characteristics. In this review, we provide an overview of the advances made in the development of toxin-targeting antibodies, and discuss the benefits and drawbacks of different antibody formats in relation to their ability to neutralize toxins, pharmacokinetic features, propensity to cause adverse reactions, formulation, and expression for research and development (R&D) purposes and large-scale manufacturing. A research trend seems to be emerging towards the use of human antibody formats as well as camelid heavy-domain antibody fragments due to their compatibility with the human immune system, beneficial therapeutic properties, and the ability to manufacture these molecules cost-effectively.

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Organisations: Department of Biotechnology and Biomedicine, Network Engineering of Eukaryotic Cell factories, Department of Bio and Health Informatics, Universidad de Costa Rica, National Institutes of Health, Technical University of Denmark, University of São Paulo, Federal University of Roraima
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Retinoic Acid Signaling in Thymic Epithelial Cells Regulates Thymopoiesis

Despite the essential role of thymic epithelial cells (TEC) in T cell development, the signals regulating TEC differentiation and homeostasis remain incompletely understood. In this study, we show a key in vivo role for the vitamin A metabolite, retinoic acid (RA), in TEC homeostasis. In the absence of RA signaling in TEC, cortical TEC (cTEC) and CD80lowMHC class IIlow medullary TEC displayed subset-specific alterations in gene expression, which in cTEC included genes involved in epithelial proliferation, development, and differentiation. Mice whose TEC were unable to respond to RA showed increased cTEC proliferation, an accumulation of stem cell Ag-1high cTEC, and, in early life, a decrease in medullary TEC numbers. These alterations resulted in reduced thymic cellularity in early life, a reduction in CD4 single-positive and CD8 single-positive numbers in both young and adult mice, and enhanced peripheral CD8+ T cell survival upon TCR stimulation. Collectively, our results identify RA as a regulator of TEC homeostasis that is essential for TEC function and normal thymopoiesis.

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Scopus rating (2013): SJR 3.909 SNIP 1.35 CiteScore 5.61
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Scopus rating (2011): SJR 4.06 SNIP 1.347 CiteScore 5.67
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Scopus rating (2010): SJR 4.165 SNIP 1.306
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Scopus rating (2009): SJR 4.157 SNIP 1.338
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Scopus rating (2008): SJR 4.609 SNIP 1.322
Web of Science (2008): Indexed yes
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SCCmecFinder, a Web-Based Tool for Typing of Staphylococcal Cassette Chromosome mec in Staphylococcus aureus Using Whole-Genome Sequence Data

Typing of methicillin-resistant Staphylococcus aureus (MRSA) is important in infection control and surveillance. The current nomenclature of MRSA includes the genetic background of the S. aureus strain determined by multilocus sequence typing (MLST) or equivalent methods like spa typing and typing of the mobile genetic element staphylococcal cassette chromosome mec (SCCmec), which carries the mecA or mecC gene. Whereas MLST and spa typing are relatively simple, typing of SCCmec is less trivial because of its heterogeneity. Whole-genome sequencing (WGS) provides the essential data for typing of the genetic background and SCCmec, but so far, no bioinformatic tools for SCCmec typing have been available. Here, we report the development and evaluation of SCCmecFinder for characterization of the SCCmec element from S. aureus WGS data. SCCmecFinder is able to identify all SCCmec element types, designated I to XIII, with subtyping of SCCmec types IV (2B) and V (5C2). SCCmec elements are characterized by two different gene prediction approaches to achieve correct annotation, a Basic Local Alignment Search Tool (BLAST)-based approach and a k-mer-based approach. Evaluation of SCCmecFinder by using a diverse collection of clinical isolates (n = 93) showed a high typeability level of 96.7%, which increased to 98.9% upon modification of the default settings. In conclusion, SCCmecFinder can be an alternative to more laborious SCCmec typing methods and is freely available at https://cge.cbs.dtu.dk/services/SCCmecFinder. IMPORTANCE SCCmec in MRSA is acknowledged to be of importance not only because it contains the mecA or mecC gene but also for staphylococcal adaptation to different environments, e.g., in hospitals, the community, and livestock. Typing of SCCmec by PCR techniques has, because of its heterogeneity, been challenging, and whole-genome sequencing has only partially solved this since no good bioinformatic tools have been available. In this article, we describe the development of a new bioinformatic tool, SCCmecFinder, that includes most of the needs for infection control professionals and researchers regarding the interpretation of SCCmec elements. The software detects all of the SCCmec elements accepted by the International Working Group on the Classification of Staphylococcal Cassette Chromosome Elements, and users will be prompted if diverging and potential new elements are uploaded. Furthermore, SCCmecFinder will be curated and updated as new elements are found and it is easy to use and freely accessible.

General information
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Organisations: National Food Institute, Research Group for Genomic Epidemiology, Department of Bio and Health Informatics, Genomic Epidemiology, Statens Seruminstitute
Authors: Kaya, H. (Intern), Hasman, H. (Ekstern), Larsen, J. (Ekstern), Stegger, M. (Ekstern), Johannesen, T. B. (Ekstern), Allesøe, R. L. (Intern), Lemvigh, C. K. (Intern), Aarestrup, F. M. (Intern), Lund, O. (Intern), Larsen, A. R. (Ekstern)
Single-tube library preparation for degraded DNA

1. In recent years, massive parallel sequencing has revolutionized the study of degraded DNA, thus enabling the field of ancient DNA to evolve into that of paleogenomics. Despite these advances, the recovery and sequencing of degraded DNA remains challenging due to limitations in the manipulation of chemically damaged and highly fragmented DNA molecules. In particular, the enzymatic reactions and DNA purification steps during library preparation can result in DNA
template loss and sequencing biases, affecting downstream analyses. The development of library preparation methods that circumvent these obstacles and enable higher throughput are therefore of interest to researchers working with degraded DNA.

2. In this study, we compare four Illumina library preparation protocols, including two “single-tube” methods developed for this study with the explicit aim of improving data quality and reducing preparation time and expenses. The methods are tested on grey wolf (Canis lupus) museum specimens.

3. We found single-tube protocols increase library complexity, yield more reads that map uniquely to the reference genome, reduce processing time, and may decrease laboratory costs by 90%.

4. Given the advantages of single-tube library preparations, we anticipate these methods will be of considerable interest to the growing field of paleogenomics and other applications investigating degraded DNA.

**General information**

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Organisations: Department of Bio and Health Informatics, Metagenomics, University of Copenhagen
Authors: Carøe, C. (Intern), Gopalakrishnan, S. (Ekstern), Vinner, L. (Ekstern), Mak, S. S. T. (Ekstern), Sinding, M. S. (Ekstern), Samaniego, J. A. (Ekstern), Wales, N. (Ekstern), Sicheritz-Pontén, T. (Intern), Gilbert, M. T. P. (Ekstern)
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**Streptococcus sanguinis and Streptococcus gordonii: virulence factors in the pan and core-genomes of clinical strains isolated from patients with infective endocarditis**

**General information**

State: Published
Systems genomics study reveals expression quantitative trait loci, regulator genes and pathways associated with boar taint in pigs

Boar taint is an offensive odour and/or taste from a proportion of non-castrated male pigs caused by skatole and androstenone accumulation during sexual maturity. Castration is widely used to avoid boar taint but is currently under debate because of animal welfare concerns. This study aimed to identify expression quantitative trait loci (eQTLs) with potential effects on boar taint compounds to improve breeding possibilities for reduced boar taint. Danish Landrace male boars with low, medium and high genetic merit for skatole and human nose score (HNS) were slaughtered at similar to 100 kg. Gene expression profiles were obtained by RNA-Seq, and genotype data were obtained by an Illumina 60K Porcine SNP chip. Following quality control and filtering, 10,545 and 12,731 genes from liver and testis were included in the eQTL analysis, together with 20,827 SNP variants. A total of 205 and 109 single-tissue eQTLs associated with 102 and 58 unique genes were identified in liver and testis, respectively. By employing a multivariate Bayesian hierarchical model, 26 eQTLs were identified as significant multi-tissue eQTLs. The highest densities of eQTLs were found on pig chromosomes SSC12, SSC1, SSC13, SSC9 and SSC14. Functional characterisation of eQTLs revealed functions within regulation of androgen and the intracellular steroid hormone receptor signalling pathway and of xenobiotic metabolism by cytochrome P450 system and cellular response to oestradiol. A QTL enrichment test revealed 89 QTL traits curated by the Animal Genome PigQTL database to be significantly overlapped by the genomic coordinates of cis-acting eQTLs. Finally, a subset of 35 cis-acting eQTLs overlapped with known boar taint QTL traits. These eQTLs could be useful in the development of a DNA test for boar taint but careful monitoring of other overlapping QTL traits should be performed to avoid any negative consequences of selection.
Taking advantage from phenotype variability in a local animal genetic resource: identification of genomic regions associated with the hairless phenotype in Casertana pigs

Casertana is an endangered autochthonous pig breed (raised in south-central Italy) that is considered to be the descendant of the influential Neapolitan pig population that was used to improve British breeds in the 19th century. Casertana pigs are characterized by a typical, almost complete, hairless phenotype, even though a few Casertana pigs are normal haired. In this work, using Illumina PorcineSNP60 BeadChip data, we carried out a genome-wide association study and an FST analysis with this breed by comparing animals showing the classical hairless phenotype (n = 81) versus pigs classified as haired (n = 15). Combining the results obtained with the two approaches, we identified two significant regions: one on porcine chromosome (SSC) 7 and one on SSC15. The SSC7 region contains the forkhead box N3 (FOXN3) gene, the most plausible candidate gene of this region, considering that mutations in another gene of the same family (forkhead box N1; Foxn1 or FOXN1) are responsible for the nude locus in rodents and alopecia in humans. Another potential candidate gene, rho guanine nucleotide exchange factor 10 (ARHGEF10), is located in the SSC15 region. FOXN3 and ARHGEF10 have been detected as differentially expressed in androgenetic and senescent alopecia respectively. This study on an autochthonous pig breed contributes to shed some light on novel genes potentially involved in hair development and growth and demonstrates that local animal breeds can be valuable genetic resources for disclosing genetic factors affecting unique traits, taking advantage of phenotype variability segregating in small populations.
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Organisations: Department of Bio and Health Informatics, University of Bologna, FAO, INIA, Associazione Nazionale Allevatori Suini
Authors: Schiavo, G. (Ekstern), Bertolini, F. (Intern), Utzeri, V. J. (Ekstern), Ribani, A. (Ekstern), Geraci, C. (Ekstern), Santoro, L. (Ekstern), Óvilo, C. (Ekstern), Fernández, A. I. (Ekstern), Gallo, M. (Ekstern), Fontanesi, L. (Ekstern)
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Publication date: 2018
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BFI (2018): BFI-level 1
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BFI (2017): BFI-level 1
Scopus rating (2017): SNIP 0.977 SJR 0.83
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 1.64 SJR 0.786 SNIP 0.798
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.931 SNIP 1.012 CiteScore 1.8
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.934 SNIP 1.131 CiteScore 2.12
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.018 SNIP 1.126 CiteScore 2.33
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.009 SNIP 1.104 CiteScore 2.19
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 0.99 SNIP 1.016 CiteScore 2
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 0.89 SNIP 0.916
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 0.953 SNIP 1.145
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 0.761 SNIP 0.725
Scopus rating (2007): SJR 0.658 SNIP 0.673
Scopus rating (2006): SJR 0.495 SNIP 0.706
Scopus rating (2005): SJR 0.638 SNIP 0.766
Scopus rating (2004): SJR 0.715 SNIP 0.809
Scopus rating (2003): SJR 0.581 SNIP 0.795
Scopus rating (2002): SJR 0.63 SNIP 1.048
Scopus rating (2001): SJR 0.584 SNIP 1.023
Scopus rating (2000): SJR 0.555 SNIP 0.774
Scopus rating (1999): SJR 0.577 SNIP 1.319
Original language: English
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The first horse herders and the impact of early Bronze Age steppe expansions into Asia

The Yamnaya expansions from the western steppe into Europe and Asia during the Early Bronze Age (~3000 BCE) are believed to have brought with them Indo-European languages and possibly horse husbandry. We analyze 74 ancient whole-genome sequences from across Inner Asia and Anatolia and show that the Botai people associated with the earliest horse husbandry derived from a hunter-gatherer population deeply diverged from the Yamnaya. Our results also suggest distinct migrations bringing West Eurasian ancestry into South Asia before and after but not at the time of Yamnaya culture. We find no evidence of steppe ancestry in Bronze Age Anatolia from when Indo-European languages are attested there. Thus, in contrast to Europe, Early Bronze Age Yamnaya-related migrations had limited direct genetic impact in Asia.

General information

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Organisations: Department of Bio and Health Informatics, Metagenomics, University of Copenhagen, Wellcome Trust Sanger Institute, Leiden University, Harvard University, Shejire DNA project, Al Farabi Kazakh National University, S. Toraighyrov Pavlodar State University, University of Chicago, Buketov Karaganda State University, University of Alaska Fairbanks, Istanbul University, University of Gothenburg, Peter the Great Museum of Anthropology and Ethnography, Japanese Institute of Anatolian Archaeology, Gazi University, Hazara University, University of Exeter, Hazara University, Directorate of Archaeology and Museums, Hazara University, Archaeological Museum Harappa, Russian Academy of Sciences, Ikrutsk State University, Margulan Joint Research Center for Archeological Studies, University of Alberta, University of California at Berkeley
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Article number: eaar7711
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BFI (2018): BFI-level 3
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 2
Scopus rating (2017): SNIP 7.154 SJR 14.142
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 14.39 SJR 13.745 SNIP 7.547
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 12.052 SNIP 8.129 CiteScore 12.68
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 12.41 SNIP 7.809 CiteScore 12.43
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
The medical threat of mamba envenoming in sub-Saharan Africa revealed by genus-wide analysis of venom composition, toxicity and antivenomics profiling of available antivenoms

Mambas (genus Dendroaspis) are among the most feared of the medically important elapid snakes found in sub-Saharan Africa, but many facets of their biology, including the diversity of venom composition, remain relatively understudied. Here, we present a reconstruction of mamba phylogeny, alongside genus-wide venom gland transcriptomic and high-resolution top-down venomic analyses. Whereas the green mambas, D. viridis, D. angusticeps, D. j. jamesoni and D. j. kaimosae, express 3FTx-predominant venoms, black mamba (D. polylepis) venom is dominated by dendrotoxins I and K. The divergent terrestrial ecology of D. polylepis compared to the arboreal niche occupied by all other mambas makes it plausible that this major difference in venom composition is due to dietary variation. The pattern of intrageneric venom variability across Dendroaspis represented a valuable opportunity to investigate, in a genus-wide context, the variant toxicity of the venom, and the degree of paraspecific cross-reactivity between antivenoms and mamba venoms. To this end, the immunological profiles of the five mamba venoms were assessed against a panel of commercial antivenoms generated for the sub-Saharan Africa market. This study provides a genus-wide overview of which available antivenoms may be more efficacious in neutralising human envenomings caused by mambas, irrespective of the species responsible. The information gathered in this study lays the foundations for rationalising the notably different potency and pharmacological profiles of Dendroaspis venoms at locus resolution. This understanding will allow selection and design of toxin immunogens with a view to generating a safer and more efficacious pan-specific antivenom against any mamba envenomation.
The SysteMHC Atlas project

Mass spectrometry (MS)-based immunopeptidomics investigates the repertoire of peptides presented at the cell surface by major histocompatibility complex (MHC) molecules. The broad clinical relevance of MHC-associated peptides, e.g. in precision medicine, provides a strong rationale for the large-scale generation of immunopeptidomic datasets and recent developments in MS-based peptide analysis technologies now support the generation of the required data. Importantly, the availability of diverse immunopeptidomic datasets has resulted in an increasing need to standardize, store and exchange this type of data to enable better collaborations among researchers, to advance the field more efficiently and to establish quality measures required for the meaningful comparison of datasets. Here we present the SysteMHC Atlas (https://systemhcatlas.org), a public database that aims at collecting, organizing, sharing, visualizing and exploring immunopeptidomic data generated by MS. The Atlas includes raw mass spectrometer output files collected from several laboratories around the globe, a catalog of context-specific datasets of MHC class I and class II peptides, standardized MHC allele-specific peptide spectral libraries consisting of consensus spectra calculated from repeat measurements of the same peptide sequence, and links to other proteomics and immunology databases. The SysteMHC Atlas project was created and will be further expanded using a uniform and open computational pipeline that controls the quality of peptide identifications and peptide annotations. Thus, the SysteMHC Atlas disseminates quality controlled immunopeptidomic information to the public domain and serves as a community resource toward the generation of a high-quality comprehensive map of the human immunopeptidome and the support of consistent measurement of immunopeptidomic sample cohorts.

General information

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Organisations: Department of Bio and Health Informatics, Immunoinformatics and Machine Learning
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BFI (2018): BFI-level 2
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 2
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 9.28 SJR 7.883 SNIP 2.744
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 7.358 SNIP 2.631 CiteScore 9.48
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Transcriptome analysis of root-knot nematode (Meloidogyne incognita)-infected tomato (Solanum lycopersicum) roots reveals complex gene expression profiles and metabolic networks of both host and nematode during susceptible and resistance responses.

Root knot nematodes (RKNs, Meloidogyne incognita) are economically important endoparasites having a wide-host range. We have taken a comprehensive transcriptomic approach to investigate the expression of both tomato and RKN genes in...
tomato roots at five infection time intervals from susceptible plants and two infection time intervals from resistant plants, grown under soil conditions. Differentially expressed genes during susceptible (1827-tomato, 462-RKN) and resistance (25-tomato, 160-RKN) interactions were identified. In susceptible responses, tomato genes involved in cell wall structure, development, primary and secondary metabolites and defense signalling pathways along with RKN genes involved in host parasitism, development and defense are discussed. In resistance responses, tomato genes involved in secondary metabolite and hormone-mediated defense responses along with RKN genes involved in starvation stress-induced apoptosis are discussed. Also, forty novel differentially expressed RKN genes encoding secretory proteins were identified. Our findings, for the first time, provide novel insights into temporal regulation of genes involved in various biological processes from tomato and RKN simultaneously during susceptible and resistance responses, and reveals involvement of a complex network of biosynthetic pathways during disease development.

**General information**
State: Published
Organisations: Department of Bio and Health Informatics, Department of Biotechnology and Biomedicine, Metagenomics, Disease Intelligence and Molecular Evolution, University of Delhi
Authors: Shukla, N. (Ekstern), Yadav, R. (Intern), Kaur, P. (Ekstern), Rasmussen, S. (Intern), Goel, S. (Ekstern), Agarwal, M. (Ekstern), Jagannath, A. (Ekstern), Gupta, R. (Intern), Kumar, A. (Ekstern)
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Journal: Molecular Plant Pathology
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Ratings: BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 2
Scopus rating (2017): SNIP 1.537 SJR 1.932
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 4.45 SJR 1.942 SNIP 1.57
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 2.167 SNIP 1.633 CiteScore 4.68
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 2.065 SNIP 1.688 CiteScore 4.48
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 2.096 SNIP 1.631 CiteScore 4.7
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 1.766 SNIP 1.587 CiteScore 4.09
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 1.897 SNIP 1.833 CiteScore 4.2
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 1.594 SNIP 1.297
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 1.758 SNIP 1.461
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 1.597 SNIP 1.315
Scopus rating (2007): SJR 1.659 SNIP 1.136
Scopus rating (2006): SJR 1.567 SNIP 1.089
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 1.47 SNIP 1.004
Transcriptome profiling of fetal Klinefelter testis tissue reveals a possible involvement of long non-coding RNAs in gonocyte maturation

In humans, the most common sex chromosomal disorder is Klinefelter syndrome (KS), caused by the presence of one or more extra X-chromosomes. KS patients display a varying adult phenotype but usually present with azoospermia due to testicular degeneration, which accelerates at puberty. The timing of the germ cell loss and whether it is caused by dysgenetic fetal development of the testes is not known. We investigated 8 fetal KS testes and found a marked reduction in MAGE-A4-positive pre-spermatogonia compared to testes from 15 age-matched controls, indicating a failure of the gonocytes to differentiate into pre-spermatogonia. Transcriptome analysis by RNA-sequencing of formalin-fixed, paraffin-embedded testes originating from 4 fetal KS and 5 age-matched controls revealed 211 differentially expressed transcripts in the fetal KS testis. We found a significant enrichment of upregulated X-chromosomal transcripts and validated the expression of the pseudoautosomal region 1 (PAR1) gene, AKAP17A. Moreover, we found enrichment of long non-coding RNAs in the KS testes (e.g. LINC01569 and RP11-485F13.1). In conclusion, our data indicates that the testicular phenotype observed among adult men with KS is initiated already in fetal life by failure of the gonocyte differentiation into pre-spermatogonia, which could be due to aberrant expression of long non-coding RNAs.
Two novel blood-based biomarker candidates measuring degradation of tau are associated with dementia: A prospective study

Truncated tau appears to be specifically related to disease pathology and recent studies have shown the presence and elevation of several truncated tau species in Cerebrospinal fluid (CSF) of subjects with Alzheimer's disease (AD); however, the relevance of truncated Tau measurements in blood is still being studied. The aim of the current study was to assess the longitudinal associations between baseline levels of two novel blood biomarker candidates measuring truncated tau, Tau-A and Tau-C, and the risk of incident dementia and AD in elderly women. Using solid phase competitive ELISA, two tau fragments were detected in serum of 5,309 women from the Prospective Epidemiological Risk Factor study. The study was an observational, prospective study of Danish postmenopausal women. Subjects were followed with registry-linkage for up to 15 years (median follow-up time 13.7 years). Cox regression was used to assess the utility of the biomarker candidates in relation to dementia and AD. High levels of Tau-A and Tau-C (above the median) in blood were associated with lower risk of dementia and AD (Tau-A: Dementia HR[95% CI] = 0.85[0.70-1.04]; AD 0.71[0.52-0.98] and Tau-C: Dementia 0.84[0.70-1.00]; AD 0.78[0.60-1.03]). Tau-C gave a very modest increase in the AUC in a 5-year prediction horizon as compared to a reference model with age and education, while a combination of the two did not improve their predictive capacity. Measurement of tau in serum is feasible. The serological tau turnover profile may be related to the diagnosis and development of dementia and AD. The exact processing and profile in serum in relation to cognitive disorders remains to be further assessed to provide simple non-invasive tests to identify subjects with progressive cognitive disorders.

General information

State: Published
Organisations: Department of Biotechnology and Biomedicine, Disease Systems Immunology, Department of Bio and Health Informatics, Nordic Bioscience A/S
Authors: Neergaard, J. S. (Intern), Dragsbæk, K. (Intern), Christiansen, C. (Ekstern), Karsdal, M. A. (Ekstern), Brix, S. (Intern), Henriksen, K. (Ekstern)
Publication date: 2018
Use of a Regression Model to Study Host-Genomic Determinants of Phage Susceptibility in MRSA

Staphylococcus aureus is a major agent of nosocomial infections. Especially in methicillin-resistant strains, conventional treatment options are limited and expensive, which has fueled a growing interest in phage therapy approaches. We have tested the susceptibility of 207 clinical S. aureus strains to 12 (nine monovalent) different therapeutic phage preparations and subsequently employed linear regression models to estimate the influence of individual host gene families on resistance to phages. Specifically, we used a two-step regression model setup with a preselection step based on gene family enrichment. We show that our models are robust and capture the data’s underlying signal by comparing their performance to that of models build on randomized data. In doing so, we have identified 167 gene families that govern phage resistance in our strain set and performed functional analysis on them. This revealed genes of possible prophage or mobile genetic element origin, along with genes involved in restriction-modification and transcription regulators, though the majority were genes of unknown function. This study is a step in the direction of understanding the intricate host-phage relationship in this important pathogen with the outlook to targeted phage therapy applications.

General information
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Organisations: Immunoinformatics and Machine Learning, Department of Bio and Health Informatics, GoSeqIt ApS, State Serum Institute, Hvidovre Hospital, Polish Academy of Sciences
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BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): SNIP 0.331 SJR 0.182
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.16 SJR 0.198 SNIP 0.187
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.29 SNIP 0.318 CiteScore 1.94
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.177 SNIP 0.349 CiteScore 1.82
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 0.228 SNIP 0.392 CiteScore 1.89
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 0.264 SNIP 0.58 CiteScore 1.91
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 0.243 SNIP 0.772 CiteScore 1.5
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 0.19 SNIP 0.441
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 0.171 SNIP 0.69
Web of Science (2009): Indexed yes
3D protein-structure-oriented discovery of clinical relation across chronic lymphocytic leukemia patients

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia with still unclear etiology. Indications of antigenic pressure have been hinted, using sequence and structure-based reasoning. The accuracy of such approaches, and in particular of the ones derived from 3D models obtained from the patient’s antibody amino acid sequences, is intimately connected to both the reliability of the models and the quality of the methods used to compare and group them. The proposed work provides a sophisticated method for the classification of CLL patients based on clustering the amino acid sequences of the clonotypic B-cell receptor immunoglobulin, which is the ideal clone-specific marker, critical for clonal behavior and patient outcome. A novel CLL patient clustering method is hereby proposed, combining bioinformatics methods with the extraction of 3D object descriptors, used in machine learning applications. The proposed methodology achieved an efficient and highly informative grouping of CLL patients in accordance to their biological and clinical properties.
A genome-wide association study of thyroid stimulating hormone and free thyroxine in Danish children and adolescents

Background: Hypothyroidism is associated with obesity, and thyroid hormones are involved in the regulation of body composition, including fat mass. Genome-wide association studies (GWAS) in adults have identified 19 and 6 loci associated with plasma concentrations of thyroid stimulating hormone (TSH) and free thyroxine (fT4), respectively.

Objective: This study aimed to identify and characterize genetic variants associated with circulating TSH and fT4 in Danish children and adolescents and to examine whether these variants associate with obesity.

Methods: Genome-wide association analyses of imputed genotype data with fasting plasma concentrations of TSH and fT4 from a population-
based sample of Danish children, adolescents, and young adults, and a group of children, adolescents, and young adults with overweight and obesity were performed (N = 1,764, mean age = 12.0 years [range 2.5-24.7]). Replication was performed in additional comparable samples (N = 2,097, mean age = 11.8 years [1.2-22.8]). Meta-analyses, using linear additive fixed-effect models, were performed on the results of the discovery and replication analyses. Results No novel loci associated with TSH or fT4 were identified. Four loci previously associated with TSH in adults were confirmed in this study population (PDE10A (rs2983511: beta = 0.112SD, p = 4.8.10(-16)), FOXE1 (rs7847663: beta = 0.223SD, p = 1.5 . 10(-20)), NR3C2 (rs9968300: beta = 0.194SD, p = 2.4 . 10(-11)), VEGFA (rs2396083: beta = 0.088SD, p = 2.2 . 10(-10))). Effect sizes of variants known to associate with TSH or fT4 in adults showed a similar direction of effect in our cohort of children and adolescents, 11 of which were associated with TSH or fT4 in our study (p

**General information**

**State:** Published

**Organisations:** Department of Bio and Health Informatics, Administration, University of Copenhagen, Copenhagen University Hospital Holbæk, McMaster University


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**Publication information**

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BFI (2018): BFI-level 1

Web of Science (2018): Indexed yes

BFI (2017): BFI-level 1

Scopus rating (2017): SJR 1.164 SNIP 1.111

Web of Science (2017): Indexed yes

BFI (2016): BFI-level 1

Scopus rating (2016): CiteScore 3.11 SJR 1.236 SNIP 1.101

Web of Science (2016): Indexed yes

BFI (2015): BFI-level 1

Scopus rating (2015): SJR 1.427 SNIP 1.136 CiteScore 3.32

Web of Science (2015): Indexed yes

BFI (2014): BFI-level 1

Scopus rating (2014): SJR 1.559 SNIP 1.148 CiteScore 3.54

Web of Science (2014): Indexed yes

BFI (2013): BFI-level 1

Scopus rating (2013): SJR 1.772 SNIP 1.153 CiteScore 3.94

ISI indexed (2013): ISI indexed yes

Web of Science (2013): Indexed yes

BFI (2012): BFI-level 1

Scopus rating (2012): SJR 1.982 SNIP 1.156 CiteScore 4.15

ISI indexed (2012): ISI indexed yes

Web of Science (2012): Indexed yes

BFI (2011): BFI-level 1

Scopus rating (2011): SJR 2.425 SNIP 1.233 CiteScore 4.58

ISI indexed (2011): ISI indexed no

Web of Science (2011): Indexed yes

BFI (2010): BFI-level 1

Scopus rating (2010): SJR 2.705 SNIP 1.178

Web of Science (2010): Indexed yes

BFI (2009): BFI-level 1

Scopus rating (2009): SJR 2.614 SNIP 1.046
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 conversion 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.

General information
State: Published
Organisations: Department of Bio and Health Informatics, Integrative Systems Biology, Department of Systems Biology, Center for Biological Sequence Analysis, Integrative Systems Biology, Disease Intelligence and Molecular Evolution, Genomic Epidemiology, Functional Human Variation, Aarhus University, Technical University of Denmark, University of Bergen, Karolinska Institutet, BGI-Europe, University of Bristol, University of Copenhagen, Københavns Universitet, BGI-Shenzhen
Number of pages: 20
Publication date: 2017
Main Research Area: Technical/natural sciences

Publication information
Journal: PLoS Genetics
Analysis of free text in electronic health records for identification of cancer patient trajectories

With an aging patient population and increasing complexity in patient disease trajectories, physicians are often met with complex patient histories from which clinical decisions must be made. Due to the increasing rate of adverse events and hospitals facing financial penalties for readmission, there has never been a greater need to enforce evidence-led medical decision-making using available health care data. In the present work, we studied a cohort of 7,741 patients, of whom 4,080 were diagnosed with cancer, surgically treated at a University Hospital in the years 2004-2012. We have developed a methodology that allows disease trajectories of the cancer patients to be estimated from free text in electronic health records (EHRs). By using these disease trajectories, we predict 80% of patient events ahead in time. By control of
confounders from 8326 quantified events, we identified 557 events that constitute high subsequent risks (risk > 20%), including six events for cancer and seven events for metastasis. We believe that the presented methodology and findings could be used to improve clinical decision support and personalize trajectories, thereby decreasing adverse events and optimizing cancer treatment.

**General information**
State: Published
Organisations: Department of Bio and Health Informatics, University Hospital of North Norway, Universidad Rey Juan Carlos, UIT The Arctic University of Norway, University of Warwick, Akershus University Hospital
Authors: Jensen, K. (Ekstern), Soguero-Ruiz, C. (Ekstern), Mikalsen, K. O. (Ekstern), Lindsetmo, R. (Ekstern), Kouskoumvekaki, E. (Intern), Girolami, M. A. (Ekstern), Skrovseth, S. O. (Ekstern), Augestad, K. M. (Ekstern)
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Web of Science (2018): Indexed yes
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Scopus rating (2017): SNIP 1.245 SJR 1.533
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 4.63 SJR 1.692 SNIP 1.354
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.034 SNIP 1.597 CiteScore 5.3
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.163 SNIP 1.554 CiteScore 4.75
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.998 SNIP 1.57 CiteScore 4.06
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.531 SNIP 0.962 CiteScore 2.44
ISI indexed (2012): ISI indexed yes
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**An Analysis of Natural T Cell Responses to Predicted Tumor Neopeptides**
Personalization of cancer immunotherapies such as therapeutic vaccines and adoptive T-cell therapy may benefit from efficient identification and targeting of patient-specific neopeptides. However, current neopeptide prediction methods based on sequencing and predictions of epitope processing and presentation result in a low rate of validation, suggesting that the determinants of peptide immunogenicity are not well understood. We gathered published data on human neopeptides originating from single amino acid substitutions for which T cell reactivity had been experimentally tested, including both immunogenic and non-immunogenic neopeptides. Out of 1,948 neopeptide-HLA (human leukocyte antigen)
combinations from 13 publications, 53 were reported to elicit a T cell response. From these data, we found an enrichment for responses among peptides of length 9. Even though the peptides had been pre-selected based on presumed likelihood of being immunogenic, we found using NetMHCpan-4.0 that immunogenic neopeptides were predicted to bind significantly more strongly to HLA compared to non-immunogenic peptides. Investigation of the HLA binding strength of the immunogenic peptides revealed that the vast majority (96%) shared very strong predicted binding to HLA and that the binding strength was comparable to that observed for pathogen-derived epitopes. Finally, we found that neopeptide dissimilarity to self is a predictor of immunogenicity in situations where neo- and normal peptides share comparable predicted binding strength. In conclusion, these results suggest new strategies for prioritization of mutated peptides, but new data will be needed to confirm their value.

**General information**

State: Published
Organisations: Department of Bio and Health Informatics, Cancer Genomics, Immunoinformatics and Machine Learning, T-cells & Cancer, National Veterinary Institute, Universidad Nacional de San Martin
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Publication date: 2017
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**Ancient genomes show social and reproductive behavior of early Upper Paleolithic foragers**

Present-day hunter-gatherers (HGs) live in multilevel social groups essential to sustain a population structure characterized by limited levels of within-band relatedness and inbreeding. When these wider social networks evolved among HGs is unknown. Here, we investigate whether the contemporary HG strategy was already present in the Upper Paleolithic (UP), using complete genome sequences from Sunghir, a site dated to ~34 thousand years BP (kya) containing multiple anatomically modern human (AMH) individuals. We demonstrate that individuals at Sunghir derive from a population of small effective size, with limited kinship and levels of inbreeding similar to HG populations. Our findings
suggest that UP social organization was similar to that of living HGs, with limited relatedness within residential groups embedded in a larger mating network.

