Evaluation of human *CYP2C8* genetic variation related to amodiaquine/chloroquine metabolism in children of two areas of Uganda exposed to *Plasmodium falciparum* malaria

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Objectives. Aim of this study was to investigate cytochrome P450 2C8 (*CYP2C8*) poor metaboliser allele frequency in two areas of Uganda with endemic *Plasmodium falciparum* malaria. CYP2C8, a polymorphic enzyme that mainly contributes to the hepatic metabolism of amodiaquine (AQ) and chloroquine (CQ), shows two important genetic variants in African populations: *CYP2C8*2* (rs11572103, 805A/T) is the allele most common in East and West Africans and associated to a poor metaboliser phenotype in subjects carrying at least one copy of the defective allele, and *CYP2C8*3* (rs11572080, 416G>A and rs10509681, 1196A>G), a very defective allele only found in Zanzibar islands (Tanzania).Human genetic variation affecting pharmacokinetic could represent a further cofactor in the spread of drug resistant *P. falciparum* malaria.

Methods. A total of 261 children and adolescents had been enrolled and genotyped for the single nucleotide polymorphisms rs11572103, rs11572080 and rs10509681. Samples were collected during cross-sectional surveys performed in Uganda (Karamoja and Kampala regions). Fingerpick blood samples were spotted on Whatman grade 1 filter papers at the time of the field survey and then air dried before being separately stored in sealed plastic containers. The PCR-RFLP technique was used to discriminate the wild-type from the defective alleles.

Fingerpick blood samples

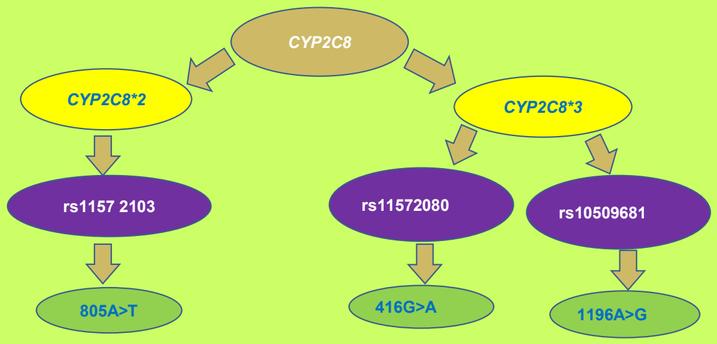
Filter papers

All genotype distributions are in Hardy-Weinberg equilibrium

SNPs	Populations	n	Allelic frequency (± SE)
*CYP2C8*2*	Urban zone (Kampala)	160	0.10 ± 0.02
	Rural zone (Karamoja)	101	0.13 ± 0.03
	Uganda	261	0.10 ± 0.02
*CYP2C8*3*	Urban zone (Kampala)	160	0.00
	Rural zone (Karamoja)	101	0.00
	Uganda	261	0.00

Results. The *CYP2C8*2* allele frequency (± SE) in rural sites of Karamoja region (North-Eastern Uganda) was **0.10 ± 0.02**, while was **0.13 ± 0.03** in the Kampala suburbs (central Uganda). Both the genotype distributions are in Hardy-Weinberg equilibrium, and the allele frequencies are not statistically different (Yates corrected $\chi 2=0.89$, P=0.346). The overall *CYP2C8*2* frequency in all sites was **0.10 ± 0.02**. The allele *CYP2C8*3* was absent for all the populations studied.

Varianti alleliche del gene CYP2C8



Conclusion. Our study confirms that *CYP2C8*2* allele is widespread in Africa and is present at an appreciable frequency also in Uganda, an area of meso-endemic malaria transmission. Moreover, the absence of the *CYP2C8*3* allele is a confirmation that it is a marker of genetic admixture of the Zanzibar population with a Caucasoid component. Antimalarial treatment in Uganda is based on artemisinin combination therapies (ACTs) with artesunate (AS) plus AQ being used as second line ACT. Consequently, the presence of the *CYP2C8*2* allele may be a potential co-factor in the onset of adverse side effects associated with AQ administration. Furthermore, we emphasize the risk related to the presence of *CYP2C8*2* in selecting AQ-resistant strains, since the interplay between host and parasite genetic variation could act as selective co-factor for drug-resistant parasite strains.

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