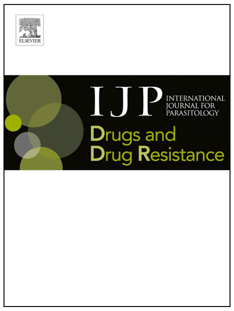

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The prevalence of molecular markers of drug resistance in *Plasmodium vivax* from the Border Regions of Thailand in 2008 and 2014

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Abstract

The prevalence of *Plasmodium vivax* is increasing in the border regions of Thailand; one potential problem confounding the control of malaria in these regions is the emergence and spread of drug resistance. The aim of this study was to determine the genetic diversity in genes potentially linked to drug resistance in *P. vivax* parasites isolated from four different border regions of Thailand; Thai-Myanmar (Tak, Mae Hong Son and Prachuap Khiri Khan Provinces), and Thai-Cambodian borders (Chanthaburi Province). Isolates were collected from 345 *P. vivax* patients in 2008 and 2014, and parasite DNA extracted and subjected to nucleotide sequencing at five putative drug-resistance loci (*Pvdhfr*, *Pvdhps*, *Pvmdr1*, *Pvcrt-o* and *Pvk12*). The prevalence of mutations in *Pvdhfr*, *Pvdhps* and *Pvmdr1* were markedly different between the Thai-Myanmar and Thai-Cambodian border areas and also varied between sampling times. All isolates carried the *Pvdhfr* (58R and 117N/T) mutation, however, whereas the quadruple mutant allele ($\underline{\mathbf{I}}_{57}\underline{\mathbf{R}}_{58}\underline{\mathbf{M}}_{61}\underline{\mathbf{T}}_{117}$) was the most prevalent (69.6%) in the Thai-Myanmar border region, the double mutant allele ($F_{57}\underline{\mathbf{R}}_{58}T_{61}\mathbf{N}_{117}$) was at fixation on the Thai-Cambodian border (100%). The most prevalent genotypes of *Pvdhps* and *Pvmdr1* were the double mutant ($S_{382}\underline{\mathbf{G}}_{383}K_{512}\underline{\mathbf{G}}_{553}$) (65.1%) and single mutant ($\underline{\mathbf{M}}_{958}Y_{976}F_{1076}$) (46.5%) alleles, respectively on the Thai-Myanmar border while the single *Pvdhps* mutant ($S_{382}\underline{\mathbf{G}}_{383}K_{512}A_{553}$) (52.7%) and the triple *Pvmdr1* mutant ($\underline{\mathbf{M}}_{958}\underline{\mathbf{F}}_{976}\underline{\mathbf{L}}_{1076}$) (81%) alleles were dominant on the Thai-Cambodian border. No mutations were observed in the *Pvcrt-o* gene in either region. Novel mutations in the *Pvk12* gene, the *P. vivax* orthologue of *PfK13*, linked to artemisinin resistance in *Plasmodium falciparum*, were observed with three nonsynonymous and three synonymous mutations in six isolates (3.3%).

Keywords: *Plasmodium vivax*, Antimalarial drugs, Drug-resistant mutations, Genetic diversity