

Population genetic structure and natural selection of *Plasmodium falciparum* apical membrane antigen-1 in Myanmar isolates.

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Abstract

BACKGROUND: *Plasmodium falciparum* apical membrane antigen-1 (PfAMA-1) is one of leading blood stage malaria vaccine candidates. However, genetic variation and antigenic diversity identified in global PfAMA-1 are major hurdles in the development of an effective vaccine based on this antigen. In this study, genetic structure and the effect of natural selection of PfAMA-1 among Myanmar *P. falciparum* isolates were analysed.

METHODS: Blood samples were collected from 58 Myanmar patients with *falciparum* malaria. Full-length PfAMA-1 gene was amplified by polymerase chain reaction and cloned into a TA cloning vector. PfAMA-1 sequence of each isolate was sequenced. Polymorphic characteristics and effect of natural selection were analysed with using DNASTAR, MEGA4, and DnaSP programs. Polymorphic nature and natural selection in 459 global PfAMA-1 were also analysed.

RESULTS: Thirty-seven different haplotypes of PfAMA-1 were identified in 58 Myanmar *P. falciparum* isolates. Most amino acid changes identified in Myanmar PfAMA-1 were found in domains I and III. Overall patterns of amino acid changes in Myanmar PfAMA-1 were similar to those in global PfAMA-1. However, frequencies of amino acid changes differed by country. Novel amino acid changes in Myanmar PfAMA-1 were also identified. Evidences for natural selection and recombination event were observed in global PfAMA-1. Among 51 commonly identified amino acid changes in global PfAMA-1 sequences, 43 were found in predicted RBC-binding sites, B-cell epitomes, or IUR regions.

CONCLUSIONS: Myanmar PfAMA-1 showed similar patterns of nucleotide diversity and amino acid polymorphisms compared to those of global PfAMA-1. Balancing natural selection and iatrogenic recombination across PfAMA-1 are likely to play major roles in generating genetic diversity in global PfAMA-1. Most common amino acid changes in global PfAMA-1 were located in predicted B-cell epitomes where high levels of nucleotide diversity and balancing natural selection were found. These results highlight the strong selective pressure of host immunity on the PfAMA-1 gene. These results have significant implications in understanding the nature of Myanmar PfAMA-1 along with global PfAMA-1. They also provide useful information for the development of effective malaria vaccine based on this antigen.

KEYWORDS: Apical membrane antigen-1; Genetic diversity; Myanmar; Natural selection; *Plasmodium falciparum*