When Standard Therapy Fails: *CYP2D6* Pharmacogenetics and *Plasmodium vivax* Relapse from the Brazil–French Guiana Border

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The therapeutic response to *Plasmodium vivax* malaria may be influenced by host pharmacogenetic factors, particularly polymorphisms in the *CYP2D6* gene that impair chloroquine/primaquine bioactivation. Here, we report a case series describing clinical outcomes and *CYP2D6**2, *4, and *10 polymorphisms genotypes in individuals with *P. vivax* malaria. This study was conducted in 2025 in Oiapoque, State of Amapá, Brazil–French Guiana border. Fifty individuals with *P. vivax* monoinfection confirmed by thick blood smear and qPCR were included. All patients were treated according to Brazilian Ministry of Health guidelines, receiving chloroquine (total dose of 25 mg/kg over 3 days) combined with primaquine (total dose of 3.5 mg/kg over 7 days). Clinical and parasitological follow-up was performed on days 0, 7, 14, 21, and 28. During the 28-day

follow-up, 34 individuals achieved parasitological cure, whereas 16 experienced *P. vivax* relapse, with nine relapses occurring on day 14 and seven on day 21. In all relapse cases, parasite reappearance was first detected by qPCR, while thick blood smears were initially negative and became positive upon reassessment the following day, indicating low parasitemia at relapse onset. Following relapse confirmation, patients were retreated according to Brazilian national guidelines for *P. vivax* relapse. Combined analysis of *CYP2D6**2, *CYP2D6**4, and *CYP2D6**10 polymorphisms allowed the inference of predicted CYP2D6 metabolic phenotypes. Thirty-nine individuals were classified as a normal metabolizer, and 11 as poor metabolizers. Notably, all relapsing individuals exhibited genotypes compatible with reduced or absent CYP2D6 activity. The specific multilocus genotype combinations observed among relapsing cases were CG/CC/AA, GG/TT/GG, and CG/CC/AG for *CYP2D6**2/*4/*10, respectively. These findings support a role for *CYP2D6* genetic variability in *P. vivax* treatment and highlight *CYP2D6* multi-polymorphisms profiling as a potential biomarker of therapeutic failure.

Keywords: Health Surveillance. Malaria relapse. Pharmacogenomics. Therapeutic failure.