ABSTRACT

In combination with antibiotics, quinine is recommended as the second-line treatment for uncomplicated malaria, alternative first-line treatment for severe malaria and for treatment of malaria in the first trimester of pregnancy. Quinine has been shown to have frequent clinical failures and yet the mechanisms of action and resistance are not been fully elucidated. However, resistance is linked to polymorphisms in multiple genes including multidrug resistance 1 (Pfmdr1), chloroquine-resistance transporter (Pfcrt) and the sodium/hydrogen exchanger gene (Pfnhe1). Here, we investigated the association between in vitro quinine susceptibility with genetic polymorphisms in Pfmdr1 codons 86 and 184, Pfcrt codon 76, and Pfnhe1 ms4760 in 88 field isolates from western Kenya. In vitro activity was assessed as the drug concentration that inhibits 50% of parasite growth (IC$_{50}$) and parasite genetic polymorphisms were determined by DNA sequencing. Data revealed there was significant association between polymorphisms in Pfmdr1-86Y, -184F and Pfcrt-76T with quinine susceptibility; all with p < 0.0001. Eighty two percent of parasites resistant to quinine carried mutant alleles at these codons (Pfmdr1-86Y, -184F and Pfcrt-76T) whereas seventy four percent of parasites susceptible to quinine carried the wild type allele (Pfmdr1-N86, -Y184 and Pfcrt-K76). In addition, quinine IC$_{50}$ of parasites with Pfnhe1 ms4760 3 DNNND repeats was significantly higher compared to those with 1 or 2 repeats (p = 0.033 and p = 0.0043 respectively). Clinical efficacy studies are required to confirm the validity of these markers and the importance of parasite genetic background.