Risk cofactor in malaria drug resistance selection: frequency of *CYP2C8*2* allele in Uganda

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Introduction and purpose. *Plasmodium falciparum* malaria is one of the leading cause of morbidity and mortality in sub-Saharan Africa and Uganda bears a particularly large burden from this parasitic infection. Unfortunately, drug resistance is a problem in the control of *P. falciparum*, its selection being influenced by several factors such as drug usage, transmission intensity, host immune status and pharmacokinetic. Human genetic variation could represent a further cofactor. All antimalarial drugs are metabolized by hepatic cytochrome P 450 enzymes. In particular, cytochrome P450 2C8 (CYP2C8) contributes to the hepatic metabolism of chloroquine (CQ) and amodiaquine (AQ) (Fig.1). This cytochrome shows a genetic variant (*CYP2C8*2,* rs11572103, A/T) associated with increased adverse side effects. Moreover a recent study found a relationship between the**2* allele (T) and with higher rate of drug-resistant parasites in the infected host. Our aim is to describe *CYP2C8*2* frequency in populations from different areas of Uganda characterised by high levels of malaria transmission intensity (Fig. 2).

Fig. 1 Antimalarial drugs

Fig.2 Sampling areas in Uganda

Methods. The samples analysed in the present study were collected during cross-sectional surveys performed during 2007 in Uganda (Karamoja and Kampala regions) (Fig.2). A total of 261 children and adolescents had been enrolled and genotyped for the polymorphism rs11572103 (A/T). The PCR-RFLP technique was used to discriminate the wild-type (A) from the defective allele (T).

Results. The *CYP2C8*2* allele (T) frequency (± SE) in rural sites of Karamoja region (North-Eastern Uganda) was **0.1 ± 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 between zones (Yates corrected $\chi2=0.89$, P=0.346). The overall *CYP2C8*2* frequency in all sites was **0.10 ± 0.02**. Genotype frequencies were in Hardy-Weinberg equilibrium ($\chi2=1.52$ P=0.221) (Tab.1).

COUNTRY	REGION	TOWN/VILLAGE	STRUCTURE	N° OF CHILDREN	AT	TT	Fr (T)
	Karamoja (North-Eastern)	Namalu	Namalu Health Centre	101	25	0	0.12
		Kakoliye	Kakoliye Moslem Primary School	40	8	0	0.10
		Rupa	Kidepo Health Centre	19	3	0	0.08
		Nadunget	Kasimeri Primary School	44	3	0	0.03
	Tot			204	39	0	0.1
	Kampala (Central Uganda)		Children Centre, Makindeye	57	13	1	0.13

Tab.1 *CYP2C8* absolute genotype frequency and T allele frequency in the different Ugandan populations

Conclusion. Our study demonstrated that *CYP2C8*2* allele is present at an appreciable frequency in Uganda: one out of five subjects is carrying the defective allele, without statistically significant differences among the localities analysed (Tab.2).
In Uganda the antimalarial policy is based on artemisinin combination therapies (ACTs), one of them being artesunate (AS) plus AQ. Moreover, despite officially banned from the marked, CQ is still used because of low price and accessibility. Consequently, the presence of the *CYP2C8*2* allele may be a potential co-factor in the onset of adverse side effects associated with AQ and CQ administration. Furthermore, we emphasize the risk related to the presence of *CYP2C8*2* in selecting drug-resistant strains (Fig.3).

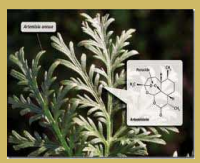

Fig.3 *Artemisia annua*

Country		*CYP2C8* (rs11572103, A>T) frequencies			
		Relative and (absolute) genotype frequencies			Allele frequency ± SE
		AA	AT	TT	T
Uganda (U)	261	0.8 (208)	0.2 (52)	0.004 (1)	0.10 ± 0.02

Tab.2 *CYP2C8* frequencies in general Ugandan populations

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