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.