General information

State: Published
Organisations: Department of Bio and Health Informatics, Metagenomics, University of Copenhagen, University of Bern, University of California at Berkeley, University of Cambridge, Russian Academy of Sciences, Lomonosov Moscow State University, University of Oxford
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Main Research Area: Technical/natural sciences
An introduction to Deep learning on biological sequence data - Examples and solutions

Deep neural network architectures such as convolutional and long short-term memory networks have become increasingly popular as machine learning tools during the recent years. The availability of greater computational resources, more data, new algorithms for training deep models and easy to use libraries for implementation and training of neural networks are the drivers of this development. The use of deep learning has been especially successful in image recognition; and the development of tools, applications and code examples are in most cases centered within this field rather than within biology. Here, we aim to further the development of deep learning methods within biology by providing application examples and ready to apply and adapt code templates. Given such examples, we illustrate how architectures consisting of convolutional and long short-term memory neural networks can relatively easily be designed and trained to state-of-the-art performance on three biological sequence problems: prediction of subcellular localization, protein secondary structure and the binding of peptides to MHC Class II molecules. All implementations and datasets are available online to the scientific community at https://github.com/vanessajurtz/lasagne4bio. Supplementary data are available at Bioinformatics online.

General information

State: Published
Organisations: Department of Bio and Health Informatics, Immunoinformatics and Machine Learning, Department of Applied Mathematics and Computer Science, Department of Electrical Engineering, Disease Intelligence and Molecular Evolution, Copenhagen Center for Health Technology, Cognitive Systems, University of Copenhagen
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Web of Science (2018): Indexed yes
BFI (2017): BFI-level 2
Application of integrative genomics and systems biology to conventional and in vitro reproductive traits in cattle

Assisted reproductive technologies (ARTs) have a strong impact on breeding especially when coupled with genomic selection (GS). The routine implementation of in vitro production (IVP) and GS of embryos before embryo transfer (ET) in breeding companies is not yet possible. Improvement of oocyte donor and embryo recipient quality is needed to make realistic a commercialization of these procedures in the near future. A better understanding of both biological mechanisms and molecular markers associated to IVPET related traits is necessary to improve the prediction of donor and recipient cow quality for IVP procedures. The huge amount of data generated from high throughput technologies has a tremendous impact in the search for biomarkers of complex traits. This paper reviews integrative genomics and systems biology approaches as applied to both Bos indicus and Bos taurus cattle reproduction by both conventional and ARTs such as OPU-IVP. The integration of systems biology information across different biological layers generates a complete view of the different molecular networks that control complex traits and can provide a strong contribution to the understanding of traits related to ARTs.
ArrayPitope: Automated Analysis of Amino Acid Substitutions for Peptide Microarray-Based Antibody Epitope Mapping

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.
Association among bile acids, the human gut microbiome and metabolic diseases

General information
State: Published
Organisations: Department of Bio and Health Informatics, Metagenomics, Department of Biotechnology and Biomedicine, Disease Systems Immunology, Clinical-Microbiomics ApS
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Number of pages: 1
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Main Research Area: Technical/natural sciences
Electronic versions:
Bacterial whole genome-based phylogeny: construction of a new benchmarking dataset and assessment of some existing methods

Background
Whole genome sequencing (WGS) is increasingly used in diagnostics and surveillance of infectious diseases. A major application for WGS is to use the data for identifying outbreak clusters, and there is therefore a need for methods that can accurately and efficiently infer phylogenies from sequencing reads. In the present study we describe a new dataset that we have created for the purpose of benchmarking such WGS-based methods for epidemiological data, and also present an analysis where we use the data to compare the performance of some current methods.

Results
Our aim was to create a benchmark data set that mimics sequencing data of the sort that might be collected during an outbreak of an infectious disease. This was achieved by letting an E. coli hypermutator strain grow in the lab for 8 consecutive days, each day splitting the culture in two while also collecting samples for sequencing. The result is a data set consisting of 101 whole genome sequences with known phylogenetic relationship. Among the sequenced samples 51 correspond to internal nodes in the phylogeny because they are ancestral, while the remaining 50 correspond to leaves. We also used the newly created data set to compare three different online available methods that infer phylogenies from whole-genome sequencing reads: NDtree, CSI Phylogeny and REALPHY. One complication when comparing the output of these methods with the known phylogeny is that phylogenetic methods typically build trees where all observed sequences are placed as leafs, even though some of them are in fact ancestral. We therefore devised a method for post processing the inferred trees by collapsing short branches (thus relocating some leafs to internal nodes), and also present two new measures of tree similarity that takes into account the identity of both internal and leaf nodes.

Conclusions
Based on this analysis we find that, among the investigated methods, CSI Phylogeny had the best performance, correctly identifying 73% of all branches in the tree and 71% of all clades. We have made all data from this experiment (raw sequencing reads, consensus whole-genome sequences, as well as descriptions of the known phylogeny in a variety of formats) publicly available, with the hope that other groups may find this data useful for benchmarking and exploring the performance of epidemiological methods. All data is freely available at: https://cge.cbs.dtu.dk/services/evolution_data.php.

General information
State: Published
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BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.327 SNIP 1.199 CiteScore 4.18
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BFI (2013): BFI-level 1
Basic and practical aspects of pregnancy establishment in cattle

Bovine embryos are increasingly produced using reproductive technologies, e.g., ovum pick-up (OPU), in vitro embryo production (IVP) and embryo transfer (ET). Such in vitro manipulated embryos are known to deviate in several aspects compared to in vivo derived embryos. Pregnancy establishment in cattle involves timed biological events including fine-tuned communication, initiated and carried out by both the embryo and the endometrium. This stimulates research to increase the understanding of events and interactions taking place in the uterus after embryo transfer, both from a biological and systems biology point of view. This review will focus on the biological events taking place during early embryonic development, implantation and beginning of placentation, with focus on transfer of in vitro produced embryos,
including a systems biology approach for selection of superior embryo recipients.

**General information**

State: Published
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**BepiPred-2.0: improving sequence-based B-cell epitope prediction using conformational epitopes**

Antibodies have become an indispensable tool for many biotechnological and clinical applications. They bind their molecular target (antigen) by recognizing a portion of its structure (epitope) in a highly specific manner. The ability to predict epitopes from antigen sequences alone is a complex task. Despite substantial effort, limited advancement has been achieved over the last decade in the accuracy of epitope prediction methods, especially for those that rely on the sequence of the antigen only. Here, we present BepiPred-2.0 (http://www.cbs.dtu.dk/services/BepiPred/), a web server for predicting B-cell epitopes from antigen sequences. BepiPred-2.0 is based on a random forest algorithm trained on epitopes annotated from antibody-antigen protein structures. This new method was found to outperform other available tools for sequence-based epitope prediction both on epitope data derived from solved 3D structures, and on a large collection of linear epitopes downloaded from the IEDB database. The method displays results in a user-friendly and informative way, both for computer-savvy and non-expert users. We believe that BepiPred-2.0 will be a valuable tool for the bioinformatics and immunology community.

**General information**

State: Published
Organisations: Department of Bio and Health Informatics, Immunoinformatics and Machine Learning, La Jolla Institute for Allergy & Immunology
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Scopus rating (2016): CiteScore 9.28 SJR 7.883 SNIP 2.744
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.
Peptide antigen-presentation by Major Histocompatibility Class (MHC) I proteins initiates CD8+ T cell mediated immunity against pathogens and cancers. MHC I molecules typically bind peptides with nine amino acids in length with both ends tucked inside the major A and F binding pocket. It has been known for a while that longer peptides can also bind by either bulging out of the groove in the middle of the peptide or by binding in a zig-zag fashion inside the groove. In a recent study, we identified an alternative binding conformation of naturally occurring peptides from Toxoplasma gondii bound by HLA-A*02:01. These peptides were extended at the C-terminus (PΩ) and contained charged amino acids not more than 3 residues after the anchor amino acid at PΩ, which enabled them to open the F pocket and expose their C-terminal extension into the solvent. Here, we show that the mechanism of F pocket opening is dictated by the charge of the first charged amino acid found within the extension. While positively charged amino acid result in the Tyr84 swing, amino acids that are negatively charged induce a not previously described Lys146 lift. Further, we demonstrate that the peptides with alternative binding modes have properties that fit very poorly to the conventional MHC class I pathway, and suggest they are presented via alternative means, potentially including cross-presentation via the MHC class II pathway.

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Organisations: Department of Systems Biology, Department of Biotechnology and Biomedicine, Department of Bio and Health Informatics
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T-cell receptor (TCR), Toxoplasma gondii, antigen presentation, major histocompatibility complex (MHC), natural killer cells (NK cells), peptide interaction, protein crystallization, protein structure

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**CD49a Expression Defines Tissue-Resident CD8+ T Cells Poised for Cytotoxic Function in Human Skin**

Tissue-resident memory T (Trm) cells form a heterogeneous population that provides localized protection against pathogens. Here, we identify CD49a as a marker that differentiates CD8+ Trm cells on a compartmental and functional basis. In human skin epithelia, CD8+CD49a+ Trm cells produced interferon-γ, whereas CD8+CD49a− Trm cells produced interleukin-17 (IL-17). In addition, CD8+CD49a+ Trm cells from healthy skin rapidly induced the expression of the effector molecules perforin and granzyme B when stimulated with IL-15, thereby promoting a strong cytotoxic response. In skin from patients with vitiligo, where melanocytes are eradicated locally, CD8+CD49a+ Trm cells that constitutively expressed perforin and granzyme B accumulated both in the epidermis and dermis. Conversely, CD8+CD49a− Trm cells from psoriasis lesions predominantly generated IL-17 responses that promote local inflammation in this skin disease. Overall, CD49a expression delineates CD8+ Trm cell specialization in human epithelial barriers and correlates with the effector cell balance found in distinct inflammatory skin diseases.

**General information**

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**Organisations**: Department of Bio and Health Informatics, Integrative Systems Biology, Karolinska Institutet, Karolinska University Hospital, University of Bergen


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- Web of Science (2017): Indexed yes
- BFI (2016): BFI-level 2
- Scopus rating (2016): CiteScore 17.17 SJR 16.957 SNIP 4.635
- Web of Science (2016): Indexed yes
- BFI (2015): BFI-level 2
- Web of Science (2015): Indexed yes
- BFI (2014): BFI-level 2
- Scopus rating (2014): SJR 16.417 SNIP 4.024 CiteScore 15.52
- BFI (2013): BFI-level 2
- Scopus rating (2013): SJR 14.618 SNIP 3.98 CiteScore 15.26
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- Web of Science (2013): Indexed yes
- BFI (2012): BFI-level 2
- Scopus rating (2012): SJR 15.902 SNIP 3.997 CiteScore 16.16
- ISI indexed (2012): ISI indexed yes
- Web of Science (2012): Indexed yes
- BFI (2011): BFI-level 2
- Scopus rating (2011): SJR 17.131 SNIP 4.027 CiteScore 15.89
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- BFI (2010): BFI-level 2
- Scopus rating (2010): SJR 18.565 SNIP 3.763
- BFI (2009): BFI-level 2
Cerebellar mutism syndrome in children with brain tumours of the posterior fossa

Background: This observational, prospective, multicentre study will include 500 children with posterior fossa tumours. It opened late 2014 with participation from 20 Nordic and Baltic centres. From 2016, five British centres and four Dutch centres will join with a total annual accrual of 130 patients. Three other major European centres are invited to join from 2016/17. Follow-up will run for 12 months after inclusion of the last patient. All patients are treated according to local practice. Clinical data are collected through standardized online registration at pre-determined time points pre- and postoperatively. Neurological status and speech functions are examined pre-operatively and postoperatively at 1-4 weeks, 2 and 12 months. Pre- and postoperative speech samples are recorded and analysed. Imaging will be reviewed centrally. Pathology is classified according to the 2007 WHO system. Germline DNA will be collected from all patients for associations between CMS characteristics and host genome variants including pathway profiles.

Discussion: Through prospective and detailed collection of information on 1) differences in incidence and clinical course of CMS for different patient and tumour characteristics, 2) standardized surgical data and their association with CMS, 3) diversities and results of other therapeutic interventions, and 4) the role of host genome variants, we aim to achieve a better understanding of risk factors for and the clinical course of CMS - with the ultimate goal of defining strategies for prevention and treatment of this severely disabling condition.
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.

Citrullination only infrequently impacts peptide binding to HLA class II MHC

It has been hypothesized that HLA class II alleles associated with rheumatoid arthritis (RA) preferentially present self-antigens altered by post-translational modification, such as citrullination. To understand the role of citrullination we tested four RA-associated citrullinated epitopes and their corresponding wild-type version for binding to 28 common HLA class II. Binding patterns were variable, and no consistent impact of citrullination was identified. Indeed, in one case citrullination significantly increased binding compared to the WT peptide, in another citrullination was associated with a reduction in promiscuity by 40%. For a more comprehensive analysis, we tested over 200 citrullinated peptides derived from vimentin and collagen II for their capacity to bind the RA-associated shared epitope alleles DRB1*01:01 and DRB1*04:01. The overall effect of citrullination on binding was found to be relatively minor, and only rarely associated with 3-fold increases or decreases in affinity. Previous studies have suggested that citrullination of MHC anchor residues, in particular P4, is associated with generation of novel RA-associated epitopes. However, analysis of the predicted MHC-binding cores of all peptides tested found that in modified peptides with increased binding affinity the citrullinated residue was predicted to occupy an anchor position in only a minority of cases. Finally, we also show that identification of citrullinated peptide binders could be facilitated by using the NetMHCIIpan 3.1 algorithm, representing citrullination as a wildcard. Our studies identify a total of 117 citrullinated peptides that bound RA-associated alleles with an affinity of 1000 nM or better.
Clustering on baseline clinical variables identifies subgroups of type 2 diabetes patients with different rate of progression over 18 months: a DIRECT study

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BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 5.23 SJR 3.25 SNIP 1.721
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 3.61 SNIP 1.933 CiteScore 5.57
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 3.243 SNIP 1.964 CiteScore 5.57
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 3.259 SNIP 2.035 CiteScore 6
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 3.235 SNIP 1.914 CiteScore 5.76
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 3.177 SNIP 1.857 CiteScore 5.47
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 3.345 SNIP 1.847
ClusterSignificance: A bioconductor package facilitating statistical analysis of class cluster separations in dimensionality reduced data

Summary
Multi-dimensional data generated via high-throughput experiments is increasingly used in conjunction with dimensionality reduction methods to ascertain if resulting separations of the data correspond with known classes. This is particularly useful to determine if a subset of the variables, e.g. genes in a specific pathway, alone can separate samples into these established classes. Despite this, the evaluation of class separations is often subjective and performed via visualization. Here we present the ClusterSignificance package; a set of tools designed to assess the statistical significance of class separations downstream of dimensionality reduction algorithms. In addition, we demonstrate the design and utility of the ClusterSignificance package and utilize it to determine the importance of long non-coding RNA expression in the identity of multiple hematological malignancies.

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Organisations: Department of Bio and Health Informatics, Integrative Systems Biology, Karolinska Institutet
Authors: Serviss, J. T. (Ekstern), Gådin, J. R. (Ekstern), Eriksson, P. (Ekstern), Folkersen, L. (Intern), Grandér, D. (Ekstern)
Pages: 3126-3128
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Scopus rating (2015): CiteScore 6.06
Combinatorial Drug Screening Identifies Ewing Sarcoma-specific Sensitivities

Improvements in survival for Ewing sarcoma pediatric and adolescent patients have been modest over the past 20 years. Combinations of anticancer agents endure as an option to overcome resistance to single treatments caused by compensatory pathways. Moreover, combinations are thought to lessen any associated adverse side effects through reduced dosing, which is particularly important in childhood tumors. Using a parallel phenotypic combinatorial screening approach of cells derived from three pediatric tumor types, we identified Ewing sarcoma-specific interactions of a diverse set of targeted agents including approved drugs. We were able to retrieve highly synergistic drug combinations specific for Ewing sarcoma and identified signaling processes important for Ewing sarcoma cell proliferation determined by EWS-FLI1. We generated a molecular target profile of PKC412, a multikinase inhibitor with strong synergistic propensity in Ewing sarcoma, revealing its targets in critical Ewing sarcoma signaling routes. Using a multilevel experimental approach including quantitative phosphoproteomics, we analyzed the molecular rationale behind the disease-specific synergistic effect of simultaneous application of PKC412 and IGF1R inhibitors. The mechanism of the drug synergy between these inhibitors is different from the sum of the mechanisms of the single agents. The combination effectively inhibited pathway crosstalk and averted feedback loop repression, in EWS-FLI1-dependent manner. Mol Cancer Ther; 16(1); 88-101. ©2016 AACR.

Combinatorial Drug Screening Identifies Ewing Sarcoma-specific Sensitivities

Improvements in survival for Ewing sarcoma pediatric and adolescent patients have been modest over the past 20 years. Combinations of anticancer agents endure as an option to overcome resistance to single treatments caused by compensatory pathways. Moreover, combinations are thought to lessen any associated adverse side effects through reduced dosing, which is particularly important in childhood tumors. Using a parallel phenotypic combinatorial screening approach of cells derived from three pediatric tumor types, we identified Ewing sarcoma-specific interactions of a diverse set of targeted agents including approved drugs. We were able to retrieve highly synergistic drug combinations specific for Ewing sarcoma and identified signaling processes important for Ewing sarcoma cell proliferation determined by EWS-FLI1. We generated a molecular target profile of PKC412, a multikinase inhibitor with strong synergistic propensity in Ewing sarcoma, revealing its targets in critical Ewing sarcoma signaling routes. Using a multilevel experimental approach including quantitative phosphoproteomics, we analyzed the molecular rationale behind the disease-specific synergistic effect of simultaneous application of PKC412 and IGF1R inhibitors. The mechanism of the drug synergy between these inhibitors is different from the sum of the mechanisms of the single agents. The combination effectively inhibited pathway crosstalk and averted feedback loop repression, in EWS-FLI1-dependent manner. Mol Cancer Ther; 16(1); 88-101. ©2016 AACR.

General information

State: Published
Organisations: Department of Bio and Health Informatics, Integrative Systems Biology, Austrian Academy of Sciences, Georgetown University Medical Center, University of Copenhagen, University of Glasgow, Children's Cancer Research Institute, Medical University of Vienna
Comparative performance of the BGISEQ-500 versus Illumina HiSeq2500 sequencing platforms for palaeogenomic sequencing

Background: Ancient DNA research has been revolutionised following development of “Next Generation” Sequencing platforms. Although a number of such platforms have been applied to ancient DNA samples, the Illumina series are the dominant choice today, mainly because of high production capacities and short read production. Recently a potentially attractive alternative platform for palaeogenomic data generation has been developed, the BGISEQ-500, whose sequence output are comparable with the Illumina series. In this study, we modified the standard BGISEQ-500 library preparation specifically for use on degraded DNA, then directly compared the sequencing performance and data quality of the BGISEQ-500 to the Illumina HiSeq2500 platform, on DNA extracted from eight historic and ancient dog and wolf samples.

Results: The data generated was largely comparable between sequencing platforms, with no statistically significant difference observed for parameters including level (p = 0.371) and average sequence length (p = 0.0718) of endogenous nuclear DNA, sequence GC content (p = 0.311), double stranded DNA damage rate (p = 0.309), and sequence clonality (p = 0.093). Small significant differences were found in single strand DNA damage rate (δS, slight lower for the BGISEQ-500, p = 0.011) and the background rate of difference from the reference genome (θ, slightly higher for BGISEQ-500, p = 0.012). This may result from the differences in amplification cycles used to PCR amplify the libraries. A significant difference was also observed in the mitochondrial DNA percentages recovered (p = 0.018), although we believe this is likely a stochastic effect relating to the extremely low levels of mitochondria that were sequenced from three of the samples with overall very low levels of endogenous DNA.

Conclusions: Although we acknowledge our analyses were limited to animal material, our observations suggest that the BGISEQ-500 holds the potential to represent valid and potentially valuable alternative platform for palaeogenomic data generation, that is worthy of future exploration by those interested in the sequencing and analysis of degraded DNA.
Comparative proteomics of oxidative stress response of Lactobacillus acidophilus NCFM reveals effects on DNA repair and cysteine de novo synthesis

Probiotic cultures encounter oxidative conditions during manufacturing, yet protein abundance changes induced by such stress have not been characterized for some of the most common probiotics and starters. This comparative proteomics investigation focuses on the response by Lactobacillus acidophilus NCFM to H2O2, simulating an oxidative environment. Bacterial growth was monitored by BioScreen and batch cultures were harvested at exponential phase for protein profiling of stress responses by 2D gel-based comparative proteomics. Proteins identified in 19 of 21 spots changing in abundance due to H2O2 were typically related to carbohydrate and energy metabolism, cysteine biosynthesis, and stress. In particular, increased cysteine synthase activity may accumulate a cysteine pool relevant for protein stability, enzyme catalysis and the disulfide-reducing pathway. The stress response further included elevated abundance of biomolecules reducing damage such as enzymes from DNA repair pathways and metabolic enzymes with active site cysteine residues. By contrast, a protein-refolding chaperone showed reduced abundance, possibly reflecting severe oxidative protein destruction that was not overcome by refolding. The proteome analysis provides novel insight into resistance mechanisms in lactic acid bacteria against reactive oxygen species and constitutes a valuable starting point for improving industrial processes, food design or strain engineering preserving microorganism viability.

General information
State: Published
Organisations: Enzyme and Protein Chemistry, Department of Biotechnology and Biomedicine, Immunoinformatics and Machine Learning, University of Torino
Authors: Calderini, E. (Ekstern), Celebioglu, H. U. (Intern), Villarroel, J. (Intern), Jacobsen, S. (Intern), Svensson, B. (Intern), Pessione, E. (Ekstern)
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Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.85 SJR 1.564 SNIP 0.889
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.48 SNIP 0.969 CiteScore 3.7
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.449 SNIP 0.973 CiteScore 3.73
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.488 SNIP 0.978 CiteScore 3.88
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.497 SNIP 1.094 CiteScore 4.1
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
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Scopus rating (2011): SJR 1.691 SNIP 1.175 CiteScore 4.49
ISI indexed (2011): ISI indexed yes
Comparison of global gene expression profiles of microdissected human foetal Leydig cells with their normal and hyperplastic adult equivalents

STUDY QUESTION: Do human adult Leydig cells (ALCs) within hyperplastic micronodules display characteristics of foetal LCs (FLCs)?

SUMMARY ANSWER: The gene expression profiles of FLCs and all ALC subgroups were clearly different, but there were no significant differences in expressed genes between the normally clustered and hyperplastic ALCs.

WHAT IS KNOWN ALREADY: LCs are the primary androgen producing cells in males throughout development and appear in chronologically distinct populations; FLCs, neonatal LCs and ALCs. ALCs are responsible for progression through puberty and for maintenance of reproductive functions in adulthood. In patients with reproductive problems, such as infertility or testicular cancer, and especially in men with high gonadotrophin levels, LC function is often impaired, and LCs may cluster abnormally into hyperplastic micronodules (defined as clusters of > 15 LCs in a cross-section).

STUDY DESIGN, SIZE, DURATION: A genome-wide microarray study of LCs microdissected from human foetal and adult tissue samples (n = 12). Additional tissue specimens (n = 15) were used for validation of the mRNA expression data at the protein level.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Frozen human tissue samples were used for the microarray study, including morphologically normal foetal (gestational week 10-11) testis samples, and adult testis specimens with normal LC distribution, LC micronodules or LC micronodules adjacent to hCG-producing testicular germ cell tumours. Transcriptome profiling was performed on Agilent whole human genome microarray 4 x 44 K chips. Microarray data pre-processing and statistical analysis were performed using the limma R/Bioconductor package in the R software, and differentially expressed genes were further analysed for gene set enrichment using the DAVID Bioinformatics software. Selected genes were studied at the protein level by immunohistochemistry.

MAIN RESULTS AND THE ROLE OF CHANCE: The transcriptomes of FLCs and ALCs differed significantly from each other, whereas the profiles of the normally clustered and hyperplastic ALCs were similar despite morphological heterogeneity. The study revealed several genes not known previously to be expressed in LCs during early development, including sulfotransferase family 2A member 1 (SULT2A1), WNT1-inducible signalling pathway protein 2 (WISP2), hydroxyprostaglandin dehydrogenase (HPGD) and insulin-like growth factor 2 mRNA binding protein 1 (IGF2BP1), whose expression changes were validated at the protein level. LARGE SCALE DATA: The transcriptomic data are deposited in ArrayExpress (accession code E-MTAB-5453).

LIMITATIONS, REASONS FOR CAUTION: The small number of biological replicates and the necessity of RNA amplification due to the scarcity of human tissues, especially foetal specimens, are the main limitations of the study. Heterogeneous subpopulations of LCs within micronodules were not discriminated during
microdissection and might have affected the expression profiling. The study was constrained by the lack of availability of truly normal controls. Testis samples used as 'controls' displayed complete spermatogenesis and were from patients with germ cell neoplasia but with undetectable hCG and normal hormone levels.

WIDER IMPLICATIONS OF THE FINDINGS:
The changes in LC morphology and function observed in patients with reproductive disorders possibly reflect subtle changes in the expression of many genes rather than regulatory changes of single genes or pathways. The study provides new insights into the development and maturation of human LCs by the identification of a number of potential functional markers for FLC and ALC.

General information
State: Published
Organisations: Department of Systems Biology, Department of Biotechnology and Biomedicine, DTU Multi Assay Core, Department of Bio and Health Informatics, Integrative Systems Biology, Copenhagen University Hospital
Authors: Lottrup, G. (Ekstern), Belling, K. G. (Intern), Leffers, H. (Ekstern), Nielsen, J. E. (Ekstern), Dalgaard, M. D. (Intern), Juul, A. (Ekstern), Skakkebæk, N. E. (Ekstern), Brunak, S. (Intern), Rajpert-De Meyts, E. (Ekstern)
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BFI (2016): BFI-level 1
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BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.713 SNIP 1.045 CiteScore 3.3
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.738 SNIP 1.144 CiteScore 3.5
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.915 SNIP 1.425 CiteScore 4.07
ISI indexed (2013): ISI indexed yes
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Scopus rating (2012): SJR 2.025 SNIP 1.463 CiteScore 4.39
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.763 SNIP 1.189 CiteScore 3.98
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.568 SNIP 1.1
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.296 SNIP 0.987
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Scopus rating (2008): SJR 1.366 SNIP 0.899
Scopus rating (2007): SJR 1.536 SNIP 1.017
Scopus rating (2006): SJR 1.502 SNIP 1.013
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Scopus rating (2005): SJR 1.564 SNIP 1.087
Scopus rating (2004): SJR 1.393 SNIP 1.095
Complete mitochondrial genome of the Oriental Hornet, Vespa orientalis F. (Hymenoptera: Vespidae)

The Oriental Hornet (Vespa orientalis) is a social insect belonging to the Vespiade family (Wasps, Hornets, Yellowjackets), genus Vespa (true Hornets). The oriental hornet is a scavenger and an agricultural pest, especially to bee farmers, but is also recently described as a harvester of solar energy. Here, we report the mitochondrial genome sequence of the Oriental Hornet, Vespa orientalis F., which may play a vital role in understanding this wasp biology, light trapping and generation of electricity. The mitochondrial genome of this hornet is 16,099 bp in length, containing 13 protein-coding genes, 21 transfer RNA genes, and 2 ribosomal RNA genes. The overall base composition of the heavy-strand is 40.3% A, 5.9% C, 13.2% G, and 40.6% T, the percentages of A and T being higher than that of G and C. The mitochondrial genome of the Oriental Hornet, Vespa orientalis F. represents the first mitogenome of a solar energy harvesting insect.

Contamination of the Arctic reflected in microbial metagenomes from the Greenland ice sheet: Letter

Globally emitted contaminants accumulate in the Arctic and are stored in the frozen environments of the cryosphere. Climate change influences the release of these contaminants through elevated melt rates, resulting in increased contamination locally. Our understanding of how biological processes interact with contamination in the Arctic is limited. Through shotgun metagenomic data and binned genomes from metagenomes we show that microbial communities, sampled from multiple surface ice locations on the Greenland ice sheet, have the potential for resistance to and
The microbial potential to degrade anthropogenic contaminants, such as toxic and persistent polychlorinated biphenyls, was found to be spatially variable and not limited to regions close to human activities. Binned genomes showed close resemblance to microorganisms isolated from contaminated habitats. These results indicate that, from a microbiological perspective, the Greenland ice sheet cannot be seen as a pristine environment.
Cross-recognition of a pit viper (Crotalinae) polyspecific antivenom explored through high-density peptide microarray epitope mapping

Snakebite antivenom is a 120 years old invention based on polyclonal mixtures of antibodies purified from the blood of hyper-immunized animals. Knowledge on antibody recognition sites (epitopes) on snake venom proteins is limited, but may be used to provide molecular level explanations for antivenom cross-reactivity. In turn, this may help guide antivenom development by elucidating immunological biases in existing antivenoms. In this study, we have identified and characterized linear elements of B-cell epitopes from 870 pit viper venom protein sequences by employing a high-throughput methodology based on custom designed high-density peptide microarrays. By combining data on antibody-peptide interactions with multiple sequence alignments of homologous toxin sequences and protein modelling, we have determined linear elements of antibody binding sites for snake venom metalloproteases (SVMPs), phospholipases A2s (PLA2s), and snake venom serine proteases (SVSPs). The studied antivenom antibodies were found to recognize linear elements in each of the three enzymatic toxin families. In contrast to a similar study of elapid (non-enzymatic) neurotoxins, these enzymatic toxins were generally not recognized at the catalytic active site responsible for toxicity, but instead at other sites, of which some are known for allosteric inhibition or for interaction with the tissue target. Antibody recognition was found to be preserved for several minor variations in the protein sequences, although the antibody-toxin interactions could often be eliminated completely by substitution of a single residue. This finding is likely to have large implications for the cross-reactivity of the antivenom and indicate that multiple different antibodies are likely to be needed for targeting an entire group of toxins in these recognized sites.

General information
State: Published
Organisations: Network Engineering of Eukaryotic Cell factories, Department of Bio and Health Informatics, Genomic Epidemiology, Department of Biotechnology and Biomedicine, Integrative Systems Biology, Universidad de Costa Rica
Authors: Engmark, M. (Intern), Lomonte, B. (Ekstern), Gutiérrez, J. M. (Ekstern), Laustsen, A. H. (Intern), De Masi, F. (Intern), Andersen, M. R. (Intern), Lund, O. (Intern)
Number of pages: 23
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Scopus rating (2014): CiteScore 4.61
Scopus rating (2013): CiteScore 4.72
Scopus rating (2012): CiteScore 4.75
Scopus rating (2011): CiteScore 4.64
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Bibliographical note
Cutavirus in Cutaneous Malignant Melanoma

A novel human protoparvovirus related to human bufavirus and preliminarily named cutavirus has been discovered. We detected cutavirus in a sample of cutaneous malignant melanoma by using viral enrichment and high-throughput sequencing. The role of cutaviruses in cutaneous cancers remains to be investigated.

General information

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Organisations: Department of Bio and Health Informatics, Integrative Systems Biology, Aarhus University, University of Copenhagen, Statens Serum Institut
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Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 4.92 SJR 3.428 SNIP 2.198
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 3.101 SNIP 2.012 CiteScore 4.23
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 3.509 SNIP 2.406 CiteScore 4.59
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 3.254 SNIP 2.266 CiteScore 4.68
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 2.858 SNIP 2.131 CiteScore 4.25
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 2.785 SNIP 2.19 CiteScore 4.46
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 3.021 SNIP 2.319
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Deep feature learning for virus detection using a Convolutional Neural Network

General information
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Organisations: Department of Bio and Health Informatics, Integrative Systems Biology, Technical University of Denmark, Universidad de Valladolid
Authors: Calvo, D. (Ekstern), de la Torre, I. (Ekstern), Franco, M. A. (Ekstern), Brunak, S. (Intern), Gonzalez-Izarzugaza, J. M. (Intern)
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Publication: Research - peer-review › Conference abstract in proceedings – Annual report year: 2017

DeepLoc: prediction of protein subcellular localization using deep learning
The prediction of eukaryotic protein subcellular localization is a well-studied topic in bioinformatics due to its relevance in proteomics research. Many machine learning methods have been successfully applied in this task, but in most of them, predictions rely on annotation of homologues from knowledge databases. For novel proteins where no annotated
homologues exist, and for predicting the effects of sequence variants, it is desirable to have methods for predicting protein properties from sequence information only. Here, we present a prediction algorithm using deep neural networks to predict protein subcellular localization relying only on sequence information. At its core, the prediction model uses a recurrent neural network that processes the entire protein sequence and an attention mechanism identifying protein regions important for the subcellular localization. The model was trained and tested on a protein dataset extracted from one of the latest UniProt releases, in which experimentally annotated proteins follow more stringent criteria than previously. We demonstrate that our model achieves a good accuracy (78% for 10 categories; 92% for membrane-bound or soluble), outperforming current state-of-the-art algorithms, including those relying on homology information. The method is available as a web server at http://www.cbs.dtu.dk/services/DeepLoc . Example code is available at https://github.com/JJAlmagro/subcellular_localization . The dataset is available at http://www.cbs.dtu.dk/services/DeepLoc/data.php . jjalma@dtu.dk.

