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# Genetic polymorphism and natural selection in the C-terminal 42 kDa region of merozoite surface protein-1 (MSP-1) among *Plasmodium knowlesi* samples from Malaysia

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## Abstract

**Background:** The merozoite surface protein-1 (MSP-1) gene encodes for a leading malaria vaccine candidate antigen. However, its extensive polymorphic nature represents a major obstacle to the development of a protective vaccine. Previously, a pilot study was carried out to explore the sequence variation of the C-terminal 42 kDa fragment within *P. knowlesi* MSP-1 gene (PkMSP-1<sub>42</sub>) based on 12 clinical samples; however, further study on an adequate sample size is vital in estimating the genetic diversity of the parasite population.

**Methods:** In the present study, we included a larger sample size of *P. knowlesi* (83 samples) covering eight states of Malaysia to determine the genetic polymorphism, natural selection and haplotype groups of the gene fragment coding PkMSP-1<sub>42</sub>. The region flanking PkMSP-1<sub>42</sub> was amplified by PCR and directly sequenced. Genetic diversity, haplotype diversity, population genetic differentiation and natural selection were determined in order to study the polymorphic characteristic of PkMSP-1<sub>42</sub>.

**Results:** A high level of genetic diversity ( $Hd = 0.970 \pm 0.007$ ;  $\pi = 0.01079 \pm 0.00033$ ) was observed among the 83 *P. knowlesi* samples, confirming the extensive genetic polymorphism exhibited among the *P. knowlesi* population found in Malaysia. A total of 18 distinct haplotypes with 17 amino acid changes were identified, whereby 15 were new haplotypes. High population differentiation values were observed within samples from Peninsular Malaysia and Malaysian Borneo. The 42 kDa fragments of *P. knowlesi* from Malaysian Borneo were found to be acting on balancing selection whilst purifying selection was suggested to act on isolates from Peninsular Malaysia. The separation of PkMSP-1<sub>42</sub> haplotypes into two main groups based on geographical separation has further supported the existence of two distinct *P. knowlesi* lineages.

**Conclusions:** A high level of genetic diversity was observed among PkMSP-1<sub>42</sub> in Malaysia, whereby most of the polymorphisms were found within the 33 kDa region. Taken together, these data will be useful in order to understand the nature of *P. knowlesi* population in Malaysia as well as the design and development of a MSP-1<sub>42</sub> based knowlesi malaria vaccine.

**Keywords:** *Plasmodium knowlesi*, Malaysia, Merozoite surface protein, Genetic polymorphism, Natural selection

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