Using expected sequence features to improve basecalling accuracy of amplicon pyrosequencing data

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

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

Many bacterial, viral and parasitic pathogens undergo antigenic variation to counter host immune defense mechanisms. In Plasmodium falciparum, the most lethal of human malaria parasites, switching of var gene expression results in alternating expression of the adhesion proteins of the Plasmodium falciparum-erythrocyte membrane protein 1 class on the infected erythrocyte surface. Recombination clearly generates var diversity, but the nature and control of the genetic exchanges involved remain unclear. By experimental and bioinformatic identification of recombination events and genome-wide recombination hotspots in var genes, we show that during the parasite’s sexual stages, ectopic recombination between isogenous var paralogs occurs near low folding free energy DNA 50-mers and that these sequences are heavily concentrated at the boundaries of regions encoding individual Plasmodium falciparum-erythrocyte membrane protein 1 structural domains. The recombinogenic potential of these 50-mers is not parasite-specific because these sequences also induce recombination when transferred to the yeast Saccharomyces cerevisiae. Genetic cross data suggest that DNA secondary structures (DSS) act as inducers of recombination during DNA replication in P. falciparum sexual stages, and that these DSS-regulated genetic exchanges generate functional and diverse P. falciparum adhesion antigens. DSS-induced recombination may represent a common mechanism for optimizing the evolvability of virulence gene families in pathogens.
A Novel Domain Cassette Identifies *Plasmodium falciparum* PfEMP1 Proteins Binding ICAM-1 and Is a Target of Cross-Reactive, Adhesion-Inhibitory Antibodies

Cerebral Plasmodium falciparum malaria is characterized by adhesion of infected erythrocytes (IEs) to the cerebral microvasculature. This has been linked to parasites expressing the structurally related group A subset of the *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) family of IE adhesion ligands and to IEs with affinity for ICAM-1. However, recent evidence has cast doubt on both these associations, tempering hopes of the feasibility of developing a vaccine based on ICAM-1-binding PfEMP1. In this study, we report the identification of a domain cassette (DC) present in group A var genes from six genetically distinct *P. falciparum* parasites. The three domains in the cassette, which we call DC4, had a high level of sequence identity and cluster together phylogenetically. Erythrocytes infected by these parasites and selected in vitro for expression of DC4 adhered specifically to ICAM-1. The ICAM-1-binding capacity of DC4 was mapped to the C-terminal third of its Duffy-binding-like beta 3 domain. DC4 was the target of broadly cross-reactive and adhesion-inhibitory IgG Abs, and levels of DC4-specific and adhesion-inhibitory IgG increased with age among *P. falciparum*-exposed children. Our study challenges earlier conclusions that group A PfEMP1 proteins are not central to ICAM-1-specific IE adhesion and support the feasibility of developing a vaccine preventing cerebral malaria by inhibiting cerebral IE sequestration. The Journal of Immunology, 2013, 190: 240-249.

**General information**

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Oxford, Liverpool School of Tropical Medicine, University of Cambridge, University of Copenhagen
Group a Pfemp1 functional domains bind icam1 and induce cross-reactive and adhesion inhibitory antibodies during malaria infections

The Plasmodium falciparum erythrocyte membrane protein 1 (PIEMP1) plays an important role in antigenic variation and pathogenesis of malaria. PIEMP1 proteins encoded by group A var genes appear to be involved in the pathogenesis of severe disease and have been suggested as attractive candidates for a vaccine against life-threatening P. falciparum malaria. In this study, we identified group A pfd1235w-like genes in Ghanaian isolates and found these to encode a three-domain cassette structure 64-80% identical to the equivalent region of P. falciparum clone 3D7 PFD1235w. Parasites expressing PFD1235w-like proteins on the surface of infected erythrocytes were found to mediate binding to ICAM1, a phenotype linked to cerebral malaria. ICAM1 binding was mediated by a particular sub-domain which induces cross-reactive and ICAM1 adhesion inhibitory antibodies during P. falciparum infections. These results have implications for our understanding of how PIEMP1 interacts with host receptors and for the development of therapeutic interventions targeting ICAM1 binding malaria parasites.