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Organisations: Department of Bio and Health Informatics, Department of Applied Mathematics and Computer Science , Disease Intelligence and Molecular Evolution, Copenhagen Center for Health Technology, Cognitive Systems, University of Copenhagen
Authors: Almagro Armenteros, J. J. (Intern), Sønderby, C. K. (Ekstern), Sønderby, S. K. (Ekstern), Nielsen, H. (Intern), Winther, O. (Intern)
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Scopus rating (2016): CiteScore 6.42
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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
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BFI (2013): BFI-level 2
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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
BFI (2009): BFI-level 2
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 2
Design, development and experimental trial of a tailored cytotoxic T-cell vaccine against Porcine Reproductive and Respiratory Syndrome Virus-2

Porcine reproductive and respiratory syndrome virus (PRRSV) is one of the most important threats against the global swine production industry. The virus infects alveolar macrophages that leads to respiratory distress, fever, pneumonia and gives way to secondary respiratory pathogens. Infection of sows in late gestation can lead to late term abortion, early farrowing and birth of litters mixed with living, stillborn and mummified fetuses. Two species of PRRSV exist that are closely related in evolution and disease: PRRSV-1 and PRRSV-2. PRRSV has a positive sense RNA genome of about 15 kb and exhibits a high mutation rate that has led to a high degree of diversity within each species. Highly pathogenic strains evolve occasionally with large impact on animal health and production economy. Since its discovery in the late 1980s, massive efforts have been put in the development of an effective vaccine. Inspite of this, the most effective commercial vaccines available are only partly capable of protecting against a heterologous challenge. Furthermore, these vaccines are based on modified live virus that at more than one occasion have mutated back to a virulent form and have thus promoted rather that prevented viral spread. PRRSV exhibits a wide range of immunoevasive mechanisms that manipulate multiple branches of the porcine immune system. However, evidence exist that a cell-mediated immune (CMI) response is capable of clearing the virus from the organism, although this response is somewhat delayed. In the present PhD thesis, I describe the development of an innovative vaccine for the induction of a cytotoxic T lymphocyte response against PRRSV-2. A major part of the project outline was to design a vaccine that would protect beyond genetic drift, why focus has been on identifying and selecting conserved epitopes specific for swine leukocyte antigen class I (SLA-I).

Briefly, all naturally occurring 9- and 10-mer peptides derived from 104 highly curated PRRSV-2 whole genome sequences were analyzed for their predicted binding capacities against five SLA-I alleles. Two methods for epitope prediction was applied (NetMHCpan and Position Scanning Combinatorial peptide library). The outputs of the two methods were combined and the top 2% best candidates were analyzed using the PopCover algorithm, serving to prioritize the candidates according to conservation and SLA allele coverage. Based on this, 53 peptides were purchased for in vitro verification. This was done using the assays Peptide Affinity Assay and Scintillation Proximity Assay for the determination of peptide-SLA (pSLA) binding affinity and stability, respectively. From these analyses it was decided to proceed with three of the five SLAs in combination with a total of 33 peptides/epitopes. A Classical swine fever virus (CSFV)-based virus replicon particle (VRP) was selected as vaccine platform. This VRP has the same tropism as CSFV and can thus infect dendritic cells that are the major inducers of a CMI response. On basis of this template VRP, 10 vaccine VRPs were designed for the expression of an inserted polyepitope with subsequent degradation via an uncleavable ubiquiting, thereby leading the epitopes into the MHC-I presentation pathway. One VRP was designed as a negative control and encoded an unrelated epitope, while the remaining nine encoded polyepitopes of different combinations of the 33 PRRSV-2 epitopes. Infectivity of the VRPs and the induced polyepitope expression and degradation was verified using flow cytometry. 718 pigs of matching SLA profiles were vaccinated three times over a 10-week period with the control VRP (N=7) or the PRRSV-VRPs (N=11). After this, all pigs were inoculated with a Danish PRRSV-2 field strain and were euthanized after an additional four weeks. Seroconversion for both VRP and PRRSV was confirmed for all pigs. The induction of a CMI response was monitored using interferon-γ (IFN-γ) enzyme-linked immunospot (ELISPOT) assay pre challenge, but did unfortunately not provide any usefull data. The setup was improved and post challenge ELISPOT provided evidence of a VRP-induced CMI. Viral load was measured post challenge in serum, but did not indicate any effects of vaccination. Viral load in lungs did however indicate an effect that was significant in one part of the lungs. Conclusively, the present study provides proof-of-concept that a peptide-specific CMI can be induced by vaccination with VRPs encoding conserved epitopes, along with indications of a protective effect on viral load in lungs. However, several improvements must be made to the concept before it can be subjected to field trials.

General information
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Organisations: National Veterinary Institute, Virology, Adaptive Immunology, Department of Bio and Health Informatics, Genomic Epidemiology
Development of a web tool for Escherichia coli subtyping based on fimH alleles: Running title: Development of E. coli fimH sub-typing web-tool

The aim of this study was to construct a valid publicly available method for in silico fimH sub-typing of Escherichia coli particularly suitable for differentiation of fine-resolution subgroups within clonal groups defined by standard multi-locus sequence typing (MLST). FimTyper was constructed as a FASTA database containing all currently known fimH alleles. The software source code is publicly available on https://bitbucket.org/genomicepidemiology/fimtyper, the database freely available at https://bitbucket.org/genomicepidemiology/fimtyper_db, and a service implementing the software available at https://cge.cbs.dtu.dk/services/FimTyper. FimTyper was validated on three datasets; (i) containing Sanger sequences of fimH alleles of 42 E. coli isolates generated prior to the current study, (ii) whole-genome sequence data of 243 third-generation cephalosporins-resistant E. coli isolates, and (iii) a randomly chosen subset of 40 E. coli isolates from dataset (ii), which were subjected to conventional fimH sub-typing. The combination of the three datasets enabled an evaluation and comparison of FimTyper on both Sanger sequences and WGS data. FimTyper correctly predicted all 40 fimH sub-types from the Sanger sequences from dataset (i), and successfully analyzed all 243 drafted genomes from dataset (ii). FimTyper sub-typing of the Sanger sequences and WGS data from dataset (iii) were in complete agreement. Additionally, fimH sub-typing was evaluated on a phylogenetic network of 122 ST131 E. coli isolates. There were perfect concordance between the typology and fimH-based sub-clones within ST131 with accurate identification of the pandemic multidrug resistant clonal subgroup ST131-H30. FimTyper provides a standardized tool, as a rapid alternative to conventional fimH sub-typing, highly suitable for surveillance and outbreak detection.
Development of genomic based diagnostics in various application domains

We will review the revolution brought about by low cost next generation sequencing in a wide array of diagnostic and industrial applications with a special emphasis on computational requirements and big data challenges.
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Organisations: Department of Bio and Health Informatics
Authors: Szallasi, Z. I. (Intern)
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BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.195 SNIP 0.331
BFI (2014): BFI-level 1
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Scopus rating (2002): SJR 0.116 SNIP 0.032
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Differential expression and co-expression gene networks reveal candidate biomarkers of boar taint in non-castrated pigs

Boar taint (BT) is an offensive odour or taste observed in pork from a proportion of non-castrated male pigs. Surgical castration is effective in avoiding BT, but animal welfare issues have created an incentive for alternatives such as genomic selection. In order to find candidate biomarkers, gene expression profiles were analysed from tissues of non-castrated pigs grouped by their genetic merit of BT. Differential expression analysis revealed substantial changes with log-transformed fold changes of liver and testis from -3.39 to 2.96 and -7.51 to 3.53, respectively. Co-expression network analysis revealed one module with a correlation of -0.27 in liver and three modules with correlations of 0.31, -0.44 and -0.49 in testis. Differential expression and co-expression analysis revealed candidate biomarkers with varying biological functions: phase I (COQ3, COX6C, CYP2J2, CYP2B6, ACOX2) and phase II metabolism (GSTO1, GSR, FMO3) of skatole and androstenone in liver to steroidogenesis (HSD17B7, HSD17B8, CYP27A1), regulation of steroidogenesis (STARD10, CYB5R3) and GnRH signalling (MAPK3, MAP2K2, MAP3K2) in testis. Overrepresented pathways included "Ribosome", "Protein export" and "Oxidative phosphorylation" in liver and "Steroid hormone biosynthesis" and "Gap junction" in testis. Future work should evaluate the biomarkers in large populations to ensure their usefulness in genomic selection programs.

General information

State: Published
Organisations: Department of Bio and Health Informatics, Administration, University of Copenhagen, McGill University
Authors: Drag, M. (Ekstern), Skinkyté-Juskiené, R. (Ekstern), Do, D. N. (Ekstern), Kogelman, L. J. A. (Ekstern), Kadarmideen, H. N. (Intern)
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Microbial communities are directly linked with process performance in several engineered systems. In the last century, intense study of microorganisms has contributed to optimize important environmental biotechnologies such as the activated sludge process or anaerobic digestion. However, less attention has been paid to the role of microorganisms in drinking water treatment technologies. In contrast, much effort has been devoted to eliminate potential pathogens in the drinking water treatment and supply systems. Nevertheless, the role of microbes in some drinking water treatments systems as biological filtration has long been acknowledged and recently been investigated. Biological filtration technology is widely used around the world and is especially important in Denmark as groundwater is the main source water for drinking water production. Because the groundwater has a relative high-quality, aeration followed by biological filtration is the only required treatment before distribution. In the last years, the microbial communities in rapid gravity sand filters, the typical biological filter used in Denmark, have been characterized, but little knowledge had been required about their physiological activity and roles in compound removal from the source water.

This PhD project focused on a comprehensive investigation of the microbial communities in rapid sand filters beyond their purely taxonomical identification. For this purpose, samples collected from a rapid sand filter were subjected to metagenomics analysis and genome recovery to identify the genetic capacities of the dominant types in the microbial community. Fourteen near-complete population genomes representing the dominant community were recovered comprising the capacity to grow on the typical compounds found in groundwater. The identified population genomes contained capabilities to oxidize ammonium, nitrite, methane, hydrogen sulfide, iron and manganese as well as to assimilate organic compounds. A composite population genome was assigned to Nitrospira. This genus had previously been found in multiple rapid sand filters at an unexplained high abundance. Nitrospira spp. are known to perform the second step of nitrification: oxidation of nitrite to nitrate. The two-step nitrification process disclosed at the end of the 19th century was assumed to be carried out by two different functional groups, ammonia oxidizing prokaryotes and nitrite oxidizing bacteria. Strikingly, the Nitrospira composite population genome not only contained the genes to oxidize nitrite to nitrate, but also the genetic potential to execute the first step of nitrification. Exhaustive bioinformatics investigation ruled out the possibility of genomic contamination and confirmed that the Nitrospira composite population genome harboured the complete ammonium oxidation (comammox) pathway. At the same time, evidence of a single microbe’s capacity to carry out complete nitrification was obtained by three other groups; in all cases the comammox type belonged to the Nitrospira genus.

To further investigate the genomic capacities of comammox Nitrospira, the Nitrospira composite genome was separated into individual population genomes using a differential coverage binning approach. As a result, five individual genomes were recovered, four of them containing the complete ammonium oxidation pathway. These genomes together with 11 high-quality publically available Nitrospira genomes (seven comammox and four strict nitrite oxidizers) were subject to a comparative genomics analysis. This examination showed specific genomic features for comammox, strict nitrite oxidizers and the two comammox clades. Thus, comammox Nitrospira harbour a higher variety of genes related to adaptation to nutrient-limited environments. The two comammox clades differ in their ammonium uptake affinity systems. Additionally, comammox Nitrospira genomes lack the genetic capacity to use nitrate as the only nitrogen source.

The evolutionary history of comammox Nitrospira was also examined based on protein dissimilarity, gene arrangement and reconciliation analysis. We detected a high probability of horizontal gene transfer events from betaproteobacterial ammonia oxidizers to comammox Nitrospira for genes belonging to the ammonium oxidation pathway as well as from comammox clade B to clade A for a subset of genes.

I investigated the abundance of comammox Nitrospira in rapid sand filters at 12 different waterworks in Denmark. As these new microorganisms are taxonomically similar to strict Nitrospira nitrite oxidizers, we developed specific primers to exclusively target comammox based on their gene encoding the ammonia monoxygenase subunit A. With these primers, we detected comammox Nitrospira as the dominant nitrifier in the biofilters with an abundance typically one order of magnitude higher than canonical ammonium oxidizing prokaryotes.

Lastly, I carried out lab-scale experiments with filter material from the top and bottom layers of a rapid sand filter containing different proportions of comammox Nitrospira, and strict nitrite and ammonia oxidizing prokaryotes under different loading conditions. Specifically, I exposed the filter material to distinct ammonium loading, under presence or absence of external carbon source as well as under oxygen limitation. In relation to the nitrifying community three main findings were made: (i) simultaneous growth of comammox Nitrospira and ammonium oxidizing prokaryotes; (ii) lower fitness of ammonium oxidizing archaea at higher temperatures; (iii) selection of comammox clade A over clade B at increasing ammonium loadings at reference temperature.
Overall, this PhD has provided insights into the genomic capabilities of the main types in the microbial community of a groundwater-fed biological filter. Moreover, the previously observed high abundances of Nitrospira spp. in rapid sand filters, has now been explained, by the discovery of complete ammonium oxidizing (comammox) Nitrospira from metagenomics analysis. In addition, this thesis presents the first extensive analysis of the genomic capabilities of comammox Nitrospira compared to canonical ammonium and nitrite oxidizers.

**General information**
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- **Organisations:** Department of Environmental Engineering, Water Technologies, Department of Bio and Health Informatics, Metagenomics
- **Authors:** Palomo, A. (Intern), Smets, B. F. (Intern), Sicheritz-Pontén, T. (Intern), Rasmussen, S. (Intern), Bælum, J. (Intern)
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- **Projects:**
  - Discovery and description of complete ammonium oxidizers in groundwater-fed rapid sand filters

**Distinct gene expression profile of Xanthomonas retroflexus engaged in synergistic multispecies biofilm formation**

It is well known that bacteria often exist in naturally formed multispecies biofilms. Within these biofilms, interspecies interactions seem to have an important role in ecological processes. Little is known about the effects of interspecies interactions on gene expression in these multispecies biofilms. This study presents a comparative gene expression analysis of the Xanthomonas retroflexus transcriptome when grown in a single-species biofilm and in dual-and four-species consortia with Stenotrophomonas rhizophila, Microbacterium oxydans and Paenibacillus amylolyticus. The results revealed complex interdependent interaction patterns in the multispecies biofilms. Many of the regulated functions are related to interactions with the external environment and suggest a high phenotypic plasticity in response to coexistence with other species. Furthermore, the changed expression of genes involved in aromatic and branched-chain amino acid biosynthesis suggests nutrient cross feeding as a contributing factor for the observed synergistic biofilm production when these four species coexists in a biofilm.

**General information**
- **State:** Published
- **Organisations:** Department of Bio and Health Informatics, Metagenomics, University of Copenhagen
- **Authors:** Hansen, L. B. S. (Intern), Ren, D. (Ekstern), Burmølle, M. (Ekstern), Sørensen, S. J. (Ekstern)
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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 persistier 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.

**General information**

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**Organisations:** Novo Nordisk Foundation Center for Biosustainability, Department of Bio and Health Informatics, Metagenomics, Infection Microbiology, Infection Microbiology, University of Oxford, Rigshospitalet

**Authors:** Breum Andersen, S. (Intern), Ghoul, M. (Ekstern), Griffin, A. S. (Ekstern), Petersen, B. (Intern), Johansen, H. K. (Ekstern), Molin, S. (Intern)
Diversity, structure, and novel physiologies in microbial communities in rapid sand filters

**General information**

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**Organisations**: Department of Environmental Engineering, Water Technologies, Department of Bio and Health Informatics, Metagenomics, Technical University of Denmark

**Authors**: Smets, B. F. (Intern), Gülay, A. (Intern), Palomo, A. (Intern), Fowler, S. J. (Ekstern), Sicheritz-Pontén, T. (Intern)

**Number of pages**: 1

**Publication date**: 2017

**Event**: Abstract from The Federation of European Microbiological Societies, Valencia, Spain.
Dual roles of heparanase in vascular calcification associated with human carotid atherosclerosis

Vascular intimal calcification is a hallmark of advanced atherosclerosis and an active process akin to bone remodeling. Heparanase (HPSE) is an endo-β-glucuronidase, which cleaves glycosaminoglycan chains of heparan sulfate proteoglycans. The role of heparanase in osteogenesis and bone remodeling is controversial. Previously, we have reported the upregulation of HPSE in human carotid endarterectomies from symptomatic patients and showed that the HPSE expression levels correlated with markers of inflammation and increased thrombogenicity.
Early differences in islets from prediabetic NOD mice: combined microarray and proteomic analysis

Type 1 diabetes is an endocrine disease where a long preclinical phase, characterised by immune cell infiltration in the islets of Langerhans, precedes elevated blood glucose levels and disease onset. Although several studies have investigated the role of the immune system in this process of insulitis, the importance of the beta cells themselves in the initiation of type 1 diabetes is less well understood. The aim of this study was to investigate intrinsic differences present in the islets from diabetes-prone NOD mice before the onset of insulitis. The islet transcriptome and proteome of 2-3-week-old mice was investigated by microarray and 2-dimensional difference gel electrophoresis (2D-DIGE), respectively. Subsequent analyses using sophisticated pathway analysis and ranking of differentially expressed genes and proteins based on their relevance in type 1 diabetes were performed. In the preinsulitic period, alterations in general pathways related to metabolism and cell communication were already present. Additionally, our analyses pointed to an important role for post-translational modifications (PTMs), especially citrullination by PAD2 and protein misfolding due to low expression levels of protein disulphide isomerases (PDIA3, 4 and 6), as causative mechanisms that induce beta cell stress and potential auto-antigen generation. We conclude that the pancreatic islets, irrespective of immune differences, may contribute to the initiation of the autoimmune process. All microarray data are available in the ArrayExpress database (www.ebi.ac.uk/arrayexpress) under accession number E-MTAB-5264.

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Organisations: Department of Bio and Health Informatics, Integrative Systems Biology, KU Leuven, Ghent University
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EBI3 regulates the NK cell response to mouse cytomegalovirus infection

Natural killer (NK) cells are key mediators in the control of cytomegalovirus infection. Here, we show that Epstein-Barr virus-induced 3 (EBI3) is expressed by human NK cells after NKG2D or IL-12 plus IL-18 stimulation and by mouse NK cells during mouse cytomegalovirus (MCMV) infection. The induction of EBI3 protein expression in mouse NK cells is a late activation event. Thus, early activation events of NK cells, such as IFNγ production and CD69 expression, were not affected in EBI3-deficient (Ebi3-/-) C57BL/6 (B6) mice during MCMV infection. Furthermore, comparable levels of early viral replication in spleen and liver were observed in MCMV-infected Ebi3-/- and wild-type (WT) B6 mice. Interestingly, the viral load in salivary glands and oral lavage was strongly decreased in the MCMV-infected Ebi3-/- B6 mice, suggesting that EBI3 plays a role in the establishment of MCMV latency. We detected a decrease in the sustained IL-10 production by NK cells and lower serum levels of IL-10 in the MCMV-infected Ebi3-/- B6 mice. Furthermore, we observed an increase in dendritic cell maturation markers and an increase in activated CD8+ T cells. Thus, EBI3 dampens the immune response against MCMV infection, resulting in prolonged viral persistence.
Erratum to: Evaluating next-generation sequencing for direct clinical diagnostics in diarrhoeal disease
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Authors: Joensen, K. G. (Intern), Engsbro, A. L. Ø. (Ekstern), Lukjancenko, O. (Intern), Kaas, R. S. (Intern), Lund, O. (Intern), Westh, H. (Ekstern), Aarestrup, F. M. (Intern)
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Evaluating next-generation sequencing for direct clinical diagnostics in diarrhoeal disease

The accurate microbiological diagnosis of diarrhoea involves numerous laboratory tests and, often, the pathogen is not identified in time to guide clinical management. With next-generation sequencing (NGS) becoming cheaper, it has huge potential in routine diagnostics. The aim of this study was to evaluate the potential of NGS-based diagnostics through direct sequencing of faecal samples. Fifty-eight clinical faecal samples were obtained from patients with diarrhoea as part of the routine diagnostics at Hvidovre University Hospital, Denmark. Ten samples from healthy individuals were also included. DNA was extracted from faecal samples and sequenced on the Illumina MiSeq system. Species distribution was determined with MGmapper and NGS-based diagnostic prediction was performed based on the relative abundance of pathogenic bacteria and Giardia and detection of pathogen-specific virulence genes. NGS-based diagnostic results were compared to conventional findings for 55 of the diarrhoeal samples; 38 conventionally positive for bacterial pathogens, two positive for Giardia, four positive for virus and 11 conventionally negative. The NGS-based approach enabled detection of the same bacterial pathogens as the classical approach in 34 of the 38 conventionally positive bacterial samples and predicted the responsible pathogens in five of the 11 conventionally negative samples. Overall, the NGS-based approach enabled pathogen detection comparable to conventional diagnostics and the approach has potential to be extended for the detection of all pathogens. At present, however, this approach is too expensive and time-consuming for routine diagnostics.

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Evaluating the significance of density, localization, and PD-1/PD-L1 immunopositivity of mononuclear cells in the clinical course of lung adenocarcinoma patients with brain metastasis

Background.
Management of lung cancer patients who suffer from brain metastases represents a major challenge. Considering the promising results with immune checkpoint inhibitor treatment, evaluating the status of immune cell (IC) infiltrates in the prognosis of brain metastasis may lead to better therapeutic strategies with these agents. The aim of this study was to characterize the distribution of ICs and determine the expression of the checkpoint molecules programmed death protein 1 (PD-1) and its ligand, PD-L1, in brain metastasis of lung adenocarcinoma (LUAD) patients and to analyze their clinicopathological correlations.

Methods.
We determined the presence of peritumoral mononuclear cells (mononuclear ring) and the density of intratumoral stromal mononuclear cells on brain metastasis tissue sections of 208 LUAD patients. PD-L1/PD-1 expressions were analyzed by immunohistochemistry.

Results.
Mononuclear rings were significantly associated with better survival after brain metastasis surgery. Cases with massive stromal IC infiltration also showed a tendency for better overall survival. Lower expression of PD-1 and PD-L1 was associated with better survival in patients who underwent surgery for the primary tumor and had multiple brain metastases. Steroid administration and chemotherapy appear not to influence the density of IC in brain metastasis.

Conclusion.
This is the first study demonstrating the independent prognostic value of mononuclear rings in LUAD cases with brain metastasis. Our results also suggest that the density of tumor-associated ICs in addition to PD-L1 expression of tumor
cells and ICs as well as PD-1 expression of ICs may hold relevant information for the appropriate selection of patients who might benefit from anti–PD-L1 or anti–PD-1 therapy.
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.

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Organisations: Molecular Evolution, Department of Biotechnology and Biomedicine, Department of Bio and Health Informatics, Disease Intelligence and Molecular Evolution, National Veterinary Institute, Virology, Kopenhagen Fur
Authors: Hagberg, E. E. (Intern), Pedersen, A. G. (Intern), Larsen, L. E. (Intern), Krarup, A. (Ekstern)
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Web of Science (2015): Indexed yes
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Exploration of immunoglobulin transcriptomes from mice immunized with three-finger toxins and phospholipases A2 from the Central American coral snake, Micrurus nigrocinctus

Snakebite envenomings represent a neglected public health issue in many parts of the rural tropical world. Animal-derived antivenoms have existed for more than a hundred years and are effective in neutralizing snake venom toxins when timely administered. However, the low immunogenicity of many small but potent snake venom toxins represents a challenge for obtaining a balanced immune response against the medically relevant components of the venom. Here, we employ high-throughput sequencing of the immunoglobulin (Ig) transcriptome of mice immunized with a three-finger toxin and a phospholipase A2 from the venom of the Central American coral snake, *Micrurus nigrocinctus*. Although exploratory in nature, our indicate results showed that only low frequencies of mRNA encoding IgG isotypes, the most relevant isotype for therapeutic purposes, were present in splenocytes of five mice immunized with 6 doses of the two types of toxins over 90 days. Furthermore, analysis of Ig heavy chain transcripts showed that no particular combination of variable (V) and joining (J) gene segments had been selected in the immunization process, as would be expected after a strong humoral immune response to a single antigen. Combined with the titration of toxin-specific antibodies in the sera of immunized mice, these data support the low immunogenicity of three-finger toxins and phospholipases A2 found in *M. nigrocinctus* venoms, and highlight the need for future studies analyzing the complexity of antibody responses to toxins at the molecular level.

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Organisations: Network Engineering of Eukaryotic Cell factories, Department of Biotechnology and Biomedicine, Department of Bio and Health Informatics, Genomic Epidemiology, Juno Therapeutics, Finch Therapeutics, Universidad de Costa Rica
Fast and accurate mutation detection in whole genome sequences of multiple isogenic samples with IsoMut

Detection of somatic mutations is one of the main goals of next generation DNA sequencing. A wide range of experimental systems are available for the study of spontaneous or environmentally induced mutagenic processes. However, most of the routinely used mutation calling algorithms are not optimised for the simultaneous analysis of multiple samples, or for non-human experimental model systems with no reliable databases of common genetic variations. Most standard tools either require numerous in-house post filtering steps with scarce documentation or take an unpractically long time to run. To overcome these problems, we designed the streamlined IsoMut tool which can be readily adapted to experimental scenarios where the goal is the identification of experimentally induced mutations in multiple isogenic samples. Using 30 isogenic samples, reliable cohorts of validated mutations were created for testing purposes. Optimal values of the filtering parameters of IsoMut were determined in a thorough and strict optimization procedure based on these test sets. We show that IsoMut, when tuned correctly, decreases the false positive rate compared to conventional tools in a 30 sample experimental setup; and detects not only single nucleotide variations, but short insertions and deletions as well. IsoMut can also be run more than a hundred times faster than the most precise state of art tool, due its straightforward and easily understandable filtering algorithm. IsoMut has already been successfully applied in multiple recent studies to find unique, treatment induced mutations in sets of isogenic samples with very low false positive rates. These types of studies provide an important contribution to determining the mutagenic effect of environmental agents or genetic defects, and IsoMut turned out to be an invaluable tool in the analysis of such data.

General information
State: Published
Organisations: Department of Bio and Health Informatics, Cancer Genomics, Eotvos Lorand University, Hungarian Academy of Sciences
Number of pages: 11
Four simple recommendations to encourage best practices in research software

Scientific research relies on computer software, yet software is not always developed following practices that ensure its quality and sustainability. This manuscript does not aim to propose new software development best practices, but rather to provide simple recommendations that encourage the adoption of existing best practices. Software development best practices promote better quality software, and better quality software improves the reproducibility and reusability of research. These recommendations are designed around Open Source values, and provide practical suggestions that contribute to making research software and its source code more discoverable, reusable and transparent. This manuscript is aimed at developers, but also at organisations, projects, journals and funders that can increase the quality and sustainability of research software by encouraging the adoption of these recommendations.

General information
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Organisations: Department of Bio and Health Informatics, IT Service, High Performance Computing, ELIXIR Hub, Netherlands eScience Center, CSL Limited, National eResearch Collaboration Tools and Resources, University of Freiburg, Stockholm University, Spanish National Bioinformatics Institute, University of Edinburgh, Repositive Ltd, University of Melbourne, EBI, Universitat de Barcelona, University of Manchester, University of Oxford, BBMRI-ERIC, Dutch TechCenter for Life Sciences, University of Illinois, University of Ljubljana, University of Aveiro, Center for Open Science, University of Cape Town, Czech Technical University, University of Klagenfurt, Universitat Pompeu Fabra, University of Illinois at Urbana-Champaign, University of Adelaide, Central European Institute of Technology, University of Tartu, Science and Technologies Facilities Council, Australian National Data Service, Radboud University Nijmegen, Sapienza University of Rome, Monash University, University of Southampton
Number of pages: 13
Functional Analysis of the Coronary Heart Disease Risk Locus on Chromosome 21q22

Background. The coronary heart disease (CHD) risk locus on 21q22 (lead SNP rs9982601) lies within a "gene desert." The aim of this study was to assess if this locus is associated with CHD risk factors and to identify the functional variant(s) and gene(s) involved. Methods. A phenome scan was performed with UCLEB Consortium data. Allele-specific protein binding was studied using electrophoretic mobility shift assays. Dual-reporter luciferase assays were used to assess the impact of genetic variation on expression. Expression quantitative trait analysis was performed with Advanced Study of Aortic Pathology (ASAP) and Genotype-Tissue Expression (GTEx) consortium data. Results. A suggestive association between QT interval and the locus was observed (rs9982601 p = 0.04). One variant at the locus, rs28451064, showed allele-specific protein binding and its minor allele showed 12% higher luciferase expression (p = 4.82 x 10(-3)) compared to the common allele. The minor allele of rs9982601 was associated with higher expression of the closest upstream genes (SLC5A3 1.30-fold increase p = 3.98 x 10(-5); MRPS6 1.15-fold increase p = 9.60 x 10(-4)) in aortic intima media in ASAP. Both rs9982601 and rs28451064 showed a suggestive association with MRPS6 expression in relevant tissues in the GTEx data. Conclusions. A candidate functional variant, rs28451064, was identified. Future work should focus on identifying the pathway(s) involved.

General information
State: Published
Organisations: Department of Bio and Health Informatics, Integrative Systems Biology, University College London, St. George's University of London, University of Bristol, University of Edinburgh, MRC Unit for Lifelong Health and Ageing, MRC Epidemiology Unit, Karolinska Institutet
Number of pages: 11
Publication date: 2017
Main Research Area: Technical/natural sciences
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

General information
State: Published
Organisations: Department of Systems Biology, Bacterial Ecophysiology and Biotechnology, Novo Nordisk Foundation Center for Biosustainability, iLoop, Center for Biological Sequence Analysis, Department of Bio and Health Informatics, Genomic Epidemiology, Department of Biotechnology and Biomedicine, Bacterial Ecophysiology and Biotechnology
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Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.42 SNIP 0.994 CiteScore 2.93
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.519 SNIP 1.069 CiteScore 2.95
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.571 SNIP 1.179 CiteScore 3.32
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.507 SNIP 1.146 CiteScore 3.38
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.487 SNIP 1.125 CiteScore 3.4
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.433 SNIP 1.034
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.474 SNIP 0.964
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 1.398 SNIP 0.979
Web of Science (2008): Indexed yes
Gene expression plasticity across hosts of an invasive scale insect species

For plant-feeding insects, we still have only a nascent understanding of the genetic basis of host-use promiscuity. Here, to improve that situation, we investigated host-induced gene expression plasticity in the invasive lobate lac scale insect, Paratachardina pseudolobata (Hemiptera: Keriidae). We were particularly interested in the differential expression of detoxification and effector genes, which are thought to be critical for overcoming a plant’s chemical defenses. We collected RNA samples from P. pseudolobata on three different host plant species, assembled transcriptomes de novo, and identified transcripts with significant host-induced gene expression changes. Gene expression plasticity was pervasive, but the expression of most detoxification and effector genes was insensitive to the host environment. Nevertheless, some types of detoxification genes were more differentially expressed than expected by chance. Moreover, we found evidence of a trade-off between expression of genes involved in primary and secondary metabolism; hosts that induced lower expression of genes for detoxification induced higher expression of genes for growth. Our findings are largely consonant with those of several recently published studies of other plant-feeding insect species. Thus, across plant-feeding insect species, there may be a common set of gene expression changes that enable host-use promiscuity.
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).

General information
State: Published
Organisations: Department of Biotechnology and Biomedicine, Department of Systems Biology, Department of Bio and Health Informatics, Metagenomics, Metagenomics, Eukaryotic Molecular Cell Biology
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Number of pages: 2
Genomic characterization, phylogenetic analysis, and identification of virulence factors in Aerococcus sanguinicola and Aerococcus urinae strains isolated from infection episodes

Aerococcus sanguinicola and Aerococcus urinae are emerging pathogens in clinical settings mostly being causative agents of urinary tract infections (UTIs), urogenic sepsis and more seldomly complicated infective endocarditis (IE). Limited knowledge exists concerning the pathogenicity of these two species. Eight clinical A. sanguinicola (isolated from 2009 to 2015) and 40 clinical A. urinae (isolated from 1984 to 2015) strains from episodes of UTIs, bacteremia, and IE were whole-genome sequenced (WGS) to analyze genomic diversity and characterization of virulence genes involved in the bacterial pathogenicity.

A. sanguinicola genome sizes were 2.06–2.12 Mb with a 47.4–47.6% GC-contents, and 1783–1905 genes were predicted whereof 1170 were core-genes. In case of A. urinae strains, the genome sizes were 1.93–2.44 Mb with 41.6–42.6% GC-contents, and 1708–2256 genes of which 907 were core-genes.

