

The Role of Pfmdr1 and Pfcr1 in Changing Chloroquine, Amodiaquine, Mefloquine and Lumefantrine Susceptibility in Western-Kenya *P. falciparum* Samples during 2008–2011

Abstract:

Single Nucleotide Polymorphisms (SNPs) in the Pfmdr1, and Pfcr1, genes of Plasmodium falciparum may confer resistance to a number of anti-malaria drugs. Pfmdr1 86Y and haplotypes at Pfcr1 72-76 have been linked to chloroquine (CQ) as well as amodiaquine (AQ) resistance. mefloquine (MQ) and lumefantrine (LU) sensitivities are linked to Pfmdr1 86Y. Additionally, Pfcr1 K76 allele carrying parasites have shown tolerance to LU. We investigated the association between Pfmdr1 86/Pfcr1 72-76 and *P. falciparum* resistance to CQ, AQ, MQ and LU using field samples collected during 2008-2011 from malaria endemic sites in western Kenya. Genomic DNA from these samples was genotyped to examine SNPs and haplotypes in Pfmdr1 and Pfcr1 respectively. Additionally, immediate ex vivo and in vitro drug sensitivity profiles were assessed using the malaria SYBR Green I fluorescence-based assay. We observed a rapid but steady percent increase in wild-type parasites with regard to both Pfmdr1 and Pfcr1 between 2008 and 2011 ($p < 0.0001$). Equally, a significant reciprocal decrease in AQ and CQ median IC₅₀ values occurred ($p < 0.0001$) during the same period. Thus, the data in this study point to a significantly rapid change in parasite response to AQ and CQ in the study period. This may be due to releasing of drug pressure on the parasite from reduced use of AQ in the face of increased Artemisinin (ART) Combination Therapy (ACT) administration following the intervention of the Global Fund in 2008. LU has been shown to select for 76K genotypes, thus the observed increase in 76K genotypes coupled with significant cross resistance between LU and MQ, may herald emergence of tolerance against both drugs in future