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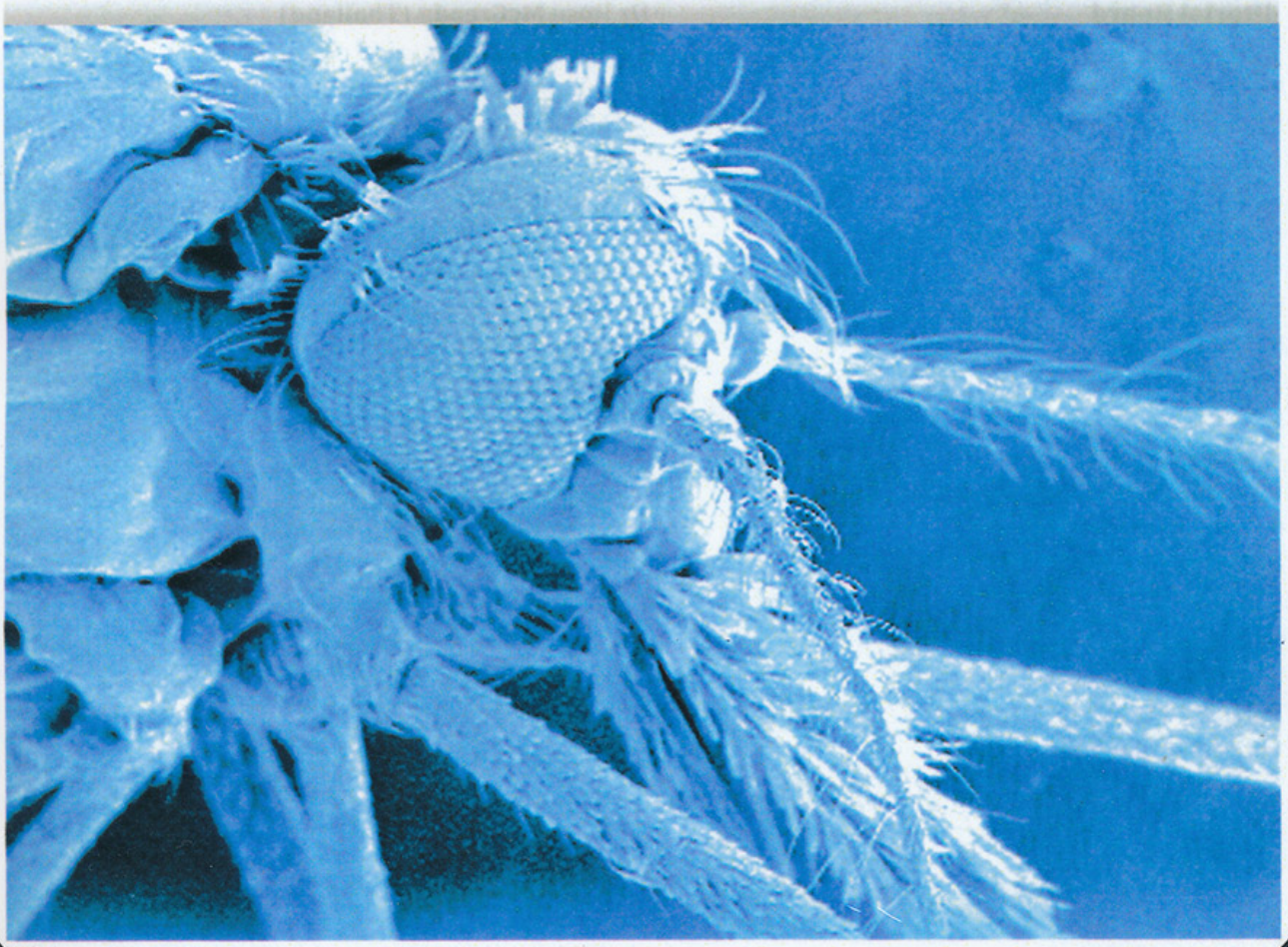

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Diversity of the *var* gene family of Indonesian *Plasmodium falciparum* isolates

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Abstract

Background: The large polymorphic protein PfEMP1 is encoded by the *var* gene family. PfEMP1 has been shown to play an important role as cytoadherence ligand on the surface of infected erythrocytes and thereby contributes to the distinct pathogenesis of malaria. The study explored the diversity of the DBL1α and DBL2β-C2 domains of the protein from Indonesian *Plasmodium falciparum* field isolates.

Methods: Samples of patients with severe and uncomplicated malaria from two different malaria-endemic areas in Indonesia were collected and DNA directly extracted. Dried blood on filter paper was prepared for RNA extraction. PCR amplicons were either cloned and subsequently sequenced or directly sequenced for analysis on nucleotide and amino acid level. Recently published as well as self-designed primers were used for amplification.

Results: Blood from eight patients was finally used for analysis. Seventy-one different sequences out of over 500 DBL1α sequenced clones were observed, resulting in an average of 8.9 different DBL1α sequences per isolate. The average DBL1α sequence similarity within isolates was similar to between isolates. Phylogenetic analysis demonstrated no clustering of sequences regarding strain or geographical origin. The DBL1α sequences were analysed by distribution of semi-conserved features (cysteine/PoLV1-4 grouping) and classified into six sequence groups. The DBL1α cys2 type was observed in all expressed sequences *in vivo*. Expression of certain DBL sequences implied potential involvement in the pathogenesis. As expected, the DBL2β-C2 domains showed high to moderate homology among each other.

Conclusion: The DBL1α domains of PfEMP1 from clinical Indonesian isolates showed high divergence among same isolates and some similarities with other Asia-Pacific strains. Further investigations of important *var* gene domains with a larger sample size are required to confirm with statistical significance observed associations with severe malaria in Indonesian samples.

Keywords: *Plasmodium falciparum*, *var* gene, PfEMP1, ICAM-1

Background

During the erythrocytic cycle, *Plasmodium falciparum* expresses a protein which is exported from the parasite to the surface of the infected erythrocyte (IE) approximately 18 hours post invasion, called *P. falciparum* erythrocyte membrane protein 1 (PfEMP1). This protein has been linked to two key phenomena responsible for the pathology associated with *P. falciparum* infection: cytoadherence of IE and antigenic variation with consequent immune evasion in the host [1-3]. PfEMP1 is a large and polymorphic protein that varies in domain composition and binding specificity. It is encoded by the highly diverse *var* gene family consisting of approximately 60 variable genes per haploid genome of the parasite. Based on chromosomal location, sequence and promoter sequence, the *var* genes are separated into three major groups (A, B, and C) [4].

Despite their diversity, the majority of *var* genes contain a number of conserved motifs. Each *var* gene potentially encodes between two to seven Duffy-binding like (DBL), and cysteine-rich interdomain regions (CIDR). Based on the consensus motifs, DBL domains have been classified into six types; α, β, γ, δ, ε, and x [5]. Specific combinations of domain subtypes are described as short tandem domain cassettes (DC). Rask *et al.* classified the PfEMP1 protein

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