Marked differences were observed within A. urinae strains with respect to the average genome sizes, number and sequence identity of core-genes, proteome conservations, phylogenetic analysis, and putative capsular polysaccharide (CPS) loci sequences. Strains of A. sanguinicola showed high degree of homology. Phylogenetic analyses showed the 40 A. urinae strains formed two clusters according to two time periods: 1984–2004 strains and 2010–2015 strains. Genes that were homologs to virulence genes associated with bacterial adhesion and antiphagocytosis were identified by aligning A. sanguinicola and A. urinae pan- and core-genes against Virulence Factors of Bacterial Pathogens (VFDB). Bacterial adherence associated gene homologs were present in genomes of A. sanguinicola (htpB, fbpA, lmb, and ilpA) and A. urinae (htpB, lap, lmb, fbp54, and ilpA). Fifteen and 11–16 CPS gene homologs were identified in genomes of A. sanguinicola and A. urinae strains, respectively. Analysis of these genes identified one type of putative CPS locus within all A. sanguinicola strains. In A. urinae genomes, five different CPS loci types were identified with variations in CPS locus sizes, genetic content, and structural organization.

In conclusion, this is the first study dealing with WGS and comparative genomics of clinical A. sanguinicola and A. urinae strains from episodes of UTIs, bacteremia, and IE. Gene homologs associated with antiphagocytosis and bacterial adherence were identified and genetic variability was observed within A. urinae genomes. These findings contributes with important knowledge and basis for future molecular and experimental pathogenicity study of UTIs, bacteremia, and IE causing A. sanguinicola and A. urinae strains.

General information
State: Published
Organisations: Department of Bio and Health Informatics, Metagenomics, Slagelse Hospital, Roskilde University, Statens Serum Institut
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Pages: 327-340
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Genomic GC-content affects the accuracy of 16S rRNA gene sequencing based microbial profiling due to PCR bias

Profiling of microbial community composition is frequently performed by partial 16S rRNA gene sequencing on benchtop platforms following PCR amplification of specific hypervariable regions within this gene. Accuracy and reproducibility of this strategy are two key parameters to consider, which may be influenced during all processes from sample collection and storage, through DNA extraction and PCR based library preparation to the final sequencing. In order to evaluate both the reproducibility and accuracy of 16S rRNA gene based microbial profiling using the Ion Torrent PGM platform, we prepared libraries and performed sequencing of a well-defined and validated 20-member bacterial DNA mock community on five separate occasions and compared results with the expected even distribution. In general the applied method had a median coefficient of variance of 11.8% (range 5.5-73.7%) for all 20 included strains in the mock community across five separate sequencing runs, with underrepresented strains generally showing the largest degree of variation. In terms of accuracy, mock community species belonging to Proteobacteria were underestimated, whereas those belonging to Firmicutes were mostly overestimated. This could be explained partly by premature read truncation, but to larger degree their genomic GC-content, which correlated negatively with the observed relative abundances, suggesting a PCR bias against GC-rich species during library preparation. Increasing the initial denaturation time during the PCR amplification from 30 to 120 s resulted in an increased average relative abundance of the three mock community members with the highest genomic GC%, but did not significantly change the overall evenness of the community distribution. Therefore, efforts should be made to optimize the PCR conditions prior to sequencing in order to maximize accuracy.

General information
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Organisations: National Food Institute, Research Group for Gut Microbiology and Immunology, Department of Bio and Health Informatics, DTU Multi Assay Core
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Scopus rating (2015): SJR 1.869 SNIP 1.193 CiteScore 4.15
Web of Science (2015): Indexed yes
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Scopus rating (2014): SJR 1.879 SNIP 1.148 CiteScore 3.76
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.776 SNIP 0.949 CiteScore 3.56
ISI indexed (2013): ISI indexed no
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.46 SNIP 0.722 CiteScore 2.78
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Microbiology, Microbiology (medical), 16S rRNA gene sequencing, Accuracy, Genomic GC content, Ion torrent PGM, Mock community, Reproducibility, ion torrent PGM, reproducibility, accuracy, mock community, genomic GC content, QR1-502
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Genomics of phages with therapeutic potential

Bacteriophages, viruses that prey on bacteria, have been applied since the 1920’s to treat and prevent bacterial infection. After the discovery of antibiotics, this route was however largely abandoned. Now, with antimicrobial resistance in human-pathogenic bacteria on the rise and a dire need for alternatives, phage therapy once again takes center stage.

Phage therapy holds the promise of substantial benefits both from the economic as well as the public health perspective but also holds distinct challenges. The aim of this PhD was to address how bioinformatics tools, specifically genomics and mathematical modelling, can be applied to move the field towards a future of actual phage therapy in humans. It is composed of three related research projects.

The first part of this thesis is an introduction to various topics and methods relevant to the research projects that jointly make up this PhD. Chapters 1 - 3 deal with phages, their use in therapy and the nosocomial pathogen Staphylococcus aureus. Following that, Chapter 4 and 5 provide an overview of Next Generation Sequencing as well as commonly employed genomics tools, while Chapter 6 details basics of Machine Learning.

The second part, divided into three chapters, presents the three research projects. In project 1, an important commercial phage cocktail with a long history was sequenced and its component phages analyzed. It was found that the cocktail is composed of at least 23 different phage types, which were present in differing abundances. Some of these phage types were successfully amplified on a collection of in-house bacteria corresponding to the cocktail’s stated bacterial targets. Further, no harmful genes were detected in the cocktail.

Project 2 deals with phage communities in sewage by comparing samples from around the world to each other as well as to databases of available phage genomes. It revealed a great diversity in the sequences, many of which were distant from all known phages. The phage content of the different sample locations exhibited a rather stable genomic distance that was not influenced by whether the locations were geographically close or not.

Project 3 had the goal of identifying gene families in the extensive accessory genome of the hospital pathogen Staphylococcus aureus that influence its susceptibility to clinical phage preparations. This was done by phage testing a set of patient-derived S. aureus isolates against a panel of phage preparations. We then sought to model the results using the bacteria’s genetic background as features. Doing so, we built nine models with sufficient explanatory power over the susceptibility outcome and from them identified a set of 167 gene families relevant for phage susceptibility.

The third part of the thesis consists of conclusive remarks and a critical reflection on how each of these projects has impacted the field and how they are connected as well as pointing out directions for future investigations.

In summary, the work included in this this thesis focuses on applying genomics and mathematical modelling to questions related to phage therapy.
Genomic study and Medical Subject Headings enrichment analysis of early pregnancy rate and antral follicle numbers in Nelore heifers

Zebu animals (Bos indicus) are known to take longer to reach puberty compared with taurine animals (Bos taurus), limiting the supply of animals for harvest or breeding and impacting profitability. Genomic information can be a helpful tool to better understand complex traits and improve genetic gains. In this study, we performed a genomewide association study (GWAS) to identify genetic variants associated with reproductive traits in Nelore beef cattle. Heifer pregnancy (HP) was recorded for 1,267 genotyped animals distributed in 12 contemporary groups (CG) with an average pregnancy rate of 0.35 (+/- 0.01). Disregarding one of these CG, the number of antral follicles (NF) was also collected for 937 of these animals, with an average of 11.53 (+/- 4.43). The animals were organized in CG: 12 and 11 for HP and NF, respectively. Genes in linkage disequilibrium (LD) with the associated variants can be considered in a functional enrichment analysis to identify biological mechanisms involved in fertility. Medical Subject Headings (MeSH) were detected using the MESHR package, allowing the extraction of broad meanings from the gene lists provided by the GWAS. The estimated heritability for HP was 0.28 +/- 0.07 and for NF was 0.49 +/- 0.09, with the genomic correlation being -0.21 +/- 0.29. The average LD between adjacent markers was 0.23 +/- 0.01, and GWAS identified genomic windows that accounted for > 1% of total genetic variance on chromosomes 5, 14, and 18 for HP and on chromosomes 2, 8, 11, 14, 15, 16, and 22 for NF. The MeSH enrichment analyses revealed significant (P <0.05) terms associated with HP-"Munc18 Proteins," "Fucose," and "Hemoglobins"-and with NF-"Cathepsin B," "Receptors, Neuropeptide," and "Palmitic Acid." This is the first study in Nelore cattle introducing the concept of MeSH analysis. The genomic analyses contributed to a better understanding of the genetic control of the reproductive traits HP and NF and provide new selection strategies to improve beef production.

General information
State: Published
Organisations: Department of Bio and Health Informatics, Administration, Universidade de Sao Paulo, Agricultural Research Service, University of Guelph, Universidade Federal de Mato Grosso, Iowa State University
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BFI (2017): BFI-level 2
Scopus rating (2017): SNIP 0.982 SJR 0.848
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 1.51 SJR 1.035 SNIP 1.152
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 1.307 SNIP 1.28 CiteScore 1.56
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 1.412 SNIP 1.397 CiteScore 2.26
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 1.211 SNIP 1.307 CiteScore 2.11
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 1.421 SNIP 1.569 CiteScore 1.71
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
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Scopus rating (2011): SJR 1.522 SNIP 1.522 CiteScore 2.17
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Receptor interactions with short linear peptide fragments (ligands) are at the base of many biological signaling processes. Conserved and information-rich amino acid patterns, commonly called sequence motifs, shape and regulate these interactions. Because of the properties of a receptor-ligand system or of the assay used to interrogate it, experimental data often contain multiple sequence motifs. GibbsCluster is a powerful tool for unsupervised motif discovery because it can simultaneously cluster and align peptide data. The GibbsCluster 2.0 presented here is an improved version incorporating insertion and deletions accounting for variations in motif length in the peptide input. In basic terms, the program takes as input a set of peptide sequences and clusters them into meaningful groups. It returns the optimal number of clusters it identified, together with the sequence alignment and sequence motif characterizing each cluster. Several parameters are available to customize cluster analysis, including adjustable penalties for small clusters and overlapping groups and a trash cluster to remove outliers. As an example application, we used the server to deconvolute multiple specificities in large-scale peptidome data generated by mass spectrometry. The server is available at http://www.cbs.dtu.dk/services/GibbsCluster-2.0.
High-density peptide microarray exploration of the antibody response in a rabbit immunized with a neurotoxic venom fraction

Polyvalent snakebite antivenoms derive their therapeutic success from the ability of their antibodies to neutralize venom toxins across multiple snake species. This ability results from a production process involving immunization of large mammals with a broad suite of toxins present in venoms. As a result of immunization with this wide range of toxins, many polyvalent antivenoms have a high degree of cross-reactivity to similar toxins in other snake venoms - a cross-reactivity which cannot easily be deconvoluted. As a proof of concept, we aimed at exploring the opposite scenario by performing a high-throughput evaluation of the extent of cross-reactivity of a polyclonal mixture of antibodies that was raised against only a single snake venom fraction. For this purpose, a venom fraction containing short neurotoxin 1 (SN-1; Uniprot accession number P01416, three-finger toxin (3FTx) family), which is the medically most important toxin from the notorious black mamba (Dendroaspis polylepis), was employed. Following immunization of a rabbit, a specific polyclonal antibody response was confirmed by ELISA and immunodiffusion. Subsequently, these antibodies were investigated by high-density peptide microarray to reveal linear elements of recognized epitopes across 742 3FTxs and 10 dendrotoxins. This exploratory study demonstrates in a single immunized animal that cross-reactivity between toxins of high similarity may be difficult to obtain when immunizing with a single 3FTx containing venom fraction. Additionally, this study explored the influence of employing different lengths of peptides in high-density peptide microarray experiments for identification of toxin epitopes. Using 8-mer, 12-mer, and 15-mer peptides, a single linear epitope element was identified in SN-1 with high precision.

General information
State: Published
Organisations: Network Engineering of Eukaryotic Cell factories, Department of Bio and Health Informatics, Genomic Epidemiology, Immunoinformatics and Machine Learning, Department of Biotechnology and Biomedicine, Universidad de Costa Rica
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Pages: 151-158
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Main Research Area: Technical/natural sciences

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Web of Science (2018): Indexed yes
High throughput resistance profiling of *Plasmodium falciparum* infections based on custom dual indexing and Illumina next generation sequencing-technology

Genetic polymorphisms in *P. falciparum* can be used to indicate the parasite’s susceptibility to antimalarial drugs as well as its geographical origin. Both of these factors are key to monitoring development and spread of antimalarial drug resistance. In this study, we combine multiplex PCR, custom designed dual indexing and Miseq sequencing for high throughput SNP-profiling of 457 malaria infections from Guinea-Bissau, at the cost of 10 USD per sample. By amplifying and sequencing 15 genetic fragments, we cover 20 resistance-conferring SNPs occurring in pfcr, pfmdr1, pfhfr, pfhps, as well as the entire length of pfK13, and the mitochondrial barcode for parasite origin. SNPs of interest were sequenced with an average depth of 2,043 reads, and bases were called for the various SNP-positions with a p-value below 0.05, for 89.8-100% of samples. The SNP data indicates that artemisinin resistance-conferring SNPs in pfK13 are absent from the studied area of Guinea-Bissau, while the pfmdr1 86 N allele is found at a high prevalence. The mitochondrial barcodes are unanimous and accommodate a West African origin of the parasites. With this method, very reliable high throughput
surveillance of antimalarial drug resistance becomes more affordable than ever before.

General information
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Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): SNIP 1.245 SJR 1.533
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 4.63 SJR 1.692 SNIP 1.354
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.034 SNIP 1.597 CiteScore 5.3
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.163 SNIP 1.554 CiteScore 4.75
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.998 SNIP 1.57 CiteScore 4.06
Web of Science (2013): Indexed yes
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Hospital epidemiology of methicillin-resistant Staphylococcus aureus (MRSA) in a tertiary care hospital in Moshi Tanzania as determined by whole genome sequencing

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How Much of the Human Genome is Functional?

Identification of immediate early gene products of bovine herpes virus 1 (BHV-1) as dominant antigens recognized by CD8 T cells in immune cattle

In common with other herpes viruses, bovine herpes virus 1 (BHV-1) induces strong virus-specific CD8 T-cell responses. However, there is a paucity of information on the antigenic specificity of the responding T-cells. The development of a system to generate virus-specific CD8 T-cell lines from BHV-1-immune cattle, employing Theileria-transformed cell lines for antigen presentation, has enabled us to address this issue. Use of this system allowed the study to screen for CD8 T-cell antigens that are efficiently presented on the surface of virus-infected cells. Screening of a panel of 16 candidate viral gene products with CD8 T-cell lines from 3 BHV-1-immune cattle of defined MHC genotypes identified 4 antigens, including 3 immediate early (IE) gene products (ICP4, ICP22 and Circ) and a tegument protein (UL49). Identification of the MHC restriction specificities revealed that the antigens were presented by two or three class I MHC alleles in each animal. Six CD8 T-cell epitopes were identified in the three IE proteins by screening of synthetic peptides. Use of an algorithm (NetMHCpan) that predicts the peptide-binding characteristics of restricting MHC alleles confirmed and, in some cases refined, the identity of the epitopes. Analyses of the epitope specificity of the CD8 T-cell lines showed that a large component of the response is directed against these IE epitopes. The results indicate that these IE gene products are dominant targets of the CD8 T-cell response in BHV-1-immune cattle and hence are prime-candidate antigens for the generation of a subunit vaccine.
Identification of potential biomarkers in donor cows for in vitro embryo production by granulosa cell transcriptomics

The Ovum Pick Up-In vitro Production (OPU-IVP) of embryos is an advanced reproductive technology used in cattle production but the complex biological mechanisms behind IVP outcomes are not fully understood. In this study we sequenced RNA of granulosa cells collected from Holstein cows at oocyte aspiration prior to IVP, to identify candidate genes and biological mechanisms for favourable IVP-related traits in donor cows where IVP was performed separately for each animal. We identified 56 genes significantly associated with IVP scores (BL rate, kinetic and morphology). Among these, BEX2, HEY2, RGN, TNFAIP6 and TXNDC11 were negatively associated while Mx1 and STC1 were positively associated with all IVP scores. Functional analysis highlighted a wide range of biological mechanisms including apoptosis, cell development and proliferation and four key upstream regulators (COX2, IL1, PRL, TRIM24) involved in these mechanisms. We found a range of evidence that good IVP outcome is positively correlated with early follicular atresia. Furthermore we showed that high genetic index bulls can be used in breeding without reducing the IVP performances. These findings can contribute to the development of biomarkers from follicular fluid content and to improving Genomic Selection (GS) methods that utilize functional information in cattle breeding, allowing a widespread large scale application of GS-IVP.
Identifiers for the 21st century: How to design, provision, and reuse persistent identifiers to maximize utility and impact of life science data

In many disciplines, data are highly decentralized across thousands of online databases (repositories, registries, and knowledgebases). Wringing value from such databases depends on the discipline of data science and on the humble bricks and mortar that make integration possible; identifiers are a core component of this integration infrastructure.

Drawing on our experience and on work by other groups, we outline 10 lessons we have learned about the identifier qualities and best practices that facilitate large-scale data integration. Specifically, we propose actions that identifier practitioners (database providers) should take in the design, provision and reuse of identifiers. We also outline the important considerations for those referencing identifiers in various circumstances, including by authors and data generators.

While the importance and relevance of each lesson will vary by context, there is a need for increased awareness about how to avoid and manage common identifier problems, especially those related to persistence and web-accessibility/resolvability. We focus strongly on web-based identifiers in the life sciences; however, the principles are broadly relevant to other disciplines.
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Identifying low density lipoprotein cholesterol associated variants in the Annexin A2 (ANXA2) gene
Background and aims: Annexin-A2 (AnxA2) is an endogenous inhibitor of proprotein convertase subtilisin/kexin type-9 (PCSK9). The repeat-one (R1) domain of AnxA2 binds to PCSK9, blocking its ability to promote degradation of low-density lipoprotein cholesterol-receptors (LDL-R) and thereby regulate low-density lipoprotein cholesterol (LDL-C) levels. Here we identify variants in ANXA2 influencing LDL-C levels and we determine the molecular mechanisms of their effects.

Results: The ANXA2 single nucleotide polymorphism (SNP) genotype-phenotype association was examined using the Second- Northwick-Park Heart Study (NPHSII) (n similar to 2700) and the UCL-LSHTM-EdinburghBristol (UCLEB) consortium (n similar to 14,600). The ANXA2-R1 domain coding-SNP rs17845226 (V98L) associated with LDL-C, homozygotes for the minor allele having approximate to 18.8% higher levels of LDL-C (p = 0.004), and higher risk of coronary heart disease (CHD) (p = 0.04). The SNP is in modest linkage disequilibrium (r(2) > 0.5) with two intergenic SNPs, rs17191344 and rs11633032. Both SNPs showed allele-specific protein binding, and the minor alleles caused significant reduction in reporter gene expression (approximate to 18%, p <0.001). In the expression quantitative trait loci (eQTL) study, minor allele homozygotes have significantly lower levels of ANXA2-mRNA expression (p = 1.36 x 10(-05)). Conclusions: Both rs11633032 and rs17191344 SNPs are functional variants, where the minor alleles create repressor-binding protein sites for transcription factors that contribute to reduced ANXA2 gene expression. Lower AnxA2 levels could increase plasma levels of PCSK9 and thus increase LDL-C levels and risk of CHD. This supports, for the first time in humans, previous observations in mouse models that changes in the levels of AnxA2 directly influence plasma LDL-C levels, and thus implicate this protein as a potential therapeutic target for LDL-C lowering. (C) 2017 The Authors. Published by Elsevier Ireland Ltd.
Induction of Antigen-Specific T Cells Targeting Endogenous Retroelements During Epigenetic Treatment of Myelodysplastic Syndrome
In silico assessment of virulence factors in strains of Streptococcus oralis and Streptococcus mitis isolated from patients with Infective Endocarditis

Streptococcus oralis and Streptococcus mitis belong to the Mitis group, which are mostly commensals in the human oral cavity. Even though S. oralis and S. mitis are oral commensals, they can be opportunistic pathogens causing infective endocarditis. A recent taxonomic re-evaluation of the Mitis group has embedded the species Streptococcus tigurinus and Streptococcus dentisani into the species S. oralis as subspecies. In this study, the distribution of virulence factors that contribute to bacterial immune evasion, colonization and adhesion was assessed in clinical strains of S. oralis (subsp.
oralis, subsp. tigurinus and subsp. dentisani) and S. mitis. Forty clinical S. oralis (subsp. oralis, subsp. dentisani and subsp. tigurinus) and S. mitis genomes were annotated with the pipeline PanFunPro and aligned against the VFDB database for assessment of virulence factors. Results/Key findings. Three homologues of pavA, psaA and lmb, encoding adhesion proteins, were present in all strains. Seven homologues of nanA, nanB, ply, lytA, lytB, lytC and iga, of importance regarding survival in blood and modulation of the human immune system, were variously present in the genomes. Few S. oralis subspecies specific differences were observed. iga homologues were identified in S. oralis subsp. oralis, whereas lytA homologues were identified in S. oralis subsp. oralis and subsp. tigurinus. Differences in the presence of virulence factors among the three S. oralis subspecies were observed. The virulence gene profiles of the 40 S. mitis and S. oralis (subsp. oralis, subsp. dentisani and subsp. tigurinus) contribute with important new knowledge regarding these species and new subspecies.
Intratumoural evolutionary landscape of high-risk prostate cancer: The PROGENY study of genomic and immune parameters

Background: Intratumoural heterogeneity (ITH) is well recognised in prostate cancer (PC), but its role in high-risk disease is uncertain. A prospective, single-arm, translational study using targeted multiregion prostate biopsies was carried out to study genomic and T-cell ITH in clinically high-risk PC aiming to identify drivers and potential therapeutic strategies.

Patients and methods: Forty-nine men with elevated prostate-specific antigen and multiparametric-magnetic resonance imaging detected PC underwent image-guided multiregion transperineal biopsy. Seventy-nine tumour regions from 25 patients with PC underwent sequencing, analysis of mutations, copy number and neoepitopes combined with tumour infiltrating T-cell subset quantification.

Results: We demonstrated extensive somatic nucleotide variation and somatic copy number alteration heterogeneity in high-risk PC. Overall, the mutational burden was low (0.93/Megabase), but two patients had hypermutation, with loss of mismatch repair (MMR) proteins, MSH2 and MSH6. Somatic copy number alteration burden was higher in patients with metastatic hormone-naive PC (mHNPC) than in those with high-risk localised PC (hrNPC), independent of Gleason grade. Mutations were rarely ubiquitous and mutational frequencies were similar for mHNPC and hrNPC patients. Enrichment of focal 3q26.2 and 3q21.3, regions containing putative metastasis drivers, was seen in mHNPC patients. We found evidence of parallel evolution with three separate clones containing activating mutations of β-catenin in a single patient. We demonstrated extensive intratumoural and intertumoural T-cell heterogeneity and high inflammatory infiltrate in the MMR-deficient (MMRD) patients and the patient with parallel evolution of β-catenin. Analysis of all patients with activating Wnt/β-catenin mutations demonstrated a low CD8+/FOXP3+ ratio, a potential surrogate marker of immune evasion. Conclusions: The PROGENY (PROstate cancer GENomic heterogeneity) study provides a diagnostic platform suitable for studying tumour ITH. Genetic aberrations in clinically high-risk PC are associated with altered patterns of immune infiltrate in tumours. Activating mutations of Wnt/β-catenin signalling pathway or MMRD could be considered as potential biomarkers for immunomodulation therapies.

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In vitro production of bovine embryos: cumulus/granulosa cell gene expression patterns point to early atresia as beneficial for oocyte competence

In vitro production (IVP) of bovine embryos has become widespread technology implemented in cattle breeding and production. Here, we review novel data on cumulus/granulosa cell gene expression, as determined by RNAseq on cellular material from pooled follicular fluids at the single animal level, and relate these findings to previous data on oocyte developmental competence and ultrastructure. The cumulus/granulosa cell gene expression patterns indicate that early follicular atresia is associated with increased blastocyst yield and this hypothesis is supported by previous data on oocyte competence and ultrastructure.

Lapatinib potentiates cytotoxicity of YM155 in neuroblastoma via inhibition of the ABCB1 efflux transporter

Adverse side effects of cancer agents are of great concern in the context of childhood tumors where they can reduce the quality of life in young patients and cause life-long adverse effects. Synergistic drug combinations can lessen potential toxic side effects through lower dosing and simultaneously help to overcome drug resistance. Neuroblastoma is the most common cancer in infancy and extremely heterogeneous in clinical presentation and features. Applying a systematic pairwise drug combination screen we observed a highly potent synergy in neuroblastoma cells between the EGFR kinase inhibitor lapatinib and the anticancer compound YM155 that is preserved across several neuroblastoma variants. Mechanistically, the synergy was based on a lapatinib induced inhibition of the multidrug-resistance efflux transporter ABCB1, which is frequently expressed in resistant neuroblastoma cells, which allowed prolonged and elevated cytotoxicity of YM155. In addition, the drug combination (i.e. lapatinib plus YM155) decreased neuroblastoma tumor size in an in vivo model.

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Lapatinib potentiates cytotoxicity of YM155 in neuroblastoma via inhibition of the ABCB1 efflux transporter

Adverse side effects of cancer agents are of great concern in the context of childhood tumors where they can reduce the quality of life in young patients and cause life-long adverse effects. Synergistic drug combinations can lessen potential toxic side effects through lower dosing and simultaneously help to overcome drug resistance. Neuroblastoma is the most common cancer in infancy and extremely heterogeneous in clinical presentation and features. Applying a systematic pairwise drug combination screen we observed a highly potent synergy in neuroblastoma cells between the EGFR kinase inhibitor lapatinib and the anticancer compound YM155 that is preserved across several neuroblastoma variants. Mechanistically, the synergy was based on a lapatinib induced inhibition of the multidrug-resistance efflux transporter ABCB1, which is frequently expressed in resistant neuroblastoma cells, which allowed prolonged and elevated cytotoxicity of YM155. In addition, the drug combination (i.e. lapatinib plus YM155) decreased neuroblastoma tumor size in an in vivo model.

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Legacy data sharing to improve drug safety assessment: the eTOX project
The sharing of legacy preclinical safety data among pharmaceutical companies and its integration with other information sources offers unprecedented opportunities to improve the early assessment of drug safety. Here, we discuss the experience of the eTOX project, which was established through the Innovative Medicines Initiative to explore this possibility.

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Loss of BRCA1 or BRCA2 markedly increases the rate of base substitution mutagenesis and has distinct effects on genomic deletions

Loss-of-function mutations in the BRCA1 and BRCA2 genes increase the risk of cancer. Owing to their function in homologous recombination repair, much research has focused on the unstable genomic phenotype of BRCA1/2 mutant cells manifest mainly as large-scale rearrangements. We used whole-genome sequencing of multiple isogenic chicken DT40 cell clones to precisely determine the consequences of BRCA1/2 loss on all types of genomic mutagenesis. Spontaneous base substitution mutation rates increased sevenfold upon the disruption of either BRCA1 or BRCA2, and the arising mutation spectra showed strong and specific correlation with a mutation signature associated with BRCA1/2 mutant tumours. To model endogenous alkylating damage, we determined the mutation spectrum caused by methyl methanesulfonate (MMS), and showed that MMS also induces more base substitution mutations in BRCA1/2-deficient cells. Spontaneously arising and MMS-induced insertion/deletion mutations and large rearrangements were also more common in BRCA1/2 mutant cells compared with the wild-type control. A difference in the short deletion phenotypes of BRCA1 and BRCA2 suggested distinct roles for the two proteins in the processing of DNA lesions, as BRCA2 mutants contained more short deletions, with a wider size distribution, which frequently showed microhomology near the breakpoints resembling repair by non-homologous end joining. An increased and prolonged gamma-H2AX signal in MMS-treated BRCA1/2 cells suggested an aberrant processing of stalled replication forks as the cause of increased mutagenesis. The high rate of base substitution mutagenesis demonstrated by our experiments is likely to significantly contribute to the oncogenic effect of the inactivation of BRCA1 or BRCA2.
Low TLR7 gene expression in atherosclerotic plaques is associated with major adverse cardio- and cerebrovascular events

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Machine Learning Reveals a Non-Canonical Mode of Peptide Binding to MHC class II Molecules
MHC class II molecules play a fundamental role in the cellular immune system: they load short peptide fragments derived from extracellular proteins and present them on the cell surface. It is currently thought that the peptide binds lying more or less flat in the MHC groove, with a fixed distance of nine amino acids between the first and last residue in contact with the MHCII. While confirming that the great majority of peptides bind to the MHC using this canonical mode, we report evidence for an alternative, less common mode of interaction. A fraction of observed ligands were shown to have an
unconventional spacing of the anchor residues that directly interact with the MHC, which could only be accommodated to the canonical MHC motif either by imposing a more stretched out peptide backbone (a 8mer core) or by the peptide bulging out of the MHC groove (a 10mer core). We estimated that on average 2% of peptides bind with a core deletion, and 0.45% with a core insertion, but the frequency of such non-canonical cores was as high as 10% for certain MHCII molecules. A mutational analysis and experimental validation of a number of these anomalous ligands demonstrated that they could only fit to their MHC binding motif with a non-canonical binding core of length different from nine. This previously undescribed mode of peptide binding to MHCII molecules gives a more complete picture of peptide presentation by MHCII and allows us to model more accurately this event. This article is protected by copyright. All rights reserved.

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Mapping of 79 loci for 83 plasma protein biomarkers in cardiovascular disease

Recent advances in highly multiplexed immunoassays have allowed systematic large-scale measurement of hundreds of plasma proteins in large cohort studies. In combination with genotyping, such studies offer the prospect to 1) identify mechanisms involved with regulation of protein expression in plasma, and 2) determine whether the plasma proteins are likely to be causally implicated in disease. We report here the results of genome-wide association (GWA) studies of 83 proteins considered relevant to cardiovascular disease (CVD), measured in 3,394 individuals with multiple CVD risk factors. We identified 79 genome-wide significant (p<5e-8) association signals, 55 of which replicated at P<0.0007 in separate validation studies (n = 2,639 individuals). Using automated text mining, manual curation, and network-based methods incorporating information on expression quantitative trait loci (eQTL), we propose plausible causal mechanisms for 25 trans-acting loci, including a potential post-translational regulation of stem cell factor by matrix metalloproteinase 9 and receptor-ligand pairs such as RANK-RANK ligand. Using public GWA study data, we further evaluate all 79 loci for their causal effect on coronary artery disease, and highlight several potentially causal associations. Overall, a majority of the plasma proteins studied showed evidence of regulation at the genetic level. Our results enable future studies of the causal architecture of human disease, which in turn should aid discovery of new drug targets.
The international Testicular Cancer Consortium (TECAC) combined five published genome-wide association studies of testicular germ cell tumor (TGCT; 3,558 cases and 13,970 controls) to identify new susceptibility loci. We conducted a fixed-effects meta-analysis, including, to our knowledge, the first analysis of the X chromosome. Eight new loci mapping to 2q14.2, 3q26.2, 4q35.2, 7q36.3, 10q26.13, 15q21.3, 15q22.31, and Xq28 achieved genome-wide significance (P < 5 × 10−8). Most loci harbor biologically plausible candidate genes. We refined previously reported associations at 9p24.3 and 19p12 by identifying one and three additional independent SNPs, respectively. In aggregate, the 39 independent markers identified to date explain 37% of father-to-son familial risk, 8% of which can be attributed to the 12 new signals reported here. Our findings substantially increase the number of known TGCT susceptibility alleles, move the field closer to a comprehensive understanding of the underlying genetic architecture of TGCT, and provide further clues to the etiology of TGCT.
Meta-analysis of proportion estimates of extended-spectrum-beta-lactamase-producing Enterobacteriaceae in East Africa hospitals

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Metagenomic Analysis of Therapeutic PYO Phage Cocktails from 1997 to 2014
Phage therapy has regained interest in recent years due to the alarming spread of antibiotic resistance. Whilst phage cocktails are commonly sold in pharmacies in countries such as Georgia and Russia, this is not the case in western countries due to western regulatory agencies requiring a thorough characterization of the drug. Here, DNA sequencing of constituent biological entities constitutes a first step. The pyophage (PYO) cocktail is one of the main commercial products of the Georgian Eliava Institute of Bacteriophage, Microbiology and Virology and is used to cure skin infections. Since its first production in the 1930s, the composition of the cocktail has been periodically modified to add phages effective against emerging pathogenic strains. In this paper, we compared the composition of three PYO cocktails from 1997 (PYO97), 2000 (PYO2000) and 2014 (PYO2014). Based on next generation sequencing, de novo assembly and binning of contigs into draft genomes based on tetranucleotide distance, thirty and twenty-nine phage draft genomes were predicted in PYO97 and PYO2014, respectively. Of these, thirteen and fifteen shared high similarity to known phages. Eleven draft genomes were found to be common in the two cocktails. One of these showed no similarity to publicly available phage genomes. Representatives of phages targeting E. faecalis, E. faecium, E. coli, Proteus, P. aeruginosa and S. aureus were found in both cocktails. Finally, we estimated larger overlap of the PYO2000 cocktail to PYO97 compared to PYO2014. Using next generation sequencing and metagenomics analysis, we were able to characterize and compare the content of PYO cocktails separated by 17 years in time. Even though the cocktail composition is upgraded every six months, we found it to remain relatively stable over the years.
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 bitbucket package (https://bitbucket.org/genomicepidemiology/mgmapper). A web-version (https://cge.cbs.dtu.dk/services/MGmapper) provides the basic functionality for analysis of small fastq datasets.

