

Genetic polymorphism and natural selection of circumsporozoite surface protein in *Plasmodium falciparum* field isolates from Myanmar.

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Abstract

BACKGROUND: *Plasmodium falciparum* circumsporozoite protein (PfCSP) is one of the most extensively studied malaria vaccine candidates, but the genetic polymorphism of PfCSP within and among the global *P. falciparum* population raises concerns regarding the efficacy of a PfCSP-based vaccine efficacy. In this study, genetic diversity and natural selection of PfCSP in Myanmar as well as global *P. falciparum* were comprehensively analysed.

METHODS: Blood samples were collected from 51 *P. falciparum* infected Myanmar patients. Fifty-one full-length PfCSP genes were amplified from the blood samples through a nested polymerase chain reaction, cloned into a TA cloning vector, and then sequenced. Polymorphic characteristics and natural selection of Myanmar PfCSP were analysed using the DNASTAR, MEGA6, and DnaSP programs. Polymorphic diversity and natural selection in publicly available global PfCSP were also analysed.

RESULTS: The N-terminal and C-terminal non-repeat regions of Myanmar PfCSP showed limited genetic variations. A comparative analysis of the two regions in global PfCSP displayed similar patterns of low genetic diversity in global population, but substantial geographic differentiation was also observed. The most notable polymorphisms identified in the N-terminal region of global PfCSP were A98G and 19-amino acid length insertion in global population with different frequencies. Major polymorphic characters in the C-terminal region of Myanmar and global PfCSP were found in the Th2R and Th3R regions, where natural selection and recombination occurred. The central repeat region of Myanmar PfCSP was highly polymorphic, with differing numbers of repetitive repeat sequences NANP and NVDP. The numbers of the NANP repeats varied among global PfCSP, with the highest number of repeats seen in Asian and Oceanian PfCSP. Haplotype network analysis of global PfCSP revealed that global PfCSP clustered into 103 different haplotypes with geographically-separated populations.

CONCLUSION: Myanmar and global PfCSP displayed genetic diversity. N-terminal and C-terminal non-repeat regions were relatively conserved, but the central repeat region displayed high levels of genetic polymorphism in Myanmar and global PfCSP. The observed geographic pattern of genetic differentiation and the points of evidence for natural selection and recombination suggest that the functional consequences of the polymorphism should be considered for developing a vaccine based on PfCSP.

KEYWORDS: Circumsporozoite protein; Genetic polymorphism; Myanmar; Natural selection; *Plasmodium falciparum*