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Conference: Joint Spring Symposium 2012 : Danish Society for Parasitology and Danish Society for Tropical Medicine & International Health, Frederiksberg, Denmark, 23/03/2012
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Plasmodium falciparum erythrocyte membrane protein 1 domain cassettes 8 and 13 are associated with severe malaria in children
The clinical outcome of Plasmodium falciparum infections ranges from asymptomatic parasitemia to severe malaria syndromes associated with high mortality. The virulence of P. falciparum infections is associated with the type of P. falciparum erythrocyte membrane protein 1 (PIEMP1) expressed on the surface of infected erythrocytes to anchor these to the vascular lining. Although var2csa, the var gene encoding the PIEMP1 associated with placental malaria, was
discovered in 2003, the identification of the var/PfEMP1 variants associated with severe malaria in children has remained elusive. To identify var/PfEMP1 variants associated with severe disease outcome, we compared var transcript levels in parasites from 88 children with severe malaria and 40 children admitted to the hospital with uncomplicated malaria. Transcript analysis was performed by RT-quantitative PCR using a set of 42 primer pairs amplifying var subtype-specific loci covering most var/PfEMP1 subtypes. In addition, we characterized the near-full-length sequence of the most prominently expressed var genes in three patients diagnosed with severe anemia and/or cerebral malaria. The combined analysis showed that severe malaria syndromes, including severe anemia and cerebral malaria, are associated with high transcript levels of PIEMP1 domain cassette 8-encoding var genes. Transcript levels of group A var genes, including genes encoding domain cassette 13, were also significantly higher in patients with severe syndromes compared with those with uncomplicated malaria. This study specifies the var/PfEMP1 types expressed in severe malaria in children, and thereby provides unique targets for future efforts to prevent and treat severe malaria infections.

**General information**

**State:** Published  
**Organisations:** Center for Biological Sequence Analysis, Department of Systems Biology, Tanga Medical Research Centre, University of Copenhagen  
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Scopus rating (2013): SJR 6.989 SNIP 2.73 CiteScore 9.5  
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BFI (2011): BFI-level 2  
Scopus rating (2011): SJR 6.771 SNIP 2.636 CiteScore 9.31  
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Web of Science (2011): Indexed yes  
BFI (2010): BFI-level 2  
Scopus rating (2010): SJR 6.769 SNIP 2.529  
Web of Science (2010): Indexed yes
The Duffy-Binding-Like β domain (DBLβ) of the Plasmodium falciparum erythrocyte membrane protein 1 (PfEMP1) variant, PFD1235w, binds ICAM1

Plasmodium falciparum is by far the most virulent human malaria parasite. P. falciparum variant erythrocyte surface antigens, known as PfEMP1, play a crucial role in malaria pathogenesis as they mediate adhesion to host endothelial receptors. The PfEMP1 variant, PFD1235w, encoded by the 3D7 group A var gene has been associated with severe malaria and erythrocytes infected with parasites expressing PFD1235w binds ICAM1. To identify the PfDF1235w domain(s) responsible for ICAM1 binding we used recombinant protein (NTS, CIDR1, DBL1-CIDR1, DBL domains, CIDR2) and ICAM1 in Enzyme-Linked Immuno-Sorbent Assay (ELISA). We identified the DBLβ3-domain 4 (D4) of the PfDF1235w to be responsible for ICAM1 binding in a concentration dependent manner and the binding could be inhibited by a panel of monoclonal ICAM1 antibodies. By using 3D protein modeling we generated different PfEMP1 hybrid molecules and truncated proteins in order to determine the essential binding region of the DBLβ3-D4 involved in the ICAM1 interaction. The hybrid molecules and truncated proteins were tested for ICAM1 binding in ELISA. Results indicate that the C-terminal of DBLβ3-D4 is directly involved in the ICAM1 interaction, while the N-terminal region is necessary for correct protein conformation. These results contribute to a greater understanding of how PfEMP1 interacts with endothelial receptors such as ICAM1 and provide a model for future analysis of other PfEMP1 variants adhering to ICAM1.