General information
State: Published
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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BFI (2018): BFI-level 1
MHC-I Ligand Discovery Using Targeted Database Searches of Mass Spectrometry Data: Implications for T-Cell Immunotherapies

Class I major histocompatibility complex (MHC-I)-bound peptide ligands dictate the activation and specificity of CD8+ T cells and thus are important for devising T-cell immunotherapies. In recent times, advances in mass spectrometry (MS) have enabled the precise identification of these MHC-I peptides, wherein MS spectra are compared against a reference proteome. Unfortunately, matching these spectra to reference proteome databases is hindered by inflated search spaces attributed to a lack of enzyme restriction in the searches, limiting the efficiency with which MHC ligands are discovered.

Here we offer a solution to this problem whereby we developed a targeted database search approach and accompanying tool SpectMHC, that is based on a priori-predicted MHC-I peptides. We first validated the approach using MS data from two different allotype-specific immunoprecipitates for the C57BL/6 mouse background. We then developed allotype-specific HLA databases to search previously published MS data sets of human peripheral blood mononuclear cells (PBMCs). This targeted search strategy improved peptide identifications for both mouse and human ligandomes by
greater than 2-fold and is superior to traditional "no enzyme" searches of reference proteomes. Our targeted database search promises to uncover otherwise missed novel T-cell epitopes of therapeutic potential.

**General information**

State: Published
Organisations: Department of Bio and Health Informatics, Immunoinformatics and Machine Learning, Dalhousie University, University of Tubingen
Authors: Murphy, J. P. (Ekstern), Konda, P. (Ekstern), Kowalewski, D. J. (Ekstern), Schuster, H. (Ekstern), Clements, D. (Ekstern), Kim, Y. (Ekstern), Cohen, A. M. (Ekstern), Sharif, T. (Ekstern), Nielsen, M. (Intern), Stevanovic, S. (Ekstern), Lee, P. W. (Ekstern), Gujar, S. (Ekstern)
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- Web of Science (2018): Indexed yes
- BFI (2017): BFI-level 2
- Scopus rating (2017): SNIP 0.982 SJR 1.818
- Web of Science (2017): Indexed yes
- BFI (2016): BFI-level 2
- Scopus rating (2016): CiteScore 4.34 SJR 1.76 SNIP 1.018
- Web of Science (2016): Indexed yes
- BFI (2015): BFI-level 2
- Scopus rating (2015): SJR 1.933 SNIP 1.08 CiteScore 4.45
- Web of Science (2015): Indexed yes
- BFI (2014): BFI-level 2
- Scopus rating (2014): SJR 1.959 SNIP 1.174 CiteScore 4.64
- Web of Science (2014): Indexed yes
- BFI (2013): BFI-level 2
- Scopus rating (2013): SJR 2.012 SNIP 1.248 CiteScore 5.16
- ISI indexed (2013): ISI indexed yes
- Web of Science (2013): Indexed yes
- BFI (2012): BFI-level 2
- Scopus rating (2012): SJR 2.04 SNIP 1.323 CiteScore 5.12
- ISI indexed (2012): ISI indexed yes
- Web of Science (2012): Indexed yes
- BFI (2011): BFI-level 1
- Scopus rating (2011): SJR 2.137 SNIP 1.261 CiteScore 5.12
- ISI indexed (2011): ISI indexed yes
- BFI (2010): BFI-level 2
- Scopus rating (2010): SJR 1.96 SNIP 1.244
- Web of Science (2010): Indexed yes
- BFI (2009): BFI-level 2
- Scopus rating (2009): SJR 2.001 SNIP 1.207
- BFI (2008): BFI-level 2
- Scopus rating (2008): SJR 2.036 SNIP 1.11
- Web of Science (2008): Indexed yes
- Scopus rating (2007): SJR 1.94 SNIP 1.099
- Web of Science (2007): Indexed yes
- Scopus rating (2006): SJR 1.774 SNIP 1.101
Microbial Biogeography of the Arctic Cryosphere

Microbial biogeography has become a recognized field of research within the science of microbial ecology. Technological advances such as the high throughput sequencing of genetic information with next-generation sequencing (NGS) technologies have made us able to "see" the diversity of microbial communities. This has considerably improved our understanding that even harsh and seemingly barren environments such as the cryosphere, the frozen parts of our planet, is inhabited by diverse life.

This thesis presents three studies in microbial biogeography of the Arctic cryosphere utilizing a range of NGS approaches. The first study of this thesis explores microbial diversity and community composition in snow on North Pole ice floes. It was the first example of 16S rRNA gene amplicon sequencing of North Pole snow. The results of this study showed that snow in different sites on the North Pole can harbor different microbial communities, but these communities are more similar to each other than they are to the surrounding ice and the ocean. The second study confirmed the hypothesis that freshwater networks connected to the cryosphere are inoculated with cryosphere-specific microbial communities. It showed also, that these communities represented about a quarter of the diversity of the microbial community in the estuary. Lastly, this study illustrates the advantages that amplicon sequencing can have over shotgun metagenomics in certain well-defined studies. The final study included in this thesis utilizes the full potential of shotgun metagenomics, which enabled the binning of microbial genomes from metagenomes. Putative genomes showed signs of adaptation to and origin from contaminated habitats. This lead to the hypothesis that the Greenland ice sheet might be a contaminated habitat to a previously unacknowledged degree.

The overall aim of this thesis is to illustrate the advantages that NGS has given in the field of microbial biogeography with the Arctic cryosphere as an example. The most important point in the following is that in order to utilize these advantages to their full potential, we need to put emphasis on hypothesis-driven research and acknowledge the caveats that come with NGS in microbial ecology. If we can do this, cryosphere microbial biogeography can be of value not only to us as microbial ecology researchers but also to researchers in other fields and finally to the inhabitants of the Arctic.

Mitochondrial genome of the North African Sahara Honeybee, Apis mellifera sahariensis (Hymenoptera: Apidae)

We present the complete mitochondrial genome of honey bee subspecies, Apis mellifera sahariensis (Apidae) belonging to the African lineage. The assembled circular genome has a length of 16,569bp which comprises 13 protein coding genes, 22 transfer RNA genes, two ribosomal RNA genes, and AT rich region.
**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.

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**General information**
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Organisations: Center for Biological sequence analysis, Department of Bio and Health Informatics, Immunoinformatics and Machine Learning, Fundación Instituto Leloir
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Number of pages: 2
Publication date: 2017
Main Research Area: Technical/natural sciences
Modifications of TIGIT expression contribute to CD8 T cell exhaustion in chronic virus infection

General information
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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
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Pages: 318
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Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): SNIP 0.621 SJR 0.891
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.03 SJR 0.979 SNIP 0.644
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.933 SNIP 0.679 CiteScore 1.97
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.901 SNIP 0.665 CiteScore 1.91
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 0.875 SNIP 0.709 CiteScore 2.05
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 0.89 SNIP 0.742 CiteScore 2.16
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 0.865 SNIP 0.654 CiteScore 2.06
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 0.859 SNIP 0.621
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 0.973 SNIP 0.659
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 0.24 SNIP 0.078
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 0.288 SNIP 0.141
Scopus rating (2006): SJR 0.426 SNIP 0.124
Scopus rating (2005): SJR 1.017 SNIP 0.641
Web of Science (2005): Indexed yes
Scopus rating (2004): SJR 0.858 SNIP 0.6
Web of Science (2004): Indexed yes
Scopus rating (2003): SJR 0.819 SNIP 0.625
Scopus rating (2002): SJR 0.74 SNIP 0.587
Web of Science (2002): Indexed yes
Scopus rating (2001): SJR 0.746 SNIP 0.63
Scopus rating (2000): SJR 0.876 SNIP 0.608
Web of Science (2000): Indexed yes
Scopus rating (1999): SJR 0.846 SNIP 0.651
Original language: English
Molecular diagnostics of aleutian mink disease virus: applied use of next generation sequencing and phylogenetics

Aleutian Mink Disease virus (AMDV) is a parvovirus causing Aleutian Mink Disease (AMD), often referred to as plasmacytosis. It is a systemic infection affecting mink of all ages, and is globally the most important pathogen impacting mink farming. In Denmark AMDV has since 1999 been monitored by a national control program, which is based on serological screening of all animals and encourages infected farms to stamp out. Historically there has been no consensus about which genomic region of the virus to analyse e.g. in relation to surveillance, and most previous studies in this regard, have been based either on partial or entire genes, or on pure epidemiological data. Thus, when initiating this project, little was known about AMDV’s total genomic diversity and how the virus was spread between farms.

Recent advances in the field of molecular diagnostics have made high throughput tools such as next generation sequencing cheaper and more easily available. Whole genome sequencing and advanced phylogenetic analyses have successfully been applied to describe the molecular evolution and transmission patterns for viruses such as Foot and Mouth Disease Virus (FMDV), Ebola, and avian influenza virus, however not previously for AMDV. The overall aim with this thesis was to investigate if next generation sequencing and phylogenetic analyses of full length isolates could improve our understanding of the total genomic diversity and evolution of AMDV. Additionally, we wanted to evaluate if this knowledge could contribute to the elucidation of AMDV transmission between farms and improve molecular diagnostics. During the first phase of this project a method for performing whole genome sequencing of AMDV was developed. This protocol enabled the sequencing of a large number of in vivo infectious AMDV isolates and provided the necessary dataset to act as foundation for the remaining analyses in the thesis. The first original paper (Manuscript 1) describes this protocol.

Manuscript 2 is a proof-of-concept study which demonstrated the advantage of using the whole genome sequence approach, compared to the in Denmark traditionally used partial NS1 gene sequencing, for the elucidation of transmission pathways between farms. The study was performed on samples from a small local AMDV outbreak, and clearly illustrated that the phylogenies based on partial NS1 gene sequencing were uninformative and could not be used for determining transmission pathways, even in the light of supporting epidemiological data. The whole-genome approach on the other hand, confirmed the epidemiological hypothesis about the direction of spread.

In Manuscript 3, the methodologies from Manuscript 1 and 2 were applied to generate the to-date most comprehensive phylogenetic and genetic analysis of full-length AMDV isolates, composed of more than 200 field strains. The study shed light on the diversity and evolutionary behaviour of two distinct AMDV strains, in addition to providing the first robust evolutionary rate-estimates. Altogether, the work presented in this thesis provides a contribution to the molecular diagnostics of AMDV, enables us better to understand the virus’ evolutionary behaviour in the context of mink farming, and is anticipated to be of value for more accurately tracing back in time the emergence of future outbreaks.

General information
State: Published
Organisations: Department of Bio and Health Informatics, Disease Intelligence and Molecular Evolution, Department of Biotechnology and Biomedicine, National Veterinary Institute, Virology, Kopenhagen Diagnostics
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Original language: English
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Multidrug-resistant Neisseria gonorrhoeae infection with ceftriaxone resistance and intermediate resistance to azithromycin, Denmark, 2017

We describe a multidrug-resistant Neisseria gonorrhoeae infection with ceftriaxone resistance and azithromycin intermediate resistance in a heterosexual man in Denmark, 2017. Whole genome sequencing of the strain GK124 identified MSLT ST1903, NG-MAST ST1614 and all relevant resistance determinants including similar penA resistance mutations previously described in ceftriaxone-resistant gonococcal strains. Although treatment with ceftriaxone 0.5 g plus
azithromycin 2 g was successful, increased awareness of spread of gonococcal strains threatening the recommended
dual therapy is crucial.

General information
State: Published
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Worning, P. (Ekstern), Unemo, M. (Ekstern), Westh, H. (Ekstern)
Number of pages: 4
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Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): SNIP 2.087 SJR 3.727
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.72 SNIP 2.311 SJR 4.072
BFI (2015): BFI-level 1
Scopus rating (2015): CiteScore 2.69 SNIP 1.864 SJR 3.11
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): CiteScore 2.83 SNIP 1.75 SJR 3.15
BFI (2013): BFI-level 1
Scopus rating (2013): CiteScore 2.62 SNIP 1.766 SJR 2.673
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): CiteScore 3.02 SNIP 2.262 SJR 2.837
ISI indexed (2012): ISI indexed no
BFI (2011): BFI-level 1
Scopus rating (2011): CiteScore 3.27 SNIP 2.5 SJR 2.678
ISI indexed (2011): ISI indexed no
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SNIP 15.968 SJR 1.831
BFI (2009): BFI-level 1
Scopus rating (2009): SNIP 4.554 SJR 0.704
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SNIP 1.037 SJR 0.461
Scopus rating (2007): SNIP 0.185 SJR 0.411
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 0.384
Scopus rating (2005): SJR 0.78
Scopus rating (2004): SJR 0.457
Scopus rating (2003): SJR 0.309
Scopus rating (2002): SJR 0.231
MuPeXI: prediction of neo-epitopes from tumor sequencing data

Personalization of immunotherapies such as cancer vaccines and adoptive T cell therapy depends on identification of patient-specific neo-epitopes that can be specifically targeted. MuPeXI, the mutant peptide extractor and informer, is a program to identify tumor-specific peptides and assess their potential to be neo-epitopes. The program input is a file with somatic mutation calls, a list of HLA types, and optionally a gene expression profile. The output is a table with all tumor-specific peptides derived from nucleotide substitutions, insertions, and deletions, along with comprehensive annotation, including HLA binding and similarity to normal peptides. The peptides are sorted according to a priority score which is intended to roughly predict immunogenicity. We applied MuPeXI to three tumors for which predicted MHC-binding peptides had been screened for T cell reactivity, and found that MuPeXI was able to prioritize immunogenic peptides with an area under the curve of 0.63. Compared to other available tools, MuPeXI provides more information and is easier to use. MuPeXI is available as stand-alone software and as a web server at http://www.cbs.dtu.dk/services/MuPeXI.
Cytotoxic T cells are of central importance in the immune system's response to disease. They recognize defective cells by binding to peptides presented on the cell surface by MHC class I molecules. Peptide binding to MHC molecules is the single most selective step in the Ag-presentation pathway. Therefore, in the quest for T cell epitopes, the prediction of peptide binding to MHC molecules has attracted widespread attention. In the past, predictors of peptide-MHC interactions have primarily been trained on binding affinity data. Recently, an increasing number of MHC-presented peptides identified by mass spectrometry have been reported containing information about peptide-processing steps in the presentation pathway and the length distribution of naturally presented peptides. In this article, we present NetMHCpan-4.0, a method trained on binding affinity and eluted ligand data leveraging the information from both data types. Large-scale benchmarking of the method demonstrates an increase in predictive performance compared with state-of-the-art methods when it comes to identification of naturally processed ligands, cancer neoantigens, and T cell epitopes.

General information
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Organisations: Department of Bio and Health Informatics, Immunoinformatics and Machine Learning, La Jolla Institute for Allergy & Immunology, Universidad Nacional de San Martin
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BFI (2018): BFI-level 2
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.

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Scopus rating (2017): SNIP 1.593 SJR 4.466
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 5.96 SJR 4.849 SNIP 1.617
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 5.042 SNIP 1.694 CiteScore 6.33
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 5.305 SNIP 1.761 CiteScore 6.66
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 5.742 SNIP 1.863 CiteScore 7.22
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 5.743 SNIP 1.963 CiteScore 7.6
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 5.864 SNIP 1.905 CiteScore 7.51
Next-generation ELISA diagnostic assay for Chagas Disease based on the combination of short peptidic epitopes

Chagas Disease, caused by the protozoan Trypanosoma cruzi, is a major health and economic problem in Latin America for which no vaccine or appropriate drugs for large-scale public health interventions are yet available. Accurate diagnosis is essential for the early identification and follow up of vector-borne cases and to prevent transmission of the disease by way of blood transfusions and organ transplantation. Diagnosis is routinely performed using serological methods, some of which require the production of parasite lysates, parasite antigenic fractions or purified recombinant antigens. Although available serological tests give satisfactory results, the production of reliable reagents remains laborious and expensive. Short peptides spanning linear B-cell epitopes have proven ideal serodiagnostic reagents in a wide range of diseases. Recently, we have conducted a large-scale screening of T. cruzi linear B-cell epitopes using high-density peptide chips, leading to the identification of several hundred novel sequence signatures associated to chronic Chagas Disease. Here, we performed a serological assessment of 27 selected epitopes and of their use in a novel multipeptide-based diagnostic method. A combination of 7 of these peptides were finally evaluated in ELISA format against a panel of 199 sera samples (Chagas-positive and negative, including sera from Leishmaniasis-positive subjects). The multipeptide formulation displayed a high diagnostic performance, with a sensitivity of 96.3% and a specificity of 99.15%. Therefore, the use of synthetic peptides as diagnostic tools are an attractive alternative in Chagas’ disease diagnosis.
Niche differentiation and evolution of comammox Nitrospira through a comparative genomics analysis

Nitrification, the biological oxidation of ammonium to nitrate, is a fundamental process in the nitrogen cycle and plays an important role in natural and engineered systems. Throughout the last century, nitrification was assumed to be a two-step process executed by two different functional groups, ammonia oxidizing prokaryotes (AOP) and nitrite oxidizing bacteria (NOB). Recently, several articles have shown the capability of a single microorganism, belonging to the genus Nitrospira, to carry out the complete oxidation of ammonia to nitrate (comammox). Nitrospira spp. are widespread in both natural and engineered ecosystems associated with nitrogen cycling and different species are frequently observed to coexist in the same environment. Besides recent discoveries pointing towards versatile metabolism in some Nitrospira species, little is known about the functional potential of the two comammox Nitrospira clades, and the factors involved in niche-partitioning between comammox and canonical Nitrospira.

A comparative genomics analysis was conducted with five genomes recovered from a groundwater-fed rapid sand filter (including both comammox clades and a nitrite-oxidizing Nitrospira population genome) and high quality published Nitrospira genomes, to reveal distinct genomic features within Nitrospira. In addition, we investigated the evolution of the ammonia oxidation pathway in comammox Nitrospira. This analysis revealed distinct genetic capabilities of the different comammox clades and canonical Nitrospira which can help to explain the coexistence and niche partitioning of Nitrospira spp. These divergences range from the nitrogen source utilization capacity to the ability for electron donor versatility, and other characteristics such as stress response. With respect to the evolutionary history of comammox Nitrospira, our analysis indicates transfer events with betaproteobacterial ammonia oxidizers. In addition, transfer events between comammox clade A and clade B were also detected for genes belonging to the ammonium oxidation pathway. Together, these results expand the actual knowledge of the ecology and evolution of the recently discovered comammox Nitrospira.
NNAlign: a platform to construct and evaluate artificial neural network models of receptor-ligand interactions

Peptides are extensively used to characterize functional or (linear) structural aspects of receptor-ligand interactions in biological systems, e.g. SH2, SH3, PDZ peptide-recognition domains, the MHC membrane receptors and enzymes such as kinases and phosphatases. NNAlign is a method for the identification of such linear motifs in biological sequences. The algorithm aligns the amino acid or nucleotide sequences provided as training set, and generates a model of the sequence motif detected in the data. The webserver allows setting up cross-validation experiments to estimate the performance of the model, as well as evaluations on independent data. Many features of the training sequences can be encoded as input, and the network architecture is highly customizable. The results returned by the server include a graphical representation of the motif identified by the method, performance values and a downloadable model that can be applied to scan protein sequences for occurrence of the motif. While its performance for the characterization of peptide-MHC interactions is widely documented, we extended NNAlign to be applicable to other receptor-ligand systems as well. Version 2.0 supports alignments with insertions and deletions, encoding of receptor pseudo-sequences, and custom alphabets for the training sequences. The server is available at http://www.cbs.dtu.dk/services/NNAlign-2.0.
Nomenclature for alleles of the human carboxylesterase 1 gene

General information
State: Published
Organisations: Department of Bio and Health Informatics, Integrative Systems Biology, Department of Biotechnology and Biomedicine

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Background: Whole-genome sequencing (WGS) projects provide short read nucleotide sequences from nuclear and possibly organelle DNA depending on the source of origin. Mitochondrial DNA is present in animals and fungi, while plants contain DNA from both mitochondria and chloroplasts. Current techniques for separating organelle reads from nuclear reads in WGS data require full reference or partial seed sequences for assembling. Results: Norgal (de Novo ORGAnELe extractor) avoids this requirement by identifying a high frequency subset of k-mers that are predominantly of mitochondrial
origin and performing a de novo assembly on a subset of reads that contains these k-mers. The method was applied to WGS data from a panda, brown algae seaweed, butterfly and filamentous fungus. We were able to extract full circular mitochondrial genomes and obtained sequence identities to the reference sequences in the range from 98.5 to 99.5%. We also assembled the chloroplasts of grape vines and cucumbers using Norgal together with seed-based de novo assemblers. Conclusion: Norgal is a pipeline that can extract and assemble full or partial mitochondrial and chloroplast genomes from WGS short reads without prior knowledge. The program is available at: https://bitbucket.org/kosaidtu/norgal.

General information
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Organisations: Department of Bio and Health Informatics, Metagenomics
Authors: Al-Nakeeb, K. A. A. (Intern), Petersen, T. N. (Intern), Sicheritz-Pontén, T. (Intern)
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Scopus rating (2014): SJR 1.916 SNIP 1.185 CiteScore 2.91
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Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.662 SNIP 1.19 CiteScore 3.34
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
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Web of Science (2010): Indexed yes
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Web of Science (2007): Indexed yes
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Scopus rating (2005): SJR 2.635 SNIP 1.61
Web of Science (2005): Indexed yes
Scopus rating (2004): SJR 3.304 SNIP 1.723
Web of Science (2004): Indexed yes
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Norwegian patients and retail chicken meat share cephalosporin-resistant Escherichia coli and IncK/bla\textsubscript{CMY-2} resistance plasmids
In 2012 and 2014 the Norwegian monitoring programme for antimicrobial resistance in the veterinary and food production sectors (NORM-VET) showed that 124 of a total of 406 samples (31%) of Norwegian retail chicken meat was contaminated with extended-spectrum cephalosporin-resistant Escherichia coli. The aim of this study was to compare selected cephalosporin-resistant E. coli from humans and poultry to determine their genetic relatedness based on whole genome sequencing (WGS). E. coli representing three prevalent cephalosporin-resistant multi-locus sequence types (STs) isolated from poultry (n=17) were selected from the NORM-VET strain collections. All strains carried an IncK plasmid with a bla\textsubscript{CMY-2} gene. Clinical E. coli isolates (n=284) with AmpC-mediated resistance were collected at Norwegian microbiology laboratories from 2010 to 2014. PCR screening showed that 29 of the clinical isolates harbouried both IncK and bla\textsubscript{CMY-2}. All IncK/bla\textsubscript{CMY-2} positive isolates were analysed by WGS-based bioinformatics tools. Analysis of single nucleotide polymorphisms (SNP) in 2.5 Mbp of shared genome sequences showed close relationship with less than 15 SNP differences between five clinical isolates from urinary tract infections, and the ST38 isolates from poultry. Furthermore, all of the 29 clinical isolates harboured IncK/bla\textsubscript{CMY-2} plasmid variants highly similar to the IncK/bla\textsubscript{CMY-2} plasmid present in the poultry isolates. Our results provide support for the hypothesis that clonal transfer of cephalosporin-resistant E. coli from chicken meat to humans may occur, and may cause difficult to treat infections. Furthermore, these E. coli can be a source of AmpC resistance plasmids for opportunistic pathogens in the human microbiota.

General information
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Organisations: Department of Bio and Health Informatics, Genomic Epidemiology, Norwegian Institute of Public Health, Norwegian Veterinary Institute, University Hospital of North Norway, Vestfold Hospital Trust, UiT The Arctic University of Norway, Stavanger University Hospital, Akershus University Hospital, Sørlandet Hospital
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Zoonotic transfer of cephalosporin resistant E. coli, Chicken meat, Plasmid-mediated AmpC transmission, Urinary tract infections

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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 (inha/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, Gnrhr, 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.

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Organisations: Department of Systems Biology, Department of Biotechnology and Biomedicine, DTU Multistage Core, Center for Biological Sequence Analysis, Department of Bio and Health Informatics, University of Turku
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Scopus rating (2011): SJR 1.794 SNIP 1.191 CiteScore 4.03
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Scopus rating (2009): SJR 1.603 SNIP 1.167
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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.

General information
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Organisations: Department of Bio and Health Informatics, Department of Systems Biology, Novo Nordisk Foundation Center for Biosustainability, Center for Biological Sequence Analysis, University of Hong Kong, NNIT A/S
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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.

General information
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Organisations: Department of Systems Biology, DTU Multi Assay Core, Department of Biotechnology and Biomedicine, DTU Multi Assay Core, Department of Bio and Health Informatics, Disease Intelligence and Molecular Evolution, University of Copenhagen, BGI-Shenzhen , National Institute for Nutrition and Seafood Research, University of California, San Francisco
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Oscillospira and related bacteria - from metagenomics species to metabolic features

Oscillospira is an under-studied anaerobic bacterial genus from Clostridial cluster IV that has resisted cultivation for over a century since the first time it was observed. In recent years its 16S rRNA gene was identified in several human gut microbiota studies where it was often associated with interesting traits, especially leanness. However, very little is known about its metabolism or physiology. Here we used nearly complete genomes derived from shot-gun metagenomic data from the human gut to analyze Oscillospira and related bacteria. We used sequence similarity, gene neighbourhood information and manual metabolic pathway curation to decipher key metabolic features of this intriguing bacterial genus. We infer that Oscillospira species are butyrate producers, and at least some of them have the ability to utilize glucuronate, a common animal-derived sugar that is both produced by the human host and consumed by that host in diets rich in animal products. These findings could help explain diet-related inter-individual variation in faecal Oscillospira levels as well as the observation that the presence of this genus is reduced in diseases that involve inflammation.
Pancreatic Islet Protein Complexes and Their Dysregulation in Type 2 Diabetes

Type 2 diabetes (T2D) is a complex disease that involves multiple genes. Numerous risk loci have already been associated with T2D, although many susceptibility genes remain to be identified given heritability estimates. Systems biology approaches hold potential for discovering novel T2D genes by considering their biological context, such as tissue-specific protein interaction partners. Pancreatic islets are a key T2D tissue and many of the known genetic risk variants lead to impaired islet function, hence a better understanding of the islet-specific dysregulation in the disease-state is essential to unveil the full potential of person-specific profiles. Here we identify 3,692 overlapping pancreatic islet protein complexes (containing 10,805 genes) by integrating islet gene and protein expression data with protein interactions. We found 24 of these complexes to be significantly enriched for genes associated with diabetic phenotypes through heterogeneous evidence sources, including genetic variation, methylation, and gene expression in islets. The analysis specifically revealed ten T2D candidate genes with probable roles in islets (ANPEP, HADH, FAM105A, PDLIM4, PDLIM5, MAP2K4, PPP2R5E, SNX13, GNAS, and FRS2), of which the last six are novel in the context of T2D and the data that went into the analysis. Fifteen of the twenty-four complexes were further enriched for combined genetic associations with glycemic traits, exemplifying how perturbation of protein complexes by multiple small effects can give rise to diabetic phenotypes. The complex nature of T2D ultimately prompts an understanding of the individual patients at the network biology level. We present the foundation for such work by exposing a subset of the global interactome that is dysregulated in T2D and consequently provides a good starting point when evaluating an individual's alterations at the genome, transcriptome, or proteome level in relation to T2D in clinical settings.
Glioblastoma is a devastating disease and despite extensive treatment, overall survival (OS) for these patients remains poor. Yet, a small proportion of glioblastoma patients present relatively long survival over 3 years, but the underlying molecular background separating these long-term survivors (LTS) from short-term survivors (STS) are still insufficiently understood. The purpose of this study was to identify independent prognostic variables for survival by examining molecular profiles of LTS and STS in a clinically well characterized cohort of glioblastoma patients. The cohort consisted of 93 patients diagnosed with primary glioblastoma and treated with radiation therapy plus concomitant and adjuvant chemotherapy as well as bevacizumab administered in the first-line setting or at time of recurrence. Among these, 14 STS (OS36 months) were identified, which were all confirmed being IDHwt. For all patients, RNA had previously been purified from microdissected tumor tissue of the diagnostic specimen and analyzed for expression levels by a customized NanoString platform. This covered 800 genes related to glioblastoma cancer hallmarks, including regulation of angiogenesis and immune response. When comparing expression of these genes in LTS vs. STS using a Welsh’s t-test, 14 candidate genes ended up significant (P
Patterns of infections, aetiological agents, and antimicrobial resistance at a tertiary care hospital in northern Tanzania

Objective
To determine the causative agents of infections and their antimicrobial susceptibility at a tertiary care hospital in Moshi, Tanzania, to guide optimal treatment.

Methods
A total of 590 specimens (stool (56), sputum (122), blood (126) and wound swabs (286)) were collected from 575 patients admitted in the medical and surgical departments. The bacterial species were determined by conventional methods and disk diffusion was used to determine the antimicrobial susceptibility pattern of the bacteria isolates.

Results
A total of 249 (42.2%) specimens were culture-positive yielding a total of 377 isolates. A wide range of bacteria was isolated, the most predominant being Gram-negative bacteria: Proteus spp. (n=48, 12.7%), Escherichia coli (n=44, 11.7%), Pseudomonas spp. (n=40, 10.6%), and Klebsiella spp (n=38, 10.1%). Wound infections were characterised by multiple isolates (n=293, 77.7%), with the most frequent being Proteus spp. (n=44, 15%), Pseudomonas (n=37, 12.6%), Staphylococcus (n=29, 9.9%), and Klebsiella spp. (n=28, 9.6%). All S. aureus tested were resistant to penicillin (n=22, 100%) and susceptible to vancomycin. Significant resistance to cephalosporins such as cefazoline (n=62, 72.9%), ceftriaxone (n=44, 51.8%) and ceftazidime (n=40, 37.4%) was observed in Gram-negative bacteria; as well as resistance to cefoxitin (n=6, 27.3%) in Staphylococcus aureus.

Conclusion
The study has revealed a wide range of causative agents, with an alarming rate of resistance to the commonly used antimicrobial agents. Furthermore, the bacterial spectrum differs from those often observed in high-income countries. This highlights the imperative of regular generation of data on aetiological agents and their antimicrobial susceptibility patterns.
especially in infectious disease endemic settings. The key steps would be to ensure the diagnostic capacity at a sufficient number of sites and implement structures to routinely exchange, compare, analyse and report data. Sentinel sites (hospitals) across the country (and region) should report on a representative subset of bacterial species and their susceptibility to drugs at least annually. A central organizing body should collate the data and report to relevant national and international stakeholders.

**General information**

State: Published
Organisations: Department of Bio and Health Informatics, Genomic Epidemiology, National Food Institute, Research Group for Genomic Epidemiology, KCRI Kilimanjaro Clinical Research Institute, University of Copenhagen, Kilimanjaro Christian Medical College
Authors: Kumburu, H. H. (Ekstern), Sonda, T. (Ekstern), Mmbaga, B. T. (Ekstern), Alifrangis, M. (Ekstern), Lund, O. (Intern), Kibiki, G. (Ekstern), Aarestrup, F. M. (Intern)
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- Scopus rating (2011): SJR 1.576 SNIP 1.133 CiteScore 2.78
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- Scopus rating (2010): SJR 1.525 SNIP 1.263
- Web of Science (2010): Indexed yes
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- BFI (2008): BFI-level 2
- Scopus rating (2008): SJR 1.233 SNIP 1.144
- Scopus rating (2007): SJR 1.603 SNIP 1.513
- Web of Science (2007): Indexed yes
- Scopus rating (2006): SJR 1.399 SNIP 1.384
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Authors: Kumburu, H. H. (Ekstern), Sonda, T. (Ekstern), Mmbaga, B. T. (Ekstern), Alifrangis, M. (Ekstern), Lund, O. (Intern), Kibiki, G. (Ekstern), Aarestrup, F. M. (Intern)
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Perturbed CD8+ T cell TIGIT/CD226/PVR axis despite early initiation of antiretroviral treatment in HIV infected individuals

HIV-specific CD8+ T cells demonstrate an exhausted phenotype associated with increased expression of inhibitory receptors, decreased functional capacity, and a skewed transcriptional profile, which are only partially restored by antiretroviral treatment (ART). Expression levels of the inhibitory receptor, T cell immunoglobulin and ITIM domain (TIGIT), the co-stimulatory receptor CD226 and their ligand PVR are altered in viral infections and cancer. However, the extent to which the TIGIT/CD226/PVR-axis is affected by HIV-infection has not been characterized. Here, we report that TIGIT expression increased over time despite early initiation of ART. HIV-specific CD8+ T cells were almost exclusively TIGIT+, had an inverse expression of the transcription factors T-bet and Eomes and co-expressed PD-1, CD160 and 2B4. HIV-specific TIGIT+ cells were negatively correlated with polyfunctionality and displayed a diminished expression of CD226. Furthermore, expression of PVR was increased on CD4+ T cells, especially T follicular helper (Tfh) cells, in HIV-infected lymph nodes. These results depict a skewing of the TIGIT/CD226 axis from CD226 co-stimulation towards TIGIT-mediated inhibition of CD8+ T cells, despite early ART. These findings highlight the importance of the TIGIT/CD226/PVR axis as an immune checkpoint barrier that could hinder future "cure" strategies requiring potent HIV-specific CD8+ T cells.

