Evolutionary insights into Kelch13 and its relationships with artemisinin resistance in Plasmodium falciparum malaria parasites

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Résumé

Multiple *kelch13* mutant alleles conferring artemisinin resistance (ART-R) were identified in Southeast Asian *Plasmodium falciparum* malaria populations, resulting in amino acid replacements that cluster in the propeller domain. It is suggested that varying fitness costs could be associated with these mutations. Here, we investigated this hypothesis by analyzing the pattern of selection acting on *kelch13* along the protein-coding DNA sequence and across the *kelch13* phylogenic tree built for 34 *Apicomplexa* species – including 16 *Plasmodium* species. Using the Phylogenetic Analysis by Maximum Likelihood (PAML) method, we estimated the non-synonymous (dN) to synonymous (dS) substitution rate ratio ω as a proxy of the long-term fitness cost. First, we found that *kelch13* has been exposed to a very high level of purifying selection throughout *Apicomplexa* and *Plasmodium* evolution. Second, positions in and around the first β-strand in the propeller domain are predominantly associated with both relaxed purifying selection and ART-R mutations. The position 580 exhibits a relatively low fitness cost, consistent with the hypothesis that *pfkelch13* C580Y mutant parasites could be fitter than other *pfkelch13* mutants. This would provide a simple explanation for the wide success of the *pfkelch13* C580Y mutant lineage in some Asian areas.

Mots-Clés: Plasmodium, falciparum, artemisinin, kelch13, resistance, evolution, selection

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