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Authors: Andersen, M. A. (Ekstern), Bengtsson, A. (Ekstern), Rask, T. S. (Intern), Jørgensen, L. (Ekstern), Jensen, A. T. R. (Ekstern)
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Publisher: Danish Society for Parasitology
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Malaria vaccine design - Identification of epitopes and characterization of antigenic variation in the PfEMP1 family

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Authors: Rask, T. S. (Intern)
Publication date: 2010

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Place of publication: Kgs. Lyngby, Denmark
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Main Research Area: Technical/natural sciences
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Plasmodium falciparum Erythrocyte Membrane Protein 1 Diversity in Seven Genomes – Divide and Conquer
The var gene encoded hyper-variable Plasmodium falciparum erythrocyte membrane protein 1 (PfEMP1) family mediates cytoadhesion of infected erythrocytes to human endothelium. Antibodies blocking cytoadhesion are important mediators of malaria immunity acquired by endemic populations. The development of a PfEMP1 based vaccine mimicking natural acquired immunity depends on a thorough understanding of the evolved PfEMP1 diversity, balancing antigenic variation against conserved receptor binding affinities. This study redefines and reclassifies the domains of PfEMP1 from seven genomes. Analysis of domains in 399 different PfEMP1 sequences allowed identification of several novel domain classes, and a high degree of PfEMP1 domain compositional order, including conserved domain cassettes not always associated with the established group A–E division of PfEMP1. A novel iterative homology block (HB) detection method was applied, allowing identification of 628 conserved minimal PfEMP1 building blocks, describing on average 83% of a PfEMP1 sequence. Using the HBs, similarities between domain classes were determined, and Duffy binding-like (DBL) domain subclasses were found in many cases to be hybrids of major domain classes. Related to this, a recombination hotspot was uncovered between DBL subdomains S2 and S3. The VarDom server is introduced, from which information on domain classes and homology blocks can be retrieved, and new sequences can be classified. Several conserved sequence elements were found, including: (1) residues conserved in all DBL domains predicted to interact and hold together the three DBL subdomains, (2) potential integrin binding sites in DBLα domains, (3) an acylation motif conserved in group A var genes suggesting N-terminal N-myristoylation, (4) PfEMP1 inter-domain regions proposed to be elastic disordered structures, and (5) several conserved predicted phosphorylation sites. Ideally, this comprehensive categorization of PfEMP1 will provide a platform for future studies on var/PfEMP1 expression and function.

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Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, University of Copenhagen
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Publication date: 2010
Main Research Area: Technical/natural sciences

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Epitope mapping and analysis of sequence variation in VAR2CSA DBL3X involved in P-falciparum placental sequestration

General information
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Organisations: Center for Biological Sequence Analysis, Department of Systems Biology
Authors: Rask, T. S. (Intern), Dahlback, M. (Ekstern), Andersen, P. H. (Ekstern), Nielsen, M. A. (Ekstern), Ndam, N. T. (Ekstern), Resende, M. (Ekstern), Turner, L. (Ekstern), Deloron, P. (Ekstern), Hviid, L. (Ekstern), Lund, O. (Intern), Pedersen, A. G. (Intern), Theander, T. G. (Ekstern), Salanti, A. (Ekstern)
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Plasmodium falciparum erythrocyte membrane protein 1 diversity analysis and classification.

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Authors: Rask, T. S. (Intern), Lavstsen, T. (Ekstern), Pedersen, A. G. (Intern)
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Structural Insight into Epitopes in the Pregnancy-Associated Malaria Protein VAR2CSA