General information

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Organisations: Department of Bio and Health Informatics, Genomic Epidemiology, Karolinska University Hospital, University of Pennsylvania, National Institute of Respiratory Diseases, University of California
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Scopus rating (2017): SNIP 1.245 SJR 1.533
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 4.63 SJR 1.692 SNIP 1.354
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.034 SNIP 1.597 CiteScore 5.3
Web of Science (2015): Indexed yes
Phylogenetic ctDNA analysis depicts early stage lung cancer evolution

The early detection of relapse following primary surgery for non-small cell lung cancer and the characterization of emerging subclones seeding metastatic sites might offer new therapeutic approaches to limit tumor recurrence. The potential to non-invasively track tumor evolutionary dynamics in ctDNA of early-stage lung cancer is not established. Here we conduct a tumour-specific phylogenetic approach to ctDNA profiling in the first 100 TRACERx (TRAcking non-small cell Lung Cancer Evolution through therapy (Rx)) study participants, including one patient co-recruited to the PEACE (Posthumous Evaluation of Advanced Cancer Environment) post-mortem study. We identify independent predictors of ctDNA release and perform tumor volume limit of detection analyses. Through blinded profiling of post-operative plasma, we observe evidence of adjuvant chemotherapy resistance and identify patients destined to experience recurrence of their lung cancer. Finally, we show that phylogenetic ctDNA profiling tracks the subclonal nature of lung cancer relapse and metastases, providing a new approach for ctDNA driven therapeutic studies.

General information

State: Published

Organisations: Department of Bio and Health Informatics, Cancer Genomics, CRUK Lung Cancer Centre of Excellence, Natera Inc., University of Leicester, University College London Hospitals NHS Foundation Trust, The Francis Crick Institute, University College London Hospitals, Harvard Medical School, University of Manchester, Christie Hospital, University Hospital of South Manchester, Birmingham Heartlands Hospital, University of Birmingham, Aberdeen University Medical School & Aberdeen Royal Infirmary, Leicester University Hospitals, North Middlesex Hospital, Royal Free Hospital, The Princess Alexandra Hospital NHS Trust, Royal Surrey County Hospital, Ashford and St. Peters' Hospital, Velindre Hospital, University Hospital Llandough, University Hospital of Wales, University College London, Whittington Hospital, MAYO CLINIC, University College London

**PointFinder: a novel web tool for WGS-based detection of antimicrobial resistance associated with chromosomal point mutations in bacterial pathogens**

**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.
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.
Predicting Secretory Proteins with SignalP
SignalP is the currently most widely used program for prediction of signal peptides from amino acid sequences. Proteins with signal peptides are targeted to the secretory pathway, but are not necessarily secreted. After a brief introduction to the biology of signal peptides and the history of signal peptide prediction, this chapter will describe all the options of the current version of SignalP and the details of the output from the program. The chapter includes a case study where the scores of SignalP were used in a novel way to predict the functional effects of amino acid substitutions in signal peptides.

General information
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Organisations: Department of Bio and Health Informatics, Disease Intelligence and Molecular Evolution
Authors: Nielsen, H. (Intern)
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Main Research Area: Technical/natural sciences

Publication information
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Ratings:
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): SNIP 0.318 SJR 0.616
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 0.76 SJR 0.585 SNIP 0.278
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.627 SNIP 0.319 CiteScore 0.82
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.735 SNIP 0.374 CiteScore 1.02
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 0.751 SNIP 0.351 CiteScore 1.17
ISI indexed (2013): ISI indexed no
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 0.753 SNIP 0.427 CiteScore 1.26
ISI indexed (2012): ISI indexed no
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 0.823 SNIP 0.431 CiteScore 1.17
ISI indexed (2011): ISI indexed no
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 0.848 SNIP 0.385
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 0.733 SNIP 0.304
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 0.594 SNIP 0.266
Scopus rating (2007): SJR 0.666 SNIP 0.181
Scopus rating (2006): SJR 0.636
Prediction and in vitro verification of potential CTL epitopes conserved among PRRSV-2 strains

Porcine Reproductive and Respiratory Syndrome Virus (PRRSV) is the causative agent of one of the most important porcine diseases with a high impact on animal health, welfare, and production economy. PRRSV exhibits a multitude of immunoevasive strategies that, in combination with a very high mutation rate, has hampered the development of safe and broadly protective vaccines. Aiming at a vaccine inducing an effective cytotoxic T cell response, a bioinformatics approach was taken to identify conserved PRRSV-derived peptides predicted to react broadly with common swine leukocyte antigen (SLA) class I alleles. Briefly, all possible 9- and 10-mer peptides were generated from 104 complete PRRSV type 2 genomes of confirmed high quality, and peptides with high binding affinity to five common SLAs were identified combining the NetMHCpan and positional scanning combinatorial peptide libraries binding predictions. Predicted binders were prioritized according to genomic conservation and SLA coverage using the PopCover algorithm. From this, 53 peptides were acquired for further analysis. Binding affinity and stability of a subset of 101 peptide-SLA combinations were validated in vitro for 4 of the 5 SLAs. Eventually, 23% of the predicted peptide-SLA combinations showed to form complexes with a dissociation half-life ≥30 min. Additionally, combining the two prediction methods proved to be more robust across alleles than either method used alone in terms of predicted-to-observed correlations. In summary, our approach represents a finely tuned epitope prediction pipeline providing a rationally selected ensemble of peptides for future in vivo experiments with pigs expressing the included SLAs.

General information
State: Published
Organisations: National Veterinary Institute, Department of Bio and Health Informatics, Immunoinformatics and Machine Learning, Adaptive Immunology, Virology, University of Copenhagen
Authors: Welner, S. (Intern), Nielsen, M. (Intern), Rasmussen, M. (Ekstern), Buus, S. (Ekstern), Jungersen, G. (Intern), Larsen, L. E. (Intern)
Pages: 689-702
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Ratings:
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Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): SNIP 0.638 SJR 0.916
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.2 SJR 1.249 SNIP 0.716
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.573 SNIP 0.813 CiteScore 2.47
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.228 SNIP 0.823 CiteScore 2.28
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.303 SNIP 0.771 CiteScore 2.48
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.382 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 1.32 SNIP 0.885 CiteScore 2.83
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.217 SNIP 0.848
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.502 SNIP 0.843
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 1.408 SNIP 0.774
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 1.266 SNIP 0.742
Scopus rating (2006): SJR 1.232 SNIP 0.767
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 1.565 SNIP 0.82
Web of Science (2005): Indexed yes
Scopus rating (2004): SJR 1.535 SNIP 0.923
Web of Science (2004): Indexed yes
Scopus rating (2003): SJR 1.382 SNIP 0.713
Web of Science (2003): Indexed yes
Scopus rating (2002): SJR 1.357 SNIP 0.712
Scopus rating (2001): SJR 1.264 SNIP 0.639
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Web of Science (2000): Indexed yes
Scopus rating (1999): SJR 1.336 SNIP 0.902
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Source-ID: 2371228449
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Prevalence and risk factors of CTX-M Enterobacteriaceae in hospitalised patients at a tertiary hospital in Kilimanjaro, Tanzania

General information
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Organisations: Department of Bio and Health Informatics, Genomic Epidemiology, National Food Institute, Research Group for Genomic Epidemiology, KCRI Kilimanjaro Clinical Research Institute, University of Copenhagen, Kilimanjaro Christian Medical College
Authors: Sonda, T. (Ekstern), Kumburu, H. (Ekstern), van Zwetselaar, M. (Ekstern), Alifrangis, M. (Ekstern), Mmbaga, B. (Ekstern), Lund, O. (Intern), Aarestrup, F. M. (Intern), Kibiki, G. (Ekstern)
Pages: 187
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BFI (2018): BFI-level 2
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 2
Scopus rating (2017): SNIP 1.291 SJR 1.731
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 2.55 SJR 1.583 SNIP 1.182
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 1.559 SNIP 1.256 CiteScore 2.4
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 1.315 SNIP 1.102 CiteScore 2.3
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 1.599 SNIP 1.173 CiteScore 2.7
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 1.562 SNIP 1.247 CiteScore 2.82
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 1.576 SNIP 1.133 CiteScore 2.78
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 1.525 SNIP 1.263
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 1.276 SNIP 1.27
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 1.233 SNIP 1.144
Scopus rating (2007): SJR 1.603 SNIP 1.513
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 1.399 SNIP 1.384
Scopus rating (2005): SJR 1.224 SNIP 1.295
Scopus rating (2004): SJR 1.276 SNIP 1.246
Scopus rating (2003): SJR 1.211 SNIP 1.468
Scopus rating (2002): SJR 1.153 SNIP 1.128
Protective role of complement C3 against cytokine-mediated beta cell apoptosis

Background and aims: Type 1 diabetes is a chronic autoimmune disease characterized by pancreatic islet inflammation and β-cell destruction by pro-inflammatory cytokines and other mediators. The complement system, a major component of the immune system, has been recently shown to also act in metabolic organs, such as liver, adipose tissue, and pancreas. In the present study we identified complement C3 as an important hub of a cytokine-modified complement network in human islets and characterized the role of C3 in β-cell survival.

General information
State: Published
Organisations: Department of Bio and Health Informatics, Universite Libre de Bruxelles, University of Pisa, Intomics A/S
Authors: Dos Santos, R. S. (Ekstern), Marroqui, L. (Ekstern), Grieco, F. A. (Ekstern), Marselli, L. (Ekstern), Henz, S. R. (Ekstern), Marchetti, P. (Ekstern), Wernersson, R. (Intern), Eizirik, D. L. (Ekstern)
Pages: S198
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Main Research Area: Technical/natural sciences

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Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): SJR 3.228 SNIP 1.619
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 5.23 SJR 3.25 SNIP 1.721
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 3.61 SNIP 1.933 CiteScore 5.57
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 3.243 SNIP 1.964 CiteScore 5.57
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 3.259 SNIP 2.035 CiteScore 6
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 3.235 SNIP 1.914 CiteScore 5.76
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 3.177 SNIP 1.857 CiteScore 5.47
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 3.345 SNIP 1.847
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Protective Role of Complement C3 Against Cytokine-Mediated beta-Cell Apoptosis

Type 1 diabetes is a chronic autoimmune disease characterized by pancreatic islet inflammation and beta-cell destruction by proinflammatory cytokines and other mediators. Based on RNA sequencing and protein-protein interaction analyses of human islets exposed to proinflammatory cytokines, we identified complement C3 as a hub for some of the effects of cytokines. The proinflammatory cytokines interleukin-1 beta plus interferon-gamma increase C3 expression in rodent and human pancreatic beta-cells, and C3 is detected by histology in and around the islets of diabetic patients. Surprisingly, C3 silencing exacerbates apoptosis under both basal condition and following exposure to cytokines, and it increases chemokine expression upon cytokine treatment. C3 exerts its prosurvival effects via AKT activation and c-Jun N-terminal kinase inhibition. Exogenously added C3 also protects against cytokine-induced beta-cell death and partially rescues the deleterious effects of inhibition of endogenous C3. These data suggest that locally produced C3 is an important prosurvival mechanism in pancreatic beta-cells under a proinflammatory assault.
Protein-altering and regulatory genetic variants near GATA4 implicated in bicuspid aortic valve

Bicuspid aortic valve (BAV) is a heritable congenital heart defect and an important risk factor for valvulopathy and aortopathy. Here we report a genome-wide association scan of 466 BAV cases and 4,660 age, sex and ethnicity-matched controls with replication in up to 1,326 cases and 8,103 controls. We identify association with a noncoding variant 151 kb from the gene encoding the cardiac-specific transcription factor, GATA4, and near-significance for p.Ser377Gly in GATA4. GATA4 was interrupted by CRISPR-Cas9 in induced pluripotent stem cells from healthy donors. The disruption of GATA4 significantly impaired the transition from endothelial cells into mesenchymal cells, a critical step in heart valve development.

General information

State: Published
Organisations: Department of Bio and Health Informatics, Integrative Systems Biology, University of Michigan, Harvard Medical School, University of Montreal, University of Texas, Icahn School of Medicine at Mount Sinai (ISMMS), Karolinska Institutet, Newcastle University, University of Manchester
Number of pages: 10
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Main Research Area: Technical/natural sciences

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Journal: Nature Communications
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Article number: 15481
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Protein features as determinants of wild-type glycoside hydrolase thermostability

Thermostable enzymes for conversion of lignocellulosic biomass into biofuels have significant advantages over enzymes with more moderate thermostability due to the challenging application conditions. Experimental discovery of thermostable enzymes is highly cost intensive, and the development of in-silico methods guiding the discovery process would be of high value. To develop such an in-silico method and provide the data foundation of it, we determined the melting temperatures of 602 fungal glycoside hydrolases from the families GH5, 6, 7, 10, 11, 43 and AA9 (formerly GH61). We, then used sequence and homology modeled structure information of these enzymes to develop the ThermoP melting temperature prediction method. Furthermore, in the context of thermostability, we determined the relative importance of 160 molecular features, such as amino acid frequencies and spatial interactions, and exemplified their biological significance. The presented prediction method is made publicly available at http://www.cbs.dtu.dk/services/ThermoP. This article is protected by copyright. All rights reserved.
Protein Sorting Prediction

Many computational methods are available for predicting protein sorting in bacteria. When comparing them, it is important to know that they can be grouped into three fundamentally different approaches: signal-based, global-property-based and homology-based prediction. In this chapter, the strengths and drawbacks of each of these approaches is described.
through many examples of methods that predict secretion, integration into membranes, or subcellular locations in general. The aim of this chapter is to provide a user-level introduction to the field with a minimum of computational theory.

**General information**

State: Published
Organisations: Department of Biotechnology and Biomedicine, Department of Bio and Health Informatics, Disease Intelligence and Molecular Evolution
Authors: Nielsen, H. (Intern)
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Machine learning, Prediction, Protein sorting, Secretion, Subcellular location, Transmembrane proteins
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Publication: Research › Book chapter – Annual report year: 2017

**PROVIDE a project aiming at protein valorization through informatics, hydrolysis, and separation**

**General information**

State: Published
Organisations: National Food Institute, Research Group for Gut Microbiology and Immunology, Research Group for Bioactives – Analysis and Application, Department of Bio and Health Informatics, Immunoinformatics and Machine Learning, Technical University of Denmark
Authors: Hansen, E. B. (Intern), Jacobsen, C. (Intern), Lund, O. (Ekstern), Marcatili, P. (Intern), García Moreno, P. J. (Intern)
Number of pages: 1
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SustainAbstracts2017c.compressed_63.pdf
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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.
Recombinant snakebite antivenoms: A cost-competitive solution to a neglected tropical disease?

Snakebite envenoming is a major public health burden in tropical parts of the developing world. In sub-Saharan Africa, neglect has led to a scarcity of antivenoms threatening the lives and limbs of snakebite victims. Technological advances within antivenom are warranted, but should be evaluated not only on their possible therapeutic impact, but also on their cost-competitiveness. Recombinant antivenoms based on oligoclonal mixtures of human IgG antibodies produced by CHO cell cultivation may be the key to obtaining better snakebite envenoming therapies. Based on industry data, the cost of treatment for a snakebite envenoming with a recombinant antivenom is estimated to be in the range USD 60-250 for the Final Drug Product. One of the effective antivenoms (SAIMR Snake Polyvalent Antivenom from the South African Vaccine Producers) currently on the market has been reported to have a wholesale price of USD 640 per treatment for an average snakebite. Recombinant antivenoms may therefore in the future be a cost-competitive alternative to existing serum-based antivenoms.
ReGaTE: Registration of Galaxy Tools in Elixir

Background: Bioinformaticians routinely use multiple software tools and data sources in their day-to-day work and have been guided in their choices by a number of cataloguing initiatives. The ELIXIR Tools and Data Services Registry (bio.tools) aims to provide a central information point, independent of any specific scientific scope within bioinformatics or technological implementation. Meanwhile, efforts to integrate bioinformatics software in workbench and workflow environments have accelerated to enable the design, automation, and reproducibility of bioinformatics experiments. One such popular environment is the Galaxy framework, with currently more than 80 publicly available Galaxy servers around the world. In the context of a generic registry for bioinformatics software, such as bio.tools, Galaxy instances constitute a major source of valuable content. Yet there has been, to date, no convenient mechanism to register such services en masse. Findings: We present ReGaTE (Registration of Galaxy Tools in Elixir), a software utility that automates the process of registering the services available in a Galaxy instance. This utility uses the BioBlend application program interface to extract service metadata from a Galaxy server, enhance the metadata with the scientific information required by bio.tools, and push it to the registry. Conclusions: ReGaTE provides a fast and convenient way to publish Galaxy services in bio.tools. By doing so, service providers may increase the visibility of their services while enriching the software discovery function that bio.tools provides for its users. The source code of ReGaTE is freely available on Github at https://github.com/C3BI-pasteur-fr/ReGaTE.
Renal Impairment Hampers Bisphosphonate Treatment in a Quarter of Lung Cancer Patients with Bone Metastasis

Renal function impairment in lung cancer patients with bone metastases was investigated, as this can limit the application of bisphosphonates representing the gold standard in the management of such cases. Clinicopathological data of 570 lung cancer patients were retrospectively analysed for changes in renal function parameters. Co-morbidities included hypertension (50%), COPD (33%) and diabetes mellitus (15%). Statistical analysis was performed with Fisher's exact tests and a Cox proportional hazards model. In patients suffering from hypertension, both median serum creatinine and blood urea nitrogen (BUN) were higher (81.9 versus 75.8 μmol/l, p
Re-theorising mobility and the formation of culture and language among the Corded Ware Culture in Europe

Recent genetic, isotopic and linguistic research has dramatically changed our understanding of how the Corded Ware Culture in Europe was formed. Here the authors explain it in terms of local adaptations and interactions between migrant Yamnaya people from the Pontic-Caspian steppe and indigenous North European Neolithic cultures. The original herding economy of the Yamnaya migrants gradually gave way to new practices of crop cultivation, which led to the adoption of new words for those crops. The result of this hybridisation process was the formation of a new material culture, the Corded Ware Culture, and of a new dialect, Proto-Germanic. Despite a degree of hostility between expanding Corded Ware groups and indigenous Neolithic groups, stable isotope data suggest that exogamy provided a mechanism facilitating their integration. This article should be read in conjunction with that by Heyd (2017, in this issue).

General information
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Organisations: Department of Bio and Health Informatics, Metagenomics, University of Gothenburg, University of Copenhagen, The National Museum of Denmark, Aarhus University, Polish Academy of Sciences, University of Wisconsin-Madison
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Main Research Area: Technical/natural sciences

Publication information
Journal: Antiquity
Volume: 91
Issue number: 356
RNA-Seq transcriptomics and pathway analyses reveal potential regulatory genes and molecular mechanisms in high- and low-residual feed intake in Nordic dairy cattle

The selective breeding of cattle with high-feed efficiencies (FE) is an important goal of beef and dairy cattle producers. Global gene expression patterns in relevant tissues can be used to study the functions of genes that are potentially involved in regulating FE. In the present study, high-throughput RNA sequencing data of liver biopsies from 19 dairy cows were used to identify differentially expressed genes (DEGs) between high- and low-FE groups of cows (based on Residual
Feed Intake or RFI). Subsequently, a profile of the pathways connecting the DEGs to FE was generated, and a list of candidate genes and biomarkers was derived for their potential inclusion in breeding programmes to improve FE. The bovine RNA-Seq gene expression data from the liver was analysed to identify DEGs and, subsequently, identify the molecular mechanisms, pathways and possible candidate biomarkers of feed efficiency. On average, 57 million reads (short reads or short mRNA sequences)

**General information**
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Organisations: Department of Bio and Health Informatics, Administration, University of Copenhagen, Aarhus University
Authors: Salleh, M. S. (Ekstern), Mazzoni, G. (Ekstern), Höglund, J. K. (Ekstern), Olijhoek, D. W. (Ekstern), Lund, P. (Ekstern), Lavendahl, P. (Ekstern), Kødamideen, H. (Intern)
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BFI (2017): BFI-level 1
Scopus rating (2017): SJR 2.11 SNIP 1.151
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 4.05 SJR 2.163 SNIP 1.096
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.348 SNIP 1.159 CiteScore 4.3
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.327 SNIP 1.199 CiteScore 4.18
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 2.195 SNIP 1.188 CiteScore 4.39
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 2.236 SNIP 1.243 CiteScore 4.61
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 2.307 SNIP 1.191 CiteScore 4.38
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 2.142 SNIP 1.037
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 2.21 SNIP 1.012
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 2.287 SNIP 1.007
Web of Science (2008): Indexed yes
RUCS: Rapid identification of PCR primers for unique core sequences

Designing PCR primers to target a specific selection of whole genome sequenced strains can be a long, arduous, and sometimes impractical task. Such tasks would benefit greatly from an automated tool to both identify unique targets, and to validate the vast number of potential primer pairs for the targets in silico. Here we present RUCS, a program that will find PCR primer pairs and probes for the unique core sequences of a positive genome dataset complement to a negative genome dataset. The resulting primer pairs and probes are in addition to simple selection also validated through a complex in silico PCR simulation. We compared our method, which identifies the unique core sequences, against an existing tool called ssGeneFinder, and found that our method was 6.5-20 times more sensitive. We used RUCS to design primer pairs that would target a set of genomes known to contain the mcr-1 colistin resistance gene. Three of the predicted pairs were chosen for experimental validation using PCR and gel electrophoresis. All three pairs successfully produced an amplicon with the target length for the samples containing mcr-1 and no amplification products were produced for the negative samples. The novel methods presented in this manuscript can reduce the time needed to identify target sequences, and provide a quick virtual PCR validation to eliminate time wasted on ambiguously binding primers. Source code is freely available on https://bitbucket.org/genomicepidemiology/rucs. Web service is freely available on https://cge.cbs.dtu.dk/services/RUCS. mcf@cbs.dtu.dk. Supplementary data is available at Bioinformatics online.
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.

General information
State: Published
Organisations: Department of Bio and Health Informatics, Metagenomics, Department of Systems Biology, Center for Biological Sequence Analysis, Integrative Systems Biology, Integrative Systems Biology, Disease Intelligence and Molecular Evolution, Genomic Epidemiology, High Performance Computing, Functional Human Variation, University of Copenhagen, Aarhus University, BGI-Shenzhen, BGI-Europe, Technical University of Denmark, University of Oslo, University of Bergen, Karolinska Institutet
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Scopus rating (2016): CiteScore 13.33
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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
Background
RNA-seq is a useful next-generation sequencing (NGS) technology that has been widely used to understand mammalian transcriptome architecture and function. In this study, a breed-specific RNA-seq experiment was utilized to detect putative single nucleotide polymorphisms (SNPs) in liver tissue of young bulls of the Polish Red, Polish Holstein-Friesian (HF) and Hereford breeds, and to understand the genomic variation in the three cattle breeds that may reflect differences in production traits.

Results
The RNA-seq experiment on bovine liver produced 107,114,4072 raw paired-end reads, with an average of approximately 60 million paired-end reads per library. Breed-wise, a total of 345.06, 290.04 and 436.03 million paired-end reads were obtained from the Polish Red, Polish HF, and Hereford breeds, respectively. Burrows-Wheeler Aligner (BWA) read alignments showed that 81.35%, 82.81% and 84.21% of the mapped sequencing reads were properly paired to the Polish Red, Polish HF, and Hereford breeds, respectively. This study identified 5,641,401 SNPs and insertion and deletion (indel) positions expressed in the bovine liver with an average of 313,411 SNPs and indel per young bull. Following the removal of the indel mutations, a total of 312,1804, 250,7120 and 205,3184 raw SNPs expressed in bovine liver were identified for the Polish Red, Polish HF, and Hereford breeds, respectively. Breed-wise, three highly reliable breed-specific SNP-databases (SNP-dbs) with 31,562, 24,945 and 28,194 SNP records were constructed for the Polish Red, Polish HF, and Hereford breeds, respectively. Using a combination of stringent parameters of a minimum depth of ≥10 mapping reads that support the polymorphic nucleotide base and 100% SNP ratio, 4,368, 3,780 and 3,800 SNP records were detected in the Polish Red, Polish HF, and Hereford breeds, respectively. The SNP detections using RNA-seq data were successfully validated by kompetitive allele-specific PCR (KASPTM) SNP genotyping assay. The comprehensive QTL/CG analysis of 110 QTL/CG with RNA-seq data identified 20 monomorphic SNP hit loci (CARTPT, GAD1, GDF5, GHRH, GHRL, GRB10, IGFBPL1, IGFL1, LEP, LHX4, MC4R, MSTN, NKAIN1, PLAG1, POU1F1, SDR16C5, SH2B2, TOX, UCP3 and WNT10B) in all three cattle breeds. However, six SNP loci (CCSER1, GHR, KCNIP4, MTSS1, EGFR and NSMCE2) were identified as highly polymorphic among the cattle breeds.

Conclusions
This study identified breed-specific SNPs with greater SNP ratio and excellent mapping coverage, as well as monomorphic and highly polymorphic putative SNP loci within QTL/CGs of bovine liver tissue. A breed-specific SNP-db constructed for bovine liver yielded nearly six million SNPs. In addition, a KASPTM SNP genotyping assay, as a reliable cost-effective method, successfully validated the breed-specific putative SNPs originating from the RNA-seq experiments.
Synthesis and biological evaluation of dihydropyrano-[2,3-c]pyrazoles as a new class of PPARγ partial agonists

Perxisome 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 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.

General information
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Organisations: Department of Chemistry, Organic Chemistry, Department of Organic Chemistry, Department of Systems Biology, Center for Biological Sequence Analysis, Department of Bio and Health Informatics, Integrative Systems Biology, Technical University of Denmark, University of Copenhagen
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Scopus rating (2015): SJR 1.427 SNIP 1.136 CiteScore 3.32
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Scopus rating (2012): SJR 1.982 SNIP 1.156 CiteScore 4.15
TANTIGEN: a comprehensive database of tumor T cell antigens

Tumor T cell antigens are both diagnostically and therapeutically valuable molecules. A large number of new peptides are examined as potential tumor epitopes each year, yet there is no infrastructure for storing and accessing the results of these experiments. We have retroactively cataloged more than 1000 tumor peptides from 368 different proteins, and implemented a web-accessible infrastructure for storing and accessing these experimental results. All peptides in TANTIGEN are labeled as one of the four categories: (1) peptides measured in vitro to bind the HLA, but not reported to elicit either in vivo or in vitro T cell response, (2) peptides found to bind the HLA and to elicit an in vitro T cell response, (3) peptides shown to elicit in vivo tumor rejection, and (4) peptides processed and naturally presented as defined by physical detection. In addition to T cell response, we also annotate peptides that are naturally processed HLA binders, e.g., peptides eluted from HLA in mass spectrometry studies. TANTIGEN provides a rich data resource for tumor-associated epitope and neoepitope discovery studies and is freely available at (mirror).

General information
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Organisations: Department of Bio and Health Informatics, Genomic Epidemiology, Dana-Farber Cancer Institute
Authors: Olsen, L. R. (Intern), Tongchusak, S. (Ekstern), Lin, H. (Ekstern), Reinherz, E. L. (Ekstern), Brusic, V. (Ekstern), Zhang, G. L. (Ekstern)
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Terminal Pleistocene Alaskan genome reveals first founding population of Native Americans

Despite broad agreement that the Americas were initially populated via Beringia, the land bridge that connected far
northeast Asia with northwestern North America during the Pleistocene epoch, when and how the peopling of the
Americas occurred remains unresolved. Analyses of human remains from Late Pleistocene Alaska are important to
resolving the timing and dispersal of these populations. The remains of two infants were recovered at Upward Sun River
(USR), and have been dated to around 11.5 thousand years ago (ka). Here, by sequencing the USR1 genome to an
average coverage of approximately 17 times, we show that USR1 is most closely related to Native Americans, but falls
basal to all previously sequenced contemporary and ancient Native Americans. As such, USR1 represents a distinct
Ancient Beringian population. Using demographic modelling, we infer that the Ancient Beringian population and ancestors
of other Native Americans descended from a single founding population that initially split from East Asians around 36 ± 1.5
ka, with gene flow persisting until around 25 ± 1.1 ka. Gene flow from ancient northern Eurasians into all Native Americans
took place 25-20 ka, with Ancient Beringians branching off around 22-18.1 ka. Our findings support a long-term genetic
structure in ancestral Native Americans, consistent with the Beringian 'standstill model'. We show that the basal northern and southern Native American branches, to which all other Native Americans belong, diverged around 17.5-14.6 ka, and that this probably occurred south of the North American ice sheets. We also show that after 11.5 ka, some of the northern Native American populations received gene flow from a Siberian population most closely related to Koryaks, but not Palaeo-Eskimos, Inuits or Kets, and that Native American gene flow into Inuits was through northern and not southern Native American groups. Our findings further suggest that the far-northern North American presence of northern Native Americans is from a back migration that replaced or absorbed the initial founding population of Ancient Beringians.

General information
State: Published
Organisations: Department of Bio and Health Informatics, Metagenomics, University of Copenhagen, University of Alaska Fairbanks, University of Massachusetts, University of California at Berkeley, Liverpool John Moores University, University of Illinois at Urbana-Champaign
Authors: Moreno-Mayar, J. V. (Ekstern), Potter, B. A. (Ekstern), Vinner, L. (Ekstern), Steinrücken, M. (Ekstern), Rasmussen, S. (Intern), Terhorst, J. (Ekstern), Kamm, J. A. (Ekstern), Albrechtsen, A. (Ekstern), Malaspinas, A. (Ekstern), Sikora, M. (Ekstern), Reuther, J. D. (Ekstern), Irish, J. D. (Ekstern), Malhi, R. S. (Ekstern), Orlando, L. (Ekstern), Song, Y. S. (Ekstern), Nielsen, R. (Ekstern), Meltzer, D. J. (Ekstern), Willerslev, E. (Ekstern)
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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
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.

General information

State: Published
Organisations: Department of Systems Biology, Department of Bio and Health Informatics, Center for Biological Sequence Analysis, Genomic Epidemiology, National Food Institute, Research Group for Genomic Epidemiology, Immunoinformatics and Machine Learning, Metagenomics, Statens Seruminstitute, Osaka University
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The first draft reference genome of the American mink (Neovison vison)

The American mink (Neovison vison) is a semiaquatic species of mustelid native to North America. It's an important animal for the fur industry. Many efforts have been made to locate genes influencing fur quality and color, but this search has been impeded by the lack of a reference genome. Here we present the first draft genome of mink. In our study, two mink individuals were sequenced by Illumina sequencing with 797 Gb sequence generated. Assembly yielded 7,175 scaffolds with an N50 of 6.3Mb and length of 2.4Gb including gaps. Repeat sequences constitute around 31% of the genome, which is lower than for dog and cat genomes. The alignments of mink, ferret and dog genomes help to illustrate the chromosomes rearrangement. Gene annotation identified 21,053 protein-coding sequences present in mink genome. The reference genome’s structure is consistent with the microsatellite-based genetic map. Mapping of well-studied genes known to be involved in coat quality and coat color, and previously located fur quality QTL provide new knowledge about putative candidate genes for fur traits. The draft genome shows great potential to facilitate genomic research towards improved breeding for high fur quality animals and strengthen our understanding on evolution of Carnivora.
The Intergenic Recombinant HLA-B*46:01 Has a Distinctive Peptidome that Includes KIR2DL3 Ligands

HLA-B*46:01 was formed by an intergenic mini-conversion, between HLA-B*15:01 and HLA-C*01:02, in Southeast Asia during the last 50,000 years, and it has since become the most common HLA-B allele in the region. A functional effect of
the mini-conversion was introduction of the C1 epitope into HLA-B*46:01, making it an exceptional HLA-B allotype that is recognized by the C1-specific natural killer (NK) cell receptor KIR2DL3. High-resolution mass spectrometry showed that HLA-B*46:01 has a low-diversity peptidome that is distinct from those of its parents. A minority (21%) of HLA-B*46:01 peptides, with common C-terminal characteristics, form ligands for KIR2DL3. The HLA-B*46:01 peptidome is predicted to be enriched for peptide antigens derived from Mycobacterium leprae. Overall, the results indicate that the distinctive peptidome and functions of HLA-B*46:01 provide carriers with resistance to leprosy, which drove its rapid rise in frequency in Southeast Asia.

**General information**

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Organisations: Department of Bio and Health Informatics, Immunoinformatics and Machine Learning, Stanford University, University of Oklahoma Health Sciences Center, Pure Protein LLC
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Scopus rating (2017): SNIP 1.648 SJR 7.552
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 8.4 SJR 8.337 SNIP 1.756
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 8.545 SNIP 1.763 CiteScore 8.15
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 8.415 SNIP 1.878 CiteScore 7.88
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**Therapeutic Vaccine Against Primate Papillomavirus Infections of the Cervix**
Currently available prophylactic vaccines have no therapeutic efficacy for preexisting human papillomavirus (HPVs) infections, do not target all oncogenic HPVs and are insufficient to eliminate the burden of HPV induced cancer. We aim to develop an alternative HPV vaccine which is broadly effective and capable of clearing preexisting infection. In an initial attempt to develop a broadly reactive therapeutic vaccine, we designed a putative papillomavirus (PV) ancestor antigen
(circulating sequence derived antigenic sequences E1E2-CDSE1E2) based on the conserved E1 and E2 protein sequences from existing oncogenic HPV strains. This antigen was found to be as related to circulating oncogenic Macaca fascicularis papillomaviruses (MfPVs) as to oncogenic HPVs. The CDSE1E2 antigen was fused to a T-cell adjuvant and encoded in chimpanzee 3 and 63 adenoviral vectors. We first showed that the combination of these 2 vaccines induced long-lasting potent CDSE1E2 specific T cell responses in outbred mice. This prime-boost regimen was then tested in female macaques naturally infected with MfPVs. All immunized animals (16/16) responded to the vaccine antigen but with reduced cross-reactivity against existing PVs. Preexisting MfPV infections did not prime vaccine inducible immune responses. Importantly, immunized oncogenic MfPV type 3 (MIPV3) infected animals that responded toward MIPV3 were able to diminish cervical MIPV3 DNA content. Although insufficient breadth was achieved, our results suggest that a relevant level of E1E2 specific T cell immunity is achievable and might be sufficient for the elimination of PV infection. Importantly, naturally infected macaques, offer a relevant model for testing vaccines aimed at eliminating mucosal PV infections.

