

Extreme geographical fixation of variation in the *Plasmodium falciparum* gamete surface protein gene *Pfs48/45* compared with microsatellite loci

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Abstract

Comparing patterns of genetic variation at multiple loci in the genome of a species can potentially identify loci which are under selection. The large number of polymorphic microsatellites in the malaria parasite *Plasmodium falciparum* are available markers to screen for selectively important loci. The *Pfs48/45* gene on Chromosome 13 encodes an antigenic protein located on the surface of parasite gametes, which is a candidate for a transmission blocking vaccine. Here, genotypic data from 255 *P. falciparum* isolates are presented, which show that alleles and haplotypes of five single nucleotide polymorphisms (SNPs) in the *Pfs48/45* gene are exceptionally skewed in frequency among different *P. falciparum* populations, compared with alleles at 11 microsatellite loci sampled widely from the parasite genome. Fixation indices measuring inter-population variance in allele frequencies (F_{ST}) were in the order of four to seven times higher for *Pfs48/45* than for the microsatellites, whether considered (i) among populations within Africa, or (ii) among different continents. Differing mutational processes at microsatellite and SNP loci could generally affect the population structure at these different types of loci, to an unknown extent which deserves further investigation. The highly contrasting population structure may also suggest divergent selection on the amino acid sequence of *Pfs48/45* in different populations, which plausibly indicates a role for the protein in determining gamete recognition and compatibility. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

A high density of informative microsatellite markers on all 14 chromosomes of the protozoan malaria parasite *Plasmodium falciparum* [1] should help studies to identify functionally important loci in the genome [2]. One approach is to identify loci with extreme statistical distributions of allele frequencies among populations. Exceptionally skewed frequency distributions may be

caused by directional selection for favoured alleles, whereas unusually even frequencies may be due to balancing selection maintaining different alleles [3,4]. Several asexual blood stage antigens of *P. falciparum* are apparently under selection which maintains allelic variation [5–9], and a detailed study of polymorphisms in the merozoite surface protein 1 gene (*msp1*) has prospectively identified a domain encoding a target of allele-specific protective immune responses [10].

In contrast to many antigens of the *P. falciparum* asexual blood stages, there is a relatively low level of sequence polymorphism in antigens of sexual gametocyte and gamete stages of the parasite. A major surface antigen of these stages is the protein *Pfs48/45* [11], which has an unusual predicted disulphide bond-depen-

Abbreviations: SMM, stepwise mutation model; SNP, single nucleotide polymorphism.

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