Pregnancy-associated malaria is caused by Plasmodium falciparum malaria parasites binding specifically to chondroitin sulfate A in the placenta. This sequestration of parasites is a major cause of low birth weight in infants and anemia in the mothers. VAR2CSA, a polymorphic multi-domain protein of the PFEMP1 family, is the main parasite ligand for CSA binding, and identification of protective antibody epitopes is essential for VAR2CSA vaccine development. Attempts to determine the crystallographic structures of VAR2CSA or its domains have not been successful yet. In this study, we propose 3D models for each of the VAR2CSA DBL domains and we show that regions in the fold of VAR2CSA inter-domain 2 and a PFEMP1 CIDR domain seem to be homologous to the EBA-175 and Pkα-DBL fold. This suggests that ID2 could be a functional domain. We also identify regions of VAR2CSA present on the surface of native VAR2CSA by comparing reactivity of plasma containing anti-VAR2CSA antibodies in peptide array experiments before and after incubation with native VAR2CSA. By this method we identify conserved VAR2CSA regions targeted by antibodies that react with the native molecule expressed on infected erythrocytes. By mapping the data onto the DBL models we present evidence suggesting that the S1+S2 DBL sub-domains are generally surface-exposed in most domains, whereas the S3 sub-domains are less exposed in native VAR2CSA. These results comprise an important step towards understanding the
structure of VAR2CSA on the surface of CSA-binding infected erythrocytes.

**General information**

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Organisations: Center for Biological Sequence Analysis, Department of Systems Biology
Authors: Andersen, P. (Ekstern), Nielsen, M. (Ekstern), Resende, M. (Ekstern), Rask, T. S. (Intern), Dahlböck, M. (Ekstern), Theander, T. (Ekstern), Lund, O. (Intern), Salanti, A. (Ekstern)
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- ISI indexed (2012): ISI indexed yes
- BFI (2011): BFI-level 2
- Scopus rating (2011): SJR 5.442 SNIP 1.933 CiteScore 8.87
- ISI indexed (2011): ISI indexed yes
- BFI (2010): BFI-level 2
- Scopus rating (2010): SJR 4.494 SNIP 1.702
- Web of Science (2010): Indexed yes
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- Scopus rating (2009): SJR 3.424 SNIP 1.435
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- Scopus rating (2008): SJR 3.262 SNIP 1.137
- Web of Science (2008): Indexed yes
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Epitope mapping and topographic analysis of VAR2CSA DBL3X involved in P-falciparum placental sequestration

Pregnancy-associated malaria is a major health problem, which mainly affects primigravidae living in malaria endemic areas. The syndrome is precipitated by accumulation of infected erythrocytes in placental tissue through an interaction between chondroitin sulphate A on syncytiotrophoblasts and a parasite-encoded protein on the surface of infected erythrocytes, believed to be VAR2CSA. VAR2CSA is a polymorphic protein of approximately 3,000 amino acids forming six Duffy-binding-like (DBL) domains. For vaccine development it is important to define the antigenic targets for protective antibodies and to characterize the consequences of sequence variation. In this study, we used a combination of in silico tools, peptide arrays, and structural modeling to show that sequence variation mainly occurs in regions under strong diversifying selection, predicted to form flexible loops. These regions are the main targets of naturally acquired immunoglobulin gamma and accessible for antibodies reacting with native VAR2CSA on infected erythrocytes. Interestingly, surface reactive anti-VAR2CSA antibodies also target a conserved DBL3X region predicted to form an alpha-helix. Finally, we could identify DBL3X sequence motifs that were more likely to occur in parasites isolated from primi- and multigravidae, respectively. These findings strengthen the vaccine candidacy of VAR2CSA and will be important for choosing epitopes and variants of DBL3X to be included in a vaccine protecting women against pregnancy-associated malaria.

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Organisations: Center for Biological Sequence Analysis, Department of Systems Biology
Authors: Dahlback, M. (Ekstern), Rask, T. S. (Intern), Andersen, P. (Intern), Nielsen, M. A. (Ekstern), Ndam, N. T. (Ekstern), Resende, M. (Ekstern), Turner, L. (Ekstern), Deloron, P. (Ekstern), Hvid, L. (Ekstern), Lund, O. (Intern), Pedersen, A. G. (Intern), Theander, T. G. (Ekstern), Salanti, A. (Ekstern)
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Projects:

**Darwinian Vaccine-Development**

Department of Systems Biology  
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