General information
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Organisations: Department of Biotechnology and Biomedicine, Department of Bio and Health Informatics, Disease Intelligence and Molecular Evolution
Authors: Ragonnaud, E. (Ekstern), Andersson, A. C. (Ekstern), Mariya, S. (Ekstern), Pedersen, A. G. (Intern), Burk, R. D. (Ekstern), Folgori, A. (Ekstern), Colloca, S. (Ekstern), Cortese, R. (Ekstern), Nicosia, A. (Ekstern), Pamungkas, J. (Ekstern), Iskandriati, D. (Ekstern), Holst, P. J. (Ekstern)
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Web of Science (2017): Indexed yes
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Scopus rating (2016): CiteScore 4.27 SJR 2.11 SNIP 0.938
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BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.73 SNIP 0.839 CiteScore 3.74
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.802 SNIP 0.819 CiteScore 3.59
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.497 SNIP 0.85 CiteScore 3.54
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.466 SNIP 0.817 CiteScore 3.42
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.784 SNIP 0.891
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.583 SNIP 0.76
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 2.166 SNIP 0.979
Scopus rating (2007): SJR 2.06 SNIP 1.065
Scopus rating (2006): SJR 1.724 SNIP 0.912
Scopus rating (2005): SJR 1.287 SNIP 0.841
Scopus rating (2004): SJR 1.427 SNIP 1.1
Scopus rating (2003): SJR 1.112 SNIP 0.872
The wolf reference genome sequence (Canis lupus lupus) and its implications for Canis spp. population genomics

Background
An increasing number of studies are addressing the evolutionary genomics of dog domestication, principally through resequencing dog, wolf and related canid genomes. There is, however, only one de novo assembled canid genome currently available against which to map such data - that of a boxer dog (Canis lupus familiaris). We generated the first de novo wolf genome (Canis lupus lupus) as an additional choice of reference, and explored what implications may arise when previously published dog and wolf resequencing data are remapped to this reference.

Results
Reassuringly, we find that regardless of the reference genome choice, most evolutionary genomic analyses yield qualitatively similar results, including those exploring the structure between the wolves and dogs using admixture and principal component analysis. However, we do observe differences in the genomic coverage of re-mapped samples, the number of variants discovered, and heterozygosity estimates of the samples.

Conclusion
In conclusion, the choice of reference is dictated by the aims of the study being undertaken; if the study focuses on the differences between the different dog breeds or the fine structure among dogs, then using the boxer reference genome is appropriate, but if the aim of the study is to look at the variation within wolves and their relationships to dogs, then there are clear benefits to using the de novo assembled wolf reference genome.

General information
State: Published
Organisations: Department of Bio and Health Informatics, Metagenomics, Barcelona Institute of Science and Technology, Swedish Museum of Natural History, University of Oxford, Københavns Universitet, University of Copenhagen
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BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 4.05 SJR 2.163 SNIP 1.096
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.348 SNIP 1.159 CiteScore 4.3
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Background Among patients with non-small-cell lung cancer (NSCLC), data on intratumor heterogeneity and cancer genome evolution have been limited to small retrospective cohorts. We wanted to prospectively investigate intratumor heterogeneity in relation to clinical outcome and to determine the clonal nature of driver events and evolutionary processes in early-stage NSCLC. Methods In this prospective cohort study, we performed multiregion whole-exome...
sequencing on 100 early-stage NSCLC tumors that had been resected before systemic therapy. We sequenced and analyzed 327 tumor regions to define evolutionary histories, obtain a census of clonal and subclonal events, and assess the relationship between intratumor heterogeneity and recurrence-free survival. Results We observed widespread intratumor heterogeneity for both somatic copy-number alterations and mutations. Driver mutations in EGFR, MET, BRAF, and TP53 were almost always clonal. However, heterogeneous driver alterations that occurred later in evolution were found in more than 75% of the tumors and were common in PIK3CA and NF1 and in genes that are involved in chromatin modification and DNA damage response and repair. Genome doubling and ongoing dynamic chromosomal instability were associated with intratumor heterogeneity and resulted in parallel evolution of driver somatic copy-number alterations, including amplifications in CDK4, FOXA1, and BCL11A. Elevated copy-number heterogeneity was associated with an increased risk of recurrence or death (hazard ratio, 4.9; P=4.4×10⁻⁴), which remained significant in multivariate analysis. Conclusions Intratumor heterogeneity mediated through chromosome instability was associated with an increased risk of recurrence or death, a finding that supports the potential value of chromosome instability as a prognostic predictor. (Funded by Cancer Research UK and others; TRACERx ClinicalTrials.gov number, NCT01888601.)

General information
State: Published
Organisations: Department of Bio and Health Informatics, Cancer Genomics, CRUK Lung Cancer Centre of Excellence, UCL Cancer Institute, Cancer Research UK, London Research Institute, The Francis Crick Institute, University of Manchester, Christie Hospital, University Hospital of South Manchester, Cancer Research UK Manchester Institute, University of Birmingham, University of Leicester, Glenfield Hospital, North Middlesex University Hospital NHS Trust, Barnet and Chase Farm Hospitals NHS Trust, Princess Alexandra Hospital, St. Luke's Cancer Centre, Velindre Hospital, University Hospital Llandough, Cardiff University, University of Oxford, Queen Elizabeth Hospital, University College London, MAX DELBRUCK CENTER FOR MOLECULAR MEDICINE, University of Leuven
Publication date: 2017
Main Research Area: Technical/natural sciences

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BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 12.82 SJR 18.009 SNIP 14.79
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BFI (2015): BFI-level 2
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BFI (2014): BFI-level 2
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 14.796 SNIP 15.59 CiteScore 12.21
ISI indexed (2013): ISI indexed yes
Transcriptional changes induced by bevacizumab combination therapy in responding and non-responding recurrent glioblastoma patients

Background: Bevacizumab combined with chemotherapy produces clinical durable response in 25-30% of recurrent glioblastoma patients. This group of patients has shown improved survival and quality of life. The aim of this study was to investigate changes in gene expression associated with response and resistance to bevacizumab combination therapy.

Methods: Recurrent glioblastoma patients who had biomarker-accessible tumor tissue surgically removed both before bevacizumab treatment and at time of progression were included. Patients were grouped into responders (n = 7) and non-responders (n = 14). Gene expression profiling of formalin-fixed paraffin-embedded tumor tissue was performed using RNA-sequencing.

Results: By comparing pretreatment samples of responders with those of non-responders no significant difference was observed. In a paired comparison analysis of pre- and posttreatment samples of non-responders 1 gene was significantly differentially expressed. In responders, this approach revealed 256 significantly differentially expressed genes (72 down- and 184 up-regulated genes at the time of progression). Genes differentially expressed in responders revealed a shift towards a more proneural and less mesenchymal phenotype at the time of progression.

Conclusions: Bevacizumab combination treatment demonstrated a significant impact on the transcriptional changes in responders; but only minimal changes in non-responders. This suggests that non-responding glioblastomas progress chaotically without following distinct gene expression changes while responding tumors adaptively respond or progress by means of the same transcriptional changes. In conclusion, we hypothesize that the identified gene expression changes of responding tumors are associated to bevacizumab response or resistance mechanisms.
Using bio.tools to generate and annotate workbench tool descriptions

Workbench and workflow systems such as Galaxy, Taverna, Chipster, or Common Workflow Language (CWL)-based frameworks, facilitate the access to bioinformatics tools in a user-friendly, scalable and reproducible way. Still, the integration of tools in such environments remains a cumbersome, time consuming and error-prone process. A major consequence is the incomplete or outdated description of tools that are often missing important information, including parameters and metadata such as publication or links to documentation. ToolDog (Tool DescriptiOn Generator) facilitates the integration of tools - which have been registered in the ELIXIR tools registry (https://bio.tools) - into workbench environments by generating tool description templates. ToolDog includes two modules. The first module analyses the source code of the bioinformatics software with language-specific plugins, and generates a skeleton for a Galaxy XML or CWL tool description. The second module is dedicated to the enrichment of the generated tool description, using metadata provided by bio.tools. This last module can also be used on its own to complete or correct existing tool descriptions with missing metadata.

General information
State: Published
Organisations: Department of Bio and Health Informatics, IT Service, Common Workflow Language Project, Institut Pasteur, University of Tartu, National Technical University of Ukraine, Kiev Polytechnic Institute, Albert Ludwigs Universität Freiburg
Authors: Hillion, K. (Ekstern), Kuzmin, I. (Ekstern), Khodak, A. (Ekstern), Rasche, E. (Ekstern), Crusoe, M. (Ekstern), Peterson, H. (Ekstern), Ison, J. (Intern), Ménager, H. (Ekstern)
Number of pages: 14
Publication date: 2017
Main Research Area: Technical/natural sciences

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Scopus rating (2016): CiteScore 1.2 SJR 0.813 SNIP 0.423
Scopus rating (2015): SJR 0.62 SNIP 0.341 CiteScore 0.87
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Scopus rating (2013): SJR 0.224 SNIP 0.077 CiteScore 0.4
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USP2 as a potential link between miR-125b and psoriasis

Background
The extensive involvement of microRNA (miRNA) in the pathophysiology of psoriasis is well documented. However, in order for this information to be useful in therapeutic manipulation of miRNA levels, it is essential that detailed functional mechanisms are elucidated. miR-125b has previously been shown to be strongly associated with psoriasis, and presents as an obvious candidate for further investigation.

Objectives
To elucidate the specific pathway and mechanism of interest in this association.

Methods
A three-step bioinformatical hypothesis-generation pipeline was performed to identify genes of interest. This pipeline was based on miR-125b binding, expression in psoriatic lesions and genome-wide association study-based evidence of involvement. The identified candidate gene was then carefully evaluated using luciferase binding assays, in vitro overexpression, small interfering RNA knock-down and downstream gene readouts.

Results
Based on our bioinformatical pipeline, ubiquitin-specific peptidase 2 was selected as a likely candidate for a mechanistic explanation for psoriasis association. After establishing a definite connection to miR-125b, we proceeded to show that modulation of nuclear factor kappa B-mediated inflammation is the likely mechanism through which this miRNA gene pair functioned.

Conclusions
Shedding further light on the multifactorial causes of psoriasis is essential, if the goal is to progress towards finer control of therapeutic tools in disease management. Findings, such as the ones presented herein, are therefore necessary in order to achieve the future of personalized medicine.
To evaluate a genome-based surveillance of all Danish third-generation cephalosporin-resistant Escherichia coli (3GC-R Ec ) from bloodstream infections between 2014 and 2015, focusing on horizontally transferable resistance mechanisms. A collection of 552 3GC-R Ec isolates were whole-genome sequenced and characterized by using the batch uploader from the Center for Genomic Epidemiology (CGE) and automatically analysed using the CGE tools according to resistance profile, MLST, serotype and fimH subtype. Additionally, the phylogenetic relationship of the isolates was analysed by SNP analysis. The majority of the 552 isolates were ESBL producers (89%), with bla CTX-M-15 being the most prevalent (50%) gene, followed by bla CTX-M-14 (14%), bla CTX-M-27 (11%) and bla CTX-M-101 (5%). ST131 was detected in 50% of the E. coli isolates, with the remaining isolates belonging to 73 other STs, including globally disseminated STs (e.g. ST10, ST38, ST58, ST69 and ST410). Five of the bloodstream isolates were carbapenemase producers, carrying bla OXA-181 (3) and bla OXA-48 (2). Phylogenetic analysis revealed 15 possible national outbreaks during the 2 year period, one caused by a novel ST131/ bla CTX-M-101 clone, here observed for the first time in Denmark. Additionally, the analysis revealed three individual cases with possible persistence of closely related clones collected more than 13 months apart.

Continuous WGS-based national surveillance of 3GC-R Ec , in combination with more detailed epidemiological information, can improve the ability to follow the population dynamics of 3GC-R Ec , thus allowing for the detection of potential outbreaks and the effects of changing treatment regimens in the future.
Main Research Area: Technical/natural sciences

**Publication information**
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- **Volume:** 72
- **ISSN (Print):** 0305-7453

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- Web of Science (2018): Indexed yes
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- Web of Science (2017): Indexed yes
- BFI (2016): BFI-level 1
- Scopus rating (2016): CiteScore 4.21 SJR 2.283 SNIP 1.521
- Web of Science (2016): Indexed yes
- BFI (2015): BFI-level 1
- Scopus rating (2015): SJR 2.259 SNIP 1.516 CiteScore 4.06
- Web of Science (2015): Indexed yes
- BFI (2014): BFI-level 1
- Scopus rating (2014): SJR 2.298 SNIP 1.765 CiteScore 4.61
- Web of Science (2014): Indexed yes
- BFI (2013): BFI-level 1
- Scopus rating (2013): SJR 2.479 SNIP 1.824 CiteScore 4.7
- ISI indexed (2013): ISI indexed yes
- Web of Science (2013): Indexed yes
- BFI (2012): BFI-level 1
- Scopus rating (2012): SJR 2.283 SNIP 1.718 CiteScore 4.35
- ISI indexed (2012): ISI indexed yes
- Web of Science (2012): Indexed yes
- BFI (2011): BFI-level 1
- Scopus rating (2011): SJR 2.341 SNIP 1.769 CiteScore 4.24
- ISI indexed (2011): ISI indexed yes
- Web of Science (2011): Indexed yes
- BFI (2010): BFI-level 1
- Scopus rating (2010): SJR 2.161 SNIP 1.643
- Web of Science (2010): Indexed yes
- BFI (2009): BFI-level 1
- Scopus rating (2009): SJR 1.902 SNIP 1.615
- Web of Science (2009): Indexed yes
- BFI (2008): BFI-level 1
- Scopus rating (2008): SJR 2.076 SNIP 1.506
- Web of Science (2008): Indexed yes
- Scopus rating (2007): SJR 1.744 SNIP 1.509
- Web of Science (2007): Indexed yes
- Scopus rating (2006): SJR 1.771 SNIP 1.437
- Web of Science (2006): Indexed yes
- Scopus rating (2005): SJR 1.768 SNIP 1.5
- Web of Science (2005): Indexed yes
- Scopus rating (2004): SJR 1.435 SNIP 1.465
- Web of Science (2004): Indexed yes
- Scopus rating (2003): SJR 1.367 SNIP 1.338
- Web of Science (2003): Indexed yes
- Scopus rating (2002): SJR 1.4 SNIP 1.284
- Scopus rating (2001): SJR 1.388 SNIP 1.232
Whole grain-rich diet reduces body weight and systemic low-grade inflammation without inducing major changes of the gut microbiome: a randomised cross-over trial

Objective To investigate whether a whole grain diet alters the gut microbiome and insulin sensitivity, as well as biomarkers of metabolic health and gut functionality. Design 60 Danish adults at risk of developing metabolic syndrome were included in a randomised cross-over trial with two 8-week dietary intervention periods comprising whole grain diet and refined grain diet, separated by a washout period of ≥6 weeks. The response to the interventions on the gut microbiome composition and insulin sensitivity as well on measures of glucose and lipid metabolism, gut functionality, inflammatory markers, anthropometry and urine metabolomics were assessed. Results 50 participants completed both periods with a whole grain intake of 179±50 g/day and 13±10 g/day in the whole grain and refined grain period, respectively. Compliance was confirmed by a difference in plasma alkylresorcinols (p<0.0001). Compared with refined grain, whole grain did not significantly alter glucose homeostasis and did not induce major changes in the faecal microbiome. Also, breath hydrogen levels, plasma short-chain fatty acids, intestinal integrity and intestinal transit time were not affected. The whole grain diet did, however, compared with the refined grain diet, decrease body weight (p<0.0001), serum inflammatory markers, interleukin (IL)-6 (p=0.009) and C-reactive protein (p=0.003). The reduction in body weight was consistent with a reduction in energy intake, and IL-6 reduction was associated with the amount of whole grain consumed, in particular with intake of rye. Conclusion Compared with refined grain diet, whole grain diet did not alter insulin sensitivity and gut microbiome but reduced body weight and systemic low-grade inflammation.

General information

State: Accepted/in press
Organisations: National Food Institute, Research Group for Gut Microbiology and Immunology, Department of Bio and Health Informatics, Metagenomics, Disease Intelligence and Molecular Evolution, Department of Biotechnology and Biomedicine, Disease Systems Immunology, Department of Chemical and Biochemical Engineering, Organic Chemistry, Center for BioProcess Engineering, DTU Multi Assay Core, Research Group for Analytical Food Chemistry, Copenhagen Center for Health Technology, University of Copenhagen, Chalmers University of Technology, Chalmers University of Technology, Bispebjerg University Hospital, Herlev and Gentofte Hospital, University of Amsterdam
Number of pages: 12
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ISSN (Print): 0017-5749
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Scopus rating (2017): SNIP 3.832 SJR 7.44
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 9.29 SJR 7.074 SNIP 3.946
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 6.809 SNIP 3.968 CiteScore 9.1
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

State: Published
Organisations: Center for Biological Sequence Analysis, Cancer Systems Biology, National Veterinary Institute, Section for Immunology and Vaccinology, Department of Bio and Health Informatics, Cancer Genomics, Department of Systems Biology
Authors: Marquard, A. M. (Intern), Eklund, A. C. (Intern), Birkbak, N. J. (Intern), Szallasi, Z. I. (Intern)
Publication date: 23 Jun 2016

Publication information
IPC: C12Q 1/68 A I
Patent number: WO2016097251
Date: 23/06/2016
Priority date: 19/12/2014
Priority number: EP20140199179
Original language: English
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

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Functional Human Variation, Department of Bio and Health Informatics, Disease Intelligence and Molecular Evolution, Copenhagen University Hospital
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Ratings:
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Web of Science (2018): Indexed yes
BFI (2017): BFI-level 2
Scopus rating (2017): SNIP 2.085 SJR 5.131
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): SJR 5.041 SNIP 2.226 CiteScore 6.47
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 5.189 SNIP 2.211 CiteScore 6.43
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 4.657 SNIP 1.952 CiteScore 5.83
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 4.388 SNIP 1.802 CiteScore 5.78
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 4.325 SNIP 1.797 CiteScore 6.3
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
Bacterial communities hitching a hike - a guide to the river system of the Red river, Disko Island, West Greenland

Glacier melting and altered precipitation patterns influence Arctic freshwater and coastal ecosystems. Arctic rivers are central to Arctic water ecosystems 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 Disko Island, West Greenland (69°N). 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 and more psychrophilic taxa were found in the dominant community supplied by the lake. At the river mouth, the dominant bacterial communities from the lake and glacier were unnoticeable but became evident again further into the estuary. On average 23% of the estuary community consisted of indicator OTUs from the river. Environmental variables showed only weak correlations with community composition.

General information

State: Published
Organisations: Department of Bio and Health Informatics, Metagenomics, Københavns Universitet, Aarhus University, Charles University, Chr. Hansen A/S
Authors: Hauptmann, A. Z. E. L. (Intern), Markussen, T. N. (Ekstern), Stibal, M. (Ekstern), Olsen, N. S. (Ekstern), Elberling, B. (Ekstern), Bælum, J. (Ekstern), Sicheritz-Pontén, T. (Intern), Jacobsen, C. S. (Ekstern)
Publication date: 2016
Event: Poster session presented at The Annual Congress of The Danish Microbiological Society 2016, Copenhagen, Denmark.
Main Research Area: Technical/natural sciences
Electronic versions:
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Source: FindIt
Source-ID: 2358193773
Publication: Research - peer-review › Poster – Annual report year: 2017
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 down-sampled 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.

General information
State: Published
Organisations: Department of Systems Biology, National Food Institute, Research Group for Genomic Epidemiology, Center for Biological Sequence Analysis, Department of Bio and Health Informatics, Technical University of Denmark
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Main Research Area: Technical/natural sciences

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BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.259 SNIP 1.516 CiteScore 4.06
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.298 SNIP 1.765 CiteScore 4.61
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
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Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 2.283 SNIP 1.718 CiteScore 4.35
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 2.341 SNIP 1.769 CiteScore 4.24
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Biotechnological Trends in Spider and Scorpion Antivenom Development

Spiders and scorpions are notorious for their fearful dispositions and their ability to inject venom into prey and predators, causing symptoms such as necrosis, paralysis, and excruciating pain. Information on venom composition and the toxins present in these species is growing due to an interest in using bioactive toxins from spiders and scorpions for drug discovery purposes and for solving crystal structures of membrane-embedded receptors. Additionally, the identification and isolation of a myriad of spider and scorpion toxins has allowed research within next generation antivenoms to progress at an increasingly faster pace. In this review, the current knowledge of spider and scorpion venoms is presented, followed by a discussion of all published biotechnological efforts within development of spider and scorpion antitoxins based on small molecules, antibodies and fragments thereof, and next generation immunization strategies. The increasing number of discovery and development efforts within this field may point towards an upcoming transition from serum-based antivenoms towards therapeutic solutions based on modern biotechnology.

General information
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Organisations: Department of Biotechnology and Biomedicine, Network Engineering of Eukaryotic Cell factories, Department of Bio and Health Informatics, Immunoinformatics and Machine Learning, Genomic Epidemiology, Technical University of Denmark
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Main Research Area: Technical/natural sciences

Publication information
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.

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, Division of Food Microbiology, DTU Multi Assay Core, Metagenomics, University of Copenhagen, Bispebjerg University Hospital
Number of pages: 9
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
State: Published
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
Number of pages: 1
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Event: Abstract from 13th NuGOweek PHENOTYPES AND PREVENTION - THE INTERPLAY OF GENES, LIFE-STYLE FACTORS AND GUT ENVIRONMENT, Copenhagen, Denmark.
Main Research Area: Technical/natural sciences
Electronic versions:
NuGOweek2016_Henrik_Munch_Roager_abstract.pdf
Source: PublicationPreSubmission
Source-ID: 127237273
Publication: Research - peer-review › Conference abstract for conference – Annual report year: 2016

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.

General information
State: Published
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
Number of pages: 1
Publication date: 2016
Event: Abstract from 11th International Veterinary Immunology Symposium, Gold Coast, Australia.
Main Research Area: Technical/natural sciences
Electronic versions:
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Publication: Research - peer-review › Conference abstract for conference – Annual report year: 2016

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 autologeous 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.

General information
State: Published
Organisations: National Veterinary Institute, Virology, Department of Bio and Health Informatics, Cancer Genomics, Immunoinformatics and Machine Learning, T-cells & Cancer, Philochem AG, Technical University of Denmark, University Hospital Herlev
Pages: 862-862
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: Suppl. 1
ISSN (Print): 0014-2980
HIV infection is associated with preservation of MAIT cells in the lungs but alteration of their phenotype and T cell receptor repertoire

Tuberculosis remains the leading cause of death in HIV-positive people. A better understanding of the impact of HIV on lung immunity may lead to novel immunotherapeutic interventions. MAIT cells are tissue-homing donor-unrestricted T cells
with broad anti-microbial activity. HIV infection causes early and irreversible depletion of MAIT cells in the peripheral circulation, but the effect of HIV on MAIT cells in the lungs is unknown. These researchers report, for the first time, that MAIT cells in the lungs are numerically preserved but phenotypically and clonotypically altered by HIV infection. They confirm previous reports that circulating MAIT cells are depleted in HIV. Their results suggest that peripheral MAIT cell depletions observed in HIV infection may be due to compartment-specific microbial alterations and/or tissue redistribution. The presenters emphasized that further study is needed to determine the mechanisms underlying the altered phenotypes of lung-resident MAITs and whether these can be targeted to improve anti-microbial lung immunity in people living with HIV.

General information
State: Published
Organisations: Department of Bio and Health Informatics, Immunoinformatics and Machine Learning, KwaZulu Natal Research Institute for Tuberculosis and HIV, Massachusetts General Hospital, Massachusetts Institute of Technology, Durban University of Technology, University of KwaZulu-Natal, Inkosi Albert Luthuli Hospital, McGill University, Oregon Health and Science University
Number of pages: 1
Publication date: 2016
Main Research Area: Technical/natural sciences

Publication information
Journal: Journal of the International Aids Society
Volume: 19
Issue number: Suppl. 5
ISSN (Print): 1758-2652
Ratings:
Web of Science (2018): Indexed yes
Scopus rating (2017): SNIP 1.307 SJR 2.092
Web of Science (2017): Indexed Yes
Scopus rating (2016): SJR 2.177 SNIP 1.342 CiteScore 3.67
Scopus rating (2015): SJR 2.467 SNIP 1.409 CiteScore 3.58
Scopus rating (2014): SJR 1.917 SNIP 1.614 CiteScore 3.22
Scopus rating (2013): SJR 1.908 SNIP 1.583 CiteScore 3.44
Scopus rating (2012): SJR 1.722 SNIP 1.199 CiteScore 2.87
Scopus rating (2011): SJR 1.311 SNIP 1.445 CiteScore 2.3
Scopus rating (2010): SJR 1.178 SNIP 0.602
Original language: English
Electronic versions:
HIV_infection_is_associated_wi_of_MAIT_cells_in_the_lungs...._17.pdf
Source: FindIt
Source-ID: 2356951405
Publication: Research - peer-review › Conference abstract in journal – Annual report year: 2017

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
invested animal. Future studies will show if these proteins represent candidates for the development of novel biomarkers or vaccines.

Metagenomics and single-cell genomics reveal high abundance of comammox Nitrospira spp. 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, 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:
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.
Multi-omic profiling of EPO producing Chinese hamster ovary cell panel reveals metabolic adaptation to heterologous protein production

Heterologous protein production 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 characterize the physiological impact of erythropoietin production, and discover production bottlenecks, in a panel of CHO-K1 cells in batch and chemostat culture.

General information
State: Published
Organisations: Novo Nordisk Foundation Center for Biosustainability, CHO Cell Line Engineering and Design, Quantitative Modeling of Cell Metabolism, Network Engineering of Eukaryotic Cell factories, Department of Bio and Health Informatics, Genomic Epidemiology, Department of Biotechnology and Biomedicine, Novo Nordisk A/S
Number of pages: 1
Publication date: 2016
Event: Poster session presented at Cell Culture Engineering XV, La Quinta, CA, United States.
Main Research Area: Technical/natural sciences
Electronic versions:
CCE_poster.pdf

Relations
Activities:
Cell Culture Engineering XV
Publication: Research - peer-review › Poster – Annual report year: 2017

Next-generation detection of antigen-responsive T cells using DNA barcode-labeled peptidemajor 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 antigenresponsive 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, T-cells & Cancer, Virology, Department of Bio and Health Informatics, Cancer Genomics, Immudex, Technical University of Denmark, Copenhagen University Hospital  
**Authors:** Bentzen, A. K. (Intern), Marquard, A. M. (Intern), Lyngaa, R. B. (Intern), Saini, S. K. (Intern), Andersen, M. R. (Intern), Donia, M. (Ekstern), Svane, I. M. (Ekstern), Straten, P. T. (Ekstern), Szallasi, Z. (Intern), Jakobsen, S. N. (Ekstern), Eklund, A. C. (Ekstern), Hadrup, S. R. (Intern)  
**Pages:** 9-9  
**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:** Suppl. 1  
**ISSN (Print):** 0014-2980  
**Ratings:**  
  - **BFI (2018):** BFI-level 1  
  - **Web of Science (2018):** Indexed yes  
  - **BFI (2017):** BFI-level 1  
  - **Scopus rating (2017):** SNIP 0.92 SJR 2.206  
  - **Web of Science (2017):** Indexed Yes  
  - **BFI (2016):** BFI-level 1  
  - **Scopus rating (2016):** CiteScore 3.61 SJR 2.525 SNIP 0.927  
  - **Web of Science (2016):** Indexed yes  
  - **BFI (2015):** BFI-level 1  
  - **Scopus rating (2015):** SJR 2.588 SNIP 0.965 CiteScore 3.85  
  - **Web of Science (2015):** Indexed yes  
  - **BFI (2014):** BFI-level 1  
  - **Scopus rating (2014):** SJR 2.672 SNIP 0.972 CiteScore 3.83  
  - **Web of Science (2014):** Indexed yes  
  - **BFI (2013):** BFI-level 1  
  - **Scopus rating (2013):** SJR 2.876 SNIP 1.05 CiteScore 4.3  
  - **ISI indexed (2013):** ISI indexed yes  
  - **Web of Science (2013):** Indexed yes  
  - **BFI (2012):** BFI-level 1  
  - **Scopus rating (2012):** SJR 2.989 SNIP 1.063 CiteScore 4.62  
  - **ISI indexed (2012):** ISI indexed yes  
  - **Web of Science (2012):** Indexed yes  
  - **BFI (2011):** BFI-level 1  
  - **Scopus rating (2011):** SJR 3.255 SNIP 1.025 CiteScore 4.69  
  - **ISI indexed (2011):** ISI indexed yes  
  - **Web of Science (2011):** Indexed yes  
  - **BFI (2010):** BFI-level 1  
  - **Scopus rating (2010):** SJR 3.363 SNIP 0.99  
  - **Web of Science (2010):** Indexed yes  
  - **BFI (2009):** BFI-level 1  
  - **Scopus rating (2009):** SJR 3.188 SNIP 1.007  
  - **Web of Science (2009):** Indexed yes  
  - **BFI (2008):** BFI-level 2  
  - **Scopus rating (2008):** SJR 3.435 SNIP 0.956  
  - **Scopus rating (2007):** SJR 3.287 SNIP 1.003
Outbreaks of Aleutian mink disease in farmed mink (Neovison vison) in Denmark: molecular characterization by partial NS1 gene sequencing

General information
State: Published
Organisations: National Veterinary Institute, Section for Virology, Department of Systems Biology, Center for Biological Sequence Analysis, Molecular Evolution, Department of Bio and Health Informatics, Kopenhagen Fur
Pages: 85-87
Publication date: 2016

Host publication information
Title of host publication: Proceedings of the XIth International Scientific Congress in Fur Animal Production
Place of publication: Helsinki, Finland
Publisher: Libris
Editors: Mäki-Tanila, A., Valaja, J., Mononen, J., Sironen, T., Vapalahti, O.
Series: Scientifur
Volume: 40
Number: 3/4
ISSN: 2445-6292
Main Research Area: Technical/natural sciences
Electronic versions:
IFASA2016_Vol.40_1_.pdf
Links:

Quality of life (QoL) and neurotoxicity in germ-cell cancer survivors (GCCS)
Background: The majority of patients with testicular cancer become long-term survivors. However, treatment is associated with late effects which may hamper QoL. The aims of the present study were to assess the impact of treatment on long-term QoL and evaluate the influence of neurotoxicity on QoL.
Methods: All GCCS identified in the Danish DaTeCa database were asked to fill in a questionnaire concerning late-effects Nov 2014 – Jan 2016. QoL was assessed with EORTC-QLQ C30 including 30 items divided into 15 subscales. Neurotoxicity was assessed with the FACT/GOG NTX12-scale including 12 items, divided into 4 subscales (neuropathy, ototoxicity, motor impairment, and dysfunction). Patients were divided into treatment groups; surveillance only (reference), n = 1092, radiotherapy (RT), n = 299, BEP chemotherapy (CT), n = 790, and more than one line of treatment (MTOL), n = 82. Outcomes were compared with ordinal logistic regression using treatment and attained age as covariates.
Results: In total, 2308 patients answered the questionnaire. Median attained age was 53.5 years (range: 24.9 - 94.5), and median time from treatment was 18.8 years (range: 7.0 - 32.2). Overall, Global health status was good, mean: 75.4, SD: 20.0. Treatments were significantly negatively associated with QoL in many subscales; CT: dyspnea, financial difficulties, impaired cognitive function, impaired social function, MTOL: impaired global health status, fatigue, dyspnea, financial difficulties, impaired physical function, impaired cognitive function, and impaired social function. Neurotoxicity was closely correlated to treatment. RT was associated with three of four subscales; CT and MTOL were associated with all subscales. When adjusting QoL outcomes for neurotoxicity, all negative associations between QoL and treatment disappeared except dyspnea and impaired social function in the MTOL-group. Neurotoxicity was associated with all EORTC-subscales (p < .001).
Conclusions: Treatment with BEP and MTOL were associated with several QoL subscales in GCCS. However, when
adjusting for neurotoxicity the associations generally disappeared. Neurotoxicity correlated strongly with QoL.
The draft genome sequence of the American mink (Neovison vison) opens new opportunities of genomic research in mink.

The American mink (Neovison vison) is a semiaquatic mustelid native to North America. It is an important animal for the fur industry. Although many efforts have been made to locate genes influencing fur quality and color, the lack of a reference genome impedes the search. American mink has the smallest chromosome number among studied Carnivora species. Genomic information about American mink is also vital to understand the evolution of Carnivora. Hence a reference genome of mink will facilitate genetic improvement of economic traits and will increase our knowledge about the evolution of Carnivora.

Here we present the draft genome sequence of American mink. In our study, a male inbred pearl mink was sequenced by Illumina paired-end and mate pair sequencing. The reads were assembled, which lead to 22,419 scaffolds with an N50 (shortest sequence length at 50% of the genome) of 646,304 bp. The assembly constituted 2.4G plus gaps, representing 90% of the estimated genome size. Repeat annotation showed that repeat sequences constitute about 25% of the mink genome. The biggest repeat family was a family of LINEs similar to LINEs found in the dog and ferret genomes. Gene annotation of our draft genome indicated our draft genome contains 87% of 1:1 Vertebrata genes (63.5% complete single copy genes, 0.5% duplicated genes and 22% fragment genes). We were able to map on the draft genome all the well-studied genes which are thought to be involved in the coat quality and coat color phenotypes. Our draft genome has great potential to facilitate genomic research towards improved breeding for high fur quality and will strengthen our understanding of Carnivora evolution.
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(I: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
Publication date: 2016
Event: Abstract from 11th International Veterinary Immunology Symposium, Gold Coast, Australia.
Main Research Area: Technical/natural sciences

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.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Department of Bio and Health Informatics, National Food Institute, Research Group for Genomic Epidemiology, Slagelse Hospital, University of Copenhagen, Roskilde University, Odense University Hospital, Vejle Hospital, Odense Universitetshospital
Authors: Rasmussen, L. H. (Ekstern), Dargis, R. (Ekstern), Iversen, K. H. (Intern), Christensen, J. J. (Ekstern), Skovgaard, O. (Ekstern), Justesen, U. S. (Ekstern), Rosenvinge, F. S. (Ekstern), Moser, C. (Ekstern), Lukjancenko, O. (Intern), Rasmussen, S. (Intern), Nielsen, X. C. (Ekstern)
Number of pages: 11
Pages: 1615-1625
Publication date: 2016
Main Research Area: Technical/natural sciences

Publication information
Journal: European Journal of Clinical Microbiology & Infectious Diseases
Volume: 35
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**

**State:** Published  
**Organisations:** Center for Biological Sequence Analysis, Functional Human Variation, Department of Bio and Health Informatics, Disease Intelligence and Molecular Evolution  
**Authors:** Gupta, R. (Intern)  
**Number of pages:** 1  
**Publication date:** 2016  
**Event:** Abstract from Sustain-ATV Conference 2016, Kgs. Lyngby, Denmark.  
**Main Research Area:** Technical/natural sciences  
**Links:**  
http://www.sustain.dtu.dk/
Projects:

**T Cell Immunoinformatics**
Department of Bio and Health Informatics  
Period: 01/04/2018 → 31/03/2021  
Number of participants: 3  
Phd Student:  
Reynisson, Birkir (Intern)  
Supervisor:  
Marcatili, Paolo (Intern)  
Main Supervisor:  
Nielsen, Morten (Intern)

**Financing sources**  
Source: Internal funding (public)  
Name of research programme: Samfinansieret - Andet  
Project: PhD

**Bioinformatics of ayurvedic medicine sources and treatment response stratification**  
Department of Bio and Health Informatics  
Period: 01/01/2018 → 31/12/2020  
Number of participants: 4  
Phd Student:  
Garcia, Sara (Intern)  
Supervisor:  
Kadarmideen, Haja (Ekstern)  
Thelma, B. K. (Ekstern)  
Main Supervisor:  
Gupta, Ramneek (Intern)

**Financing sources**  
Source: Internal funding (public)  
Name of research programme: Samfinansieret - Andet  
Project: PhD

**Bioinformatics of the germline-somatic continuum in cancer**  
Department of Bio and Health Informatics  
Period: 01/01/2018 → 31/12/2020  
Number of participants: 4  
Phd Student:  
Pastori, Ambra (Intern)  
Supervisor:  
Pedersen, Anders Gorm (Intern)  
Schmiegelow, Kjeld (Ekstern)  
Main Supervisor:  
Gupta, Ramneek (Intern)

**Financing sources**  
Source: Internal funding (public)
Identification of Genetic Associations within childhood Asthma using Probabilistic

Department of Bio and Health Informatics
Period: 15/10/2017 → 14/10/2020
Number of participants: 6
PhD Student:
Eliasen, Anders Ulrik (Intern)
Supervisor:
Ahluwalia, Tarunveer Singh (Ekstern)
Bisgaard, Hans (Ekstern)
Bønnelykke, Klaus (Ekstern)
Rasmussen, Morten Arendt (Ekstern)
Main Supervisor:
Pedersen, Anders Gorm (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Samfinansieret - Andet
Project: PhD

PROVIDE - Protein valorization through informatics, hydrolysis, and separation
PROVIDE is a project to develop bioinformatics technology for the discovery of protein based food ingredients. Five enterprises and two universities collaborate with the aim to create the technology and develop new high value food and feed ingredients from protein sources that are currently under-utilized. We will use bioinformatics to predict and identify embedded peptides that can be released from proteins through hydrolysis, fermentation and separation. The targeted functionalities are antimicrobials, antioxidants, gelation, emulsifying and flavoring properties. Functional assays will be established and synthetic peptides will be used for validation. Release of the active peptides from the protein matrix will be obtained by enzymatic hydrolysis and fermentation. The participating companies utilize specific protein sources, mainly plant based, and are united in the desire to develop novel high value food and feed functional ingredients through the proposed technology.

National Food Institute
Research Group for Bioactives – Analysis and Application
Research Group for Gut Microbiology and Immunology
Department of Bio and Health Informatics
AKV Langholt
CP Kelco ApS
KMC
Lihme Protein Solutions
Unibio A/S
Aalborg University
Period: 01/09/2017 → 31/08/2021
Number of participants: 7
Peptides, by-products, bioinformatics, ingredients
Acronym: PROVIDE
Project participant:
Holdt, Susan Løvstad (Intern)
Jacobsen, Charlotte (Intern)
Hansen, Egon Bech (Intern)
Garcia Moreno, Pedro Jesús (Intern)
Lund, Ole (Intern)
Bang-Berthelsen, Iben (Intern)
Marcatili, Paolo (Intern)
Fast-tracking the identification of safe and effective probiotic bacteria by in silico prediction of bacterial genomic features

Department of Bio and Health Informatics
Period: 01/08/2017 → 31/07/2020
Number of participants: 4
Phd Student:
Tang Karlsen, Signe (Intern)
Supervisor:
Bælum, Jacob (Intern)
Henderson, Gemma (Ekstern)
Main Supervisor:
Lund, Ole (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Industrial PhD
Project: PhD

Systems Genomic and Transcriptomics approaches for simultaneous improvement of feed efficiency and production in Danish Pigs

Department of Bio and Health Informatics
Period: 01/08/2017 → 31/07/2019
Number of participants: 3
Phd Student:
Carmelo, Victor Adriano Okstoft (Intern)
Supervisor:
Ekstrøm, Claus Thorn (Ekstern)
Main Supervisor:
Kadarmideen, Haja (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Samfinansieret - Andet
Project: PhD

Genomics, epigenetic and metabolomics analysis of production and welfare in Danish cattle and pigs

Department of Bio and Health Informatics
Period: 15/06/2017 → 14/06/2019
Number of participants: 3
Phd Student:
Wang, Xiao (Intern)
Supervisor:
Ekstrøm, Claus Thorn (Ekstern)
Main Supervisor:
Kadarmideen, Haja (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Stipendie fra udlandet
Project: PhD

Augmenting metagenomic-wide association studies by grouping species that share a functional potential or ecological role

Department of Bio and Health Informatics
Period: 15/02/2017 → 14/02/2020
Number of participants: 3
Phd Student:
Petersen, Anders Østergaard (Intern)
Supervisor:
Nielsen, Henrik Bjørn (Intern)
Main Supervisor:
Rasmussen, Simon (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Samfinansieret - Andet
Project: PhD

Pre-clinical exploration of cancer neoepitope immunotherapy
Department of Bio and Health Informatics
Period: 01/01/2017 → 31/12/2019
Number of participants: 3
PhD Student:
Jappe, Emma Christine (Intern)
Supervisor:
Kringelum, Jens Vindahl (Intern)
Main Supervisor:
Nielsen, Morten (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Industrial PhD
Project: PhD

Protein sorting in pathogenic unicellular eukaryotes
Department of Bio and Health Informatics
Period: 01/12/2016 → 30/11/2019
Number of participants: 3
PhD Student:
Almagro Armenteros, Jose Juan (Intern)
Supervisor:
Winther, Ole (Intern)
Main Supervisor:
Nielsen, Henrik (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Institut stipendie (DTU)
Project: PhD

Biomarkers for prognosis and prediction of childhood ALL treatment outcome
Department of Bio and Health Informatics
Period: 01/11/2016 → 31/10/2019
Number of participants: 5
PhD Student:
Nielsen, Rikke Linnemann (Intern)
Supervisor:
Pedersen, Anders Gorm (Intern)
Schmiegelow, Kjeld (Ekstern)
Wang, XiuJie (Ekstern)
Main Supervisor:
Gupta, Ramneek (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Samfinansieret - Andet
Project: PhD
Metagenomic Data Stratified using Artificial Intelligence
Department of Bio and Health Informatics
Period: 01/11/2016 → 21/03/2020
Number of participants: 3
Phd Student:
Nissen, Jakob Nybo (Intern)
Supervisor:
Nielsen, Morten (Intern)
Main Supervisor:
Rasmussen, Simon (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Institut stipendie (DTU)
Project: PhD

DNA repair pathway aberrations in personalized chemotherapy and immunotherapy of cancer
Department of Bio and Health Informatics
Period: 01/09/2016 → 31/08/2019
Number of participants: 3
Phd Student:
Diossy, Miklos (Intern)
Supervisor:
Eklund, Aron Charles (Intern)
Main Supervisor:
Pedersen, Anders Gorm (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Samfinansieret - Andet
Project: PhD

B-cell immunoinformatics
Department of Bio and Health Informatics
Period: 01/08/2016 → 31/07/2019
Number of participants: 3
Phd Student:
Jespersen, Martin Closter (Intern)
Supervisor:
Marcatili, Paolo (Intern)
Main Supervisor:
Nielsen, Morten (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Samfinansieret - Andet
Project: PhD

Development of Immunoinformatics prediction methods for improved understanding of TCR-peptide-MHC interactions
Department of Bio and Health Informatics
Period: 01/08/2016 → 31/07/2019
Number of participants: 3
Phd Student:
Jensen, Kamilla Kjærgaard (Intern)
Supervisor:
Marcatili, Paolo (Intern)
Main Supervisor:
Nielsen, Morten (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Samfinansieret - Andet
Project: PhD

Whole genome comparison and evolutionary analysis of Mitis group streptococci - a causative agent of infective endocarditis

Department of Bio and Health Informatics
Period: 01/12/2015 → 07/12/2019
Number of participants: 4
Phd Student:
Iversen, Katrine Højholt (Intern)
Supervisor:
Christensen, Jens Jørgen Elmer (Ekstern)
Nielsen, Xiaohui Chen (Ekstern)
Main Supervisor:
Rasmussen, Simon (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Samfinansieret - Andet
Project: PhD

Development bioinformatics tools for wine fermentation, wine quality and wine health

Department of Bio and Health Informatics
Period: 01/09/2015 → 31/08/2018
Number of participants: 3
Phd Student:
Klincke, Franziska (Intern)
Supervisor:
Gilbert, M. Thomas P. (Ekstern)
Main Supervisor:
Rasmussen, Simon (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Marie Curie (EU-stipendium)
Project: PhD

Understanding aetiology and treatment trajectories in childhood leukemia through advanced data integration

Department of Bio and Health Informatics
Period: 01/08/2015 → 31/07/2019
Number of participants: 4
Phd Student:
Grosjean, Marie (Intern)
Supervisor:
Pedersen, Anders Gorm (Intern)
Schmiegelow, Kjeld (Ekstern)
Main Supervisor:
Gupta, Ramneek (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Institut stipendie (DTU)
Project: PhD
The gut microbiota and bone dynamics
Department of Bio and Health Informatics
Period: 01/02/2015 → 31/08/2017
Number of participants: 4
Phd Student: Bresciani, Anne Gøther (Intern)
Supervisor: Nielsen, Henrik Bjørn (Intern)
Nielsen, Morten (Intern)
Main Supervisor: Nielsen, Morten (Intern)
Financing sources
Source: Internal funding (public)
Name of research programme: Institut stipendie (DTU)
Project: PhD

Benchmarking of phylogeny methods based on whole genome sequencing
Department of Bio and Health Informatics
Period: 15/12/2014 → 16/05/2018
Number of participants: 6
Phd Student: Ahrenfeldt, Johanne (Intern)
Supervisor: Hasman, Henrik (Intern)
Main Supervisor: Lund, Ole (Intern)
Examiner: Marcatili, Paolo (Intern)
Litrup, Eva (Ekstern)
Pettengill, James B. (Ekstern)
Financing sources
Source: Internal funding (public)
Name of research programme: Anden EU-finansiering
Project: PhD

Diagnostic use of Microbial Whole Genome Sequencing (WGS)
Department of Bio and Health Informatics
Period: 15/12/2014 → 05/07/2019
Number of participants: 4
Phd Student: Tetzschner, Anna Maria Malberg (Intern)
Supervisor: Aarestrup, Frank Møller (Intern)
Pamp, Sünje Johanna (Intern)
Main Supervisor: Lund, Ole (Intern)
Financing sources
Source: Internal funding (public)
Name of research programme: Samfinansieret - Andet
Project: PhD

High Performance Machine Learning Methods applied within Bioinformatics
Department of Bio and Health Informatics
Period: 15/12/2014 → 22/01/2018  
Number of participants: 7  
Phd Student:  
Jurtz, Vanessa Isabell (Intern)  
Supervisor:  
Lund, Ole (Intern)  
Winther, Ole (Intern)  
Main Supervisor:  
Nielsen, Morten (Intern)  
Examiner:  
Petersen, Thomas Nordahl (Intern)  
Buus, Søren (Ekstern)  
Gfeller, David (Ekstern)  

**Financing sources**  
Source: Internal funding (public)  
Name of research programme: Samfinansieret - Andet  
Project: PhD

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**High-throughput discovery of tumor antigens**  
Department of Bio and Health Informatics  
Period: 15/12/2014 → 21/03/2018  
Number of participants: 6  
Phd Student:  
Bjerregaard, Anne-Mette (Intern)  
Supervisor:  
Eklund, Aron Charles (Intern)  
Main Supervisor:  
Szallasi, Zoltan Imre (Intern)  
Examiner:  
Gonzalez-Izarzugaza, Jose Maria (Intern)  
Kesmir, Can (Intern)  
Quezada, Sergio A. (Ekstern)  

**Financing sources**  
Source: Internal funding (public)  
Name of research programme: Institut stipendie (DTU)  
Project: PhD

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**Metagenomic tools for tapping into the Koala's lignin and terpenoid degrading enzymes**  
Department of Bio and Health Informatics  
Period: 15/12/2014 → 18/04/2018  
Number of participants: 6  
Phd Student:  
Al-Nakeeb, Kosai Ali Ahmed (Intern)  
Supervisor:  
Petersen, Thomas Nordahl (Intern)  
Main Supervisor:  
Sicheritz-Pontén, Thomas (Intern)  
Examiner:  
Lund, Ole (Intern)  
Ahrén, Dag Gustaf (Ekstern)  
Tolstrup, Niels (Intern)  

**Financing sources**  
Source: Internal funding (public)  
Name of research programme: Institut stipendie (DTU)  
Project: PhD
Optimal client-server methods for Next Generation Sequencing Analysis

Department of Bio and Health Informatics
Period: 15/12/2014 → 13/12/2018
Number of participants: 3
Phd Student:
Bellod Cisneros, Jose Luis (Intern)
Supervisor:
Aarestrup, Frank Møller (Intern)
Main Supervisor:
Lund, Ole (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Anden EU-finansiering
Project: PhD

Combating Methicillin Resistant Staphylococcus aureus (MRSA) with bacteriophages

Department of Bio and Health Informatics
Period: 01/12/2014 → 22/01/2018
Number of participants: 7
Phd Student:
Zschach, Henrike (Intern)
Supervisor:
Hasman, Henrik (Intern)
Larsen, Mette Voldby (Intern)
Main Supervisor:
Nielsen, Morten (Intern)
Examiner:
Petersen, Bent (Intern)
Clokie, Martha Rebecca Jane (Ekstern)
Vogensen, Finn Kvist (Ekstern)

Financing sources
Source: Internal funding (public)
Name of research programme: Institut stipendie (DTU)

Relations
Publications:
Genomics of phages with therapeutic potential
Project: PhD

Protein network rewiring due to somatic driver mutations in cancers

Department of Bio and Health Informatics
Period: 01/11/2014 → 30/06/2018
Number of participants: 3
Phd Student:
Jespersen, Jakob Berg (Intern)
Supervisor:
Hansen, Kasper Lage (Intern)
Main Supervisor:
Lund, Ole (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Eksternt finansieret virksomhed
Project: PhD
Rapid computational identification and elucidation of infectious disease outbreak

Department of Bio and Health Informatics
Period: 15/04/2014 → 29/07/2017
Number of participants: 6
PhD Student: Thomsen, Martin Christen Frølund (Intern)
Supervisor: Aarestrup, Frank Møller (Intern)
Main Supervisor: Lund, Ole (Intern)
Examiner: Petersen, Bent (Intern)
Dallman, Tim (Ekstern)
Hansen, Dennis Schrøder (Ekstern)

Financing sources
Source: Internal funding (public)
Name of research programme: Forskningsrådsfinansiering
Project: PhD

Isolation and characterization of bacteriophages with therapeutic potential

Department of Bio and Health Informatics
Period: 01/12/2013 → 28/02/2018
Number of participants: 7
PhD Student: Villarroel, Julia (Intern)
Supervisor: Kilstrup, Mogens (Intern)
Main Supervisor: Larsen, Mette Voldby (Intern)
Examiner: Nielsen, Morten (Intern)
Nielsen, Henrik (Intern)
Lavigne, Rob (Ekstern)
Nielsen, Dennis Sandris (Ekstern)

Financing sources
Source: Internal funding (public)
Name of research programme: Institut stipendie (DTU)
Project: PhD

Characterization and Validation of Biomarkers Reflecting Extracellular Matrix Remodelling in Cancer - Potential markers of early cancer development

Department of Bio and Health Informatics
Period: 01/11/2013 → 08/02/2017
Number of participants: 8
PhD Student: Bager, Cecilie Liv (Intern)
Supervisor: Christiansen, Pernille (Ekstern)
Høgdall, Estrid (Ekstern)
Karsdal, Morten A. (Ekstern)
Main Supervisor: Eklund, Aron Charles (Intern)
Examiner: Hadrup, Sine Reker (Intern)
Erler, Janine Terra (Ekstern)
Sund, Malin (Ekstern)

**Financing sources**

Source: Internal funding (public)
Name of research programme: Institut stipendie (DTU) Samf.
Project: PhD

**Development of a recombinant antibody-based treatment of snakebites**

Department of Bio and Health Informatics
Period: 01/11/2013 → 05/12/2017
Number of participants: 7
Phd Student:
Engmark, Mikael (Intern)
Supervisor:
Andersen, Mikael Rørdam (Intern)
De Masi, Federico (Intern)
Main Supervisor:
Lund, Ole (Intern)
Examiner:
Marcatili, Paolo (Intern)
Billiald, Philippe (Ekstern)
Buus, Søren (Ekstern)

**Financing sources**

Source: Internal funding (public)
Name of research programme: Eksternt finansieret virksomhed

**Relations**

Activities:
The Oxford Venoms Symposium 2016
The 12th Congress of the Pan-American Section of the International Society on Toxinology

**Identification of risk factors for acquiring ADV in Danish mink farms**

Department of Bio and Health Informatics
Period: 01/08/2013 → 06/06/2017
Number of participants: 7
Phd Student:
Hagberg, Emma Elisabeth (Intern)
Supervisor:
Krarup, Anders (Ekstern)
Larsen, Lars Erik (Intern)
Main Supervisor:
Pedersen, Anders Gorm (Intern)
Examiner:
Sicheritz-Pontén, Thomas (Intern)
Decaro, Nicola (Ekstern)
Fischer, Thea Kølsen (Ekstern)

**Financing sources**

Source: Internal funding (public)
Name of research programme: Industrial PhD
Project: PhD

**Temporal Characterization and Fingerprinting of Wine**

Department of Bio and Health Informatics
Pharmacogenomics and personalized medicine in the treatment of ADHD

Department of Bio and Health Informatics
Period: 15/01/2013 → 06/06/2017
Number of participants: 6
Phd Student:
Nzabonimpa, Grace Shema (Intern)
Supervisor:
Brunak, Søren (Intern)
Main Supervisor:
Taboureau, Olivier (Intern)
Examiner:
De Masi, Federico (Intern)
Jørgensen, Flemming Steen (Ekstern)
Xhaard, Henri (Ekstern)

Financing sources
Source: Internal funding (public)
Name of research programme: Institut stipendie (DTU)
Project: PhD

Microbial Community Interactions in Arctic Environments using a Metagenomics Approach

Department of Bio and Health Informatics
Period: 15/12/2012 → 26/04/2017
Number of participants: 6
Phd Student:
Hauptmann, Aviaja Zenia Edna Lyberth (Intern)
Main Supervisor:
Sicheritz-Pontén, Thomas (Intern)
Examiner:
Pedersen, Anders Gorm (Intern)
Winding, Anne (Ekstern)
Øvreås, Lise (Ekstern)
Øvreås, Lise (Ekstern)

Financing sources
Source: Internal funding (public)
Name of research programme: Institut stipendie (DTU) Samf.

Relations
Publications:
Microbial Biogeography of the Arctic Cryosphere
**Systems biology of diseases and their co-morbidities**
Department of Bio and Health Informatics  
Period: 15/12/2012 → 01/12/2016  
Number of participants: 5  
Phd Student: Beck, Mette Kristina (Intern)  
Main Supervisor: Brunak, Søren (Intern)  
Examiner: Gonzalez-Izarzugaza, Jose Maria (Intern)  
Franke, Andre W. (Ekstern)  
Westendorp, Rudi GJ (Ekstern)

**Financing sources**  
Source: Internal funding (public)  
Name of research programme: Forskningsrådsfinansiering  
Project: PhD

**Therapeutic applications of cancer type-specific mutation patterns**
Department of Bio and Health Informatics  
Period: 01/12/2012 → 01/12/2016  
Number of participants: 7  
Phd Student: Marquard, Andrea Marion (Intern)  
Supervisor: Birkbak, Nicolai Juul (Intern)  
Eklund, Aron Charles (Intern)  
Main Supervisor: Szallasi, Zoltan Imre (Intern)  
Examiner: Lund, Ole (Intern)  
Besenbacher, Søren (Ekstern)  
Lawrence, Michael S. (Ekstern)

**Financing sources**  
Source: Internal funding (public)  
Name of research programme: Institut stipendie (DTU) Samf.  
Project: PhD

**Machine Learning and Oncoviral Genomics**
Department of Bio and Health Informatics  
Period: 01/05/2012 → 26/09/2016  
Number of participants: 5  
Phd Student: Friis-Nielsen, Jens (Intern)  
Supervisor: Sorgenfrei Blom, Nikolaj (Intern)  
Gonzalez-Izarzugaza, Jose Maria (Intern)  
Sicheritz-Pontén, Thomas (Intern)  
Main Supervisor: Brunak, Søren (Intern)

**Financing sources**  
Source: Internal funding (public)  
Name of research programme: Institut stipendie (DTU) Samf.  
Project: PhD
Pangenome tools for rapid, large scale analysis of bacterial genomes
Department of Bio and Health Informatics
Period: 15/03/2012 → 29/09/2016
Number of participants: 7
Phd Student:
Pedersen, Thomas Lin (Intern)
Supervisor:
Månsson, Maria (Intern)
Ussery, David (Intern)
Main Supervisor:
Lund, Ole (Intern)
Examiner:
Petersen, Bent (Intern)
Page, Andrew (Ekstern)
Sutton, Granger G. (Ekstern)

Financing sources
Source: Internal funding (public)
Name of research programme: ErhvervsPhD-ordningen VTU
Project: PhD

Fjerkæprojektet. Serotypning beredskabs-aftale.
National Food Institute
Division of Risk Assessment and Nutrition
Division of Food Production Engineering
Genomic Epidemiology
Period: 01/01/2012 → …
Number of participants: 1
Project participant:
Christensen, Julia (Intern)

Udvikling af featurebaseret in silico-metoder til diskrimination af immunogene og beskyttende antigener
Department of Bio and Health Informatics
Period: 15/12/2011 → 21/04/2016
Number of participants: 4
Phd Student:
Mattsson, Andreas Holm (Intern)
Supervisor:
Møller, Niels Iversen (Ekstern)
Poznansky, Mark C. (Ekstern)
Main Supervisor:
Nielsen, Morten (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Ansat eksternt
Project: PhD

Translational informatics in Toxicology
Department of Bio and Health Informatics
Period: 01/11/2011 → 02/06/2016
Number of participants: 2
Phd Student:
Jacobsen, Ulrik Plesner (Intern)
Main Supervisor:
Lund, Ole (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Samfinansierede - Virksomhed
Project: PhD

Activities:

Allelic Imbalance usage in functional genetics
Period: 13 Nov 2017
Lasse Westergaard Folkersen (Invited speaker)
Department of Bio and Health Informatics
Integrative Systems Biology

Related event
World Gene Convention-2017
12/11/2017 → 14/11/2017
Macao, China
Activity: Talks and presentations › Conference presentations

DeepLoc: Prediction of protein subcellular localization using deep learning
Period: 3 Nov 2017
Henrik Nielsen (Guest lecturer)
Jose Juan Almagro Armenteros (Guest lecturer)
Department of Bio and Health Informatics
Disease Intelligence and Molecular Evolution
Department of Applied Mathematics and Computer Science

Related external organisation
Intomics A/S
Denmark
Activity: Talks and presentations › Conference presentations

Scientific Reports (Journal)
Period: 1 Oct 2017 → …
Bent Petersen (Editor)
Department of Bio and Health Informatics

**Metagenomics**

**Description**
Editorial Board Member for Scientific Reports, a Nature Research journal. [http://www.nature.com/srep/](http://www.nature.com/srep/)
Degree of recognition: International

**Related journal**

Scientific Reports
2045-2322
Indexed in DOAJ
Central database
Activity: Communication › Journal editor

**DeepLoc: Prediction of protein subcellular localization using deep learning**
Period: 29 Aug 2017
Henrik Nielsen (Guest lecturer)
Department of Bio and Health Informatics
Disease Intelligence and Molecular Evolution

**Related external organisation**

Stockholm University
Sweden
Activity: Talks and presentations › Conference presentations

**DeepLoc: Prediction of protein subcellular localization using deep learning**
Period: 25 Aug 2017
Henrik Nielsen (Guest lecturer)
Department of Bio and Health Informatics
Disease Intelligence and Molecular Evolution

**Related event**

Annual Danish Bioinformatics Conference 2017: Elixir
23/08/2017 → 25/08/2017
Odense, Denmark
Activity: Talks and presentations › Conference presentations

Annual Danish Bioinformatics Conference 2017
Period: 23 Aug 2017 → 24 Aug 2017
Lasse Westergaard Folkersen (Organizer)
Department of Bio and Health Informatics
Integrative Systems Biology

**Description**
Organizer, Elixir-DK 2017
Links:
[http://elixir-node.cbs.dtu.dk](http://elixir-node.cbs.dtu.dk)

**Related event**

Annual Danish Bioinformatics Conference 2017: Elixir
23/08/2017 → 25/08/2017
Odense, Denmark
Innovation on Big Data for Healthy Living
Period: 12 Jul 2017
Lasse Westergaard Folkersen (Invited speaker)
Department of Bio and Health Informatics
Integrative Systems Biology

Description

Links:
http://www.biohealth-computing.eu/innovation-on-big-data-for-healthy-living/

Related event

IBD4Health
12/07/2017 → 12/07/2017
Geneva, Switzerland
Activity: Talks and presentations › Conference presentations

Diversity, structure, and novel physiologies in microbial communities in rapid sand filters
Period: 9 Jul 2017 → 13 Jul 2017
Barth F. Smets (Invited speaker)
Arda Gülay (Other)
Alejandro Palomo (Other)
Jane Fowler (Other)
Thomas Sicheritz-Pontén (Other)
Department of Environmental Engineering
Water Technologies
Department of Bio and Health Informatics
Metagenomics
Degree of recognition: International
Documents:
fems 2

Related event

The Federation of European Microbiological Societies
09/07/2017 → 13/07/2017
Valencia, Spain
Activity: Talks and presentations › Conference presentations

How Much of the Human Genome is Functional?
Period: 8 Jun 2017
Henrik Nielsen (Guest lecturer)
Department of Bio and Health Informatics
Disease Intelligence and Molecular Evolution
Documents:
Abstract

Related event

Seventeenth Annual Gatherings in Biosemiotics
06/06/2017 → 10/06/2017
Lausanne, Switzerland
Activity: Talks and presentations › Conference presentations
Danish researchers have sequenced and analyzed the genome of a bacterium that can feed off coal tar. It lives in symbiosis with another bacterium that can recycle its partner’s waste. Researchers hope that this sustainable bacterial duo can transform toxic substances into useful materials. Nevertheless, mapping the genome also led to an unpleasant surprise.

**Tar-Eating Bacterial Duo may Transform Toxic Compounds into New Usable Materials**  
Period: 16 May 2017  
Sünje Johanna Pamp (Participant)  
Department of Biotechnology and Biomedicine  
Department of Bio and Health Informatics  
National Food Institute  
Research Group for Genomic Epidemiology  

**Description**  
Danish researchers have sequenced and analyzed the genome of a bacterium that can feed off coal tar. It lives in symbiosis with another bacterium that can recycle its partner’s waste. Researchers hope that this sustainable bacterial duo can transform toxic substances into useful materials. Nevertheless, mapping the genome also led to an unpleasant surprise.

**Interview person.**  
Degree of recognition: International  
Documents:  
Tar-eating bacterial duo may transform toxic compounds into new usable materials | Sciencenews.dk  
Links:  
Activity: Other

**Week of Health and INNovation**  
Lasse Westegaard Folkersen (Panel member)  
Department of Bio and Health Informatics  
Integrative Systems Biology  
Links:  

**Related event**

**Week of Health and INNovation**  
03/10/2016 → 07/10/2016  
Odense, Denmark  
Activity: Talks and presentations › Conference presentations

**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: Talks and presentations › Conference presentations

Press clippings:

Is there too little control with direct-to-consumer genetics tests (Danish language only)
Lasse Westergaard Folkersen
19/05/2017

Description
Debate between Lasse Folkersen and Thomas Ploug on the uses and potential pitfalls of modern direct-to-consumer genetics, and their analysis on sites such as www.impute.me
Department of Bio and Health Informatics, Integrative Systems Biology

Media contribution (1)
Is there too little control with direct-to-consumer genetics tests (Danish language only)
19/05/2017
videnskab.dk, Denmark
ais Baggestrøm Koch
https://soundcloud.com/videnskabdk/slar-forbrugergentest-plat-pa-sygdomsangste-mennesker
Debate between Lasse Folkersen and Thomas Ploug on the uses and potential pitfalls of modern direct-to-consumer genetics, and their analysis on sites such as www.impute.me
Lasse Westergaard Folkersen
Department of Bio and Health Informatics, Integrative Systems Biology

Web analytics server gives access to medical genetics information (Danish language only)
Lasse Westergaard Folkersen
08/05/2017
Department of Bio and Health Informatics, Integrative Systems Biology

Media coverage (1)
Kontroversiel hjemmeside afslører, hvilke sygdomme du er disponeret for
08/05/2017
Videnskab-dk, Denmark
Anne Ringgaard
http://Kontroversiel hjemmeside afslører, hvilke sygdomme du er disponeret for
Lasse Westergaard Folkersen
Department of Bio and Health Informatics, Integrative Systems Biology

Bedre smittesporing med supercomputer
Emma Elisabeth Hagberg
17/09/2016
**Subject**
gener og genomer; husdyrøgdomme; 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
http://www.dtu.dk/Om-DTU/Nyheder-og-presse/Dynamo
Emma Elisabeth Hagberg
Molecular Evolution, Department of Bio and Health Informatics, Disease Intelligence and Molecular Evolution
Press / Media

**Computerome - Kopenhagen Fur**
Emma Elisabeth Hagberg
10/12/2015
Molecular Evolution, Department of Bio and Health Informatics, Disease Intelligence and Molecular Evolution

**Media contribution (1)**

**Computerome - Kopenhagen Fur**
10/12/2015
Youtube, Web
Julie Iben Schmidt
https://www.youtube.com/watch?v=HPsWZzi5Gkg
Emma Elisabeth Hagberg
Molecular Evolution, Department of Bio and Health Informatics, Disease Intelligence and Molecular Evolution
Press / Media