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Clinical probe of Cyp2C8*2 mutants in a malaria hyperendemic zone: Evidence from North-Central Nigeria



Olalere Shittu^{1*}, Olufunke Adenike Opeyemi¹, Olumuyiwa Babagbemi Omotesho², Oluwatosin Fakayode³,
Nnaemeka Asogwa⁴, Opeyemi Margaret Adeniyi¹, Ifeoluwa Margaret Fatoba¹, Kayode Muritala Salawu⁵, Olusola Ajibaye⁶, Iyiola
Akeem Oluyinka⁸, Olarewaju Abdulkareem Babamale¹, Olusola Isaac Aremu⁷

Affiliation

1. Parasitology Unit, Department of Zoology, University of Ilorin, Ilorin, Nigeria. 2. Unilorin Clinic, University of Ilorin, Ilorin, Nigeria. 3. Children Specialist Hospital, Centre Igboro, Ilorin, Nigeria. 4. Department of Biochemistry, University of Ilorin, Ilorin, Nigeria. 5. Department of Pharmacognosy and Drug Development, University of Ilorin, Ilorin, Nigeria. 6. Biochemistry Division, Nigerian Institute of Medical Research, Lagos, Nigeria. 7. Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmaceutical Sciences, University of Ilorin, Ilorin, Nigeria. 8. Cell Biology and Genetics Unit, Department of Zoology, University of Ilorin, Ilorin, Nigeria.

*Correspondence email: shittu.o@unilorin.edu.ng, eternity403@yahoo.com, Tel.: +2348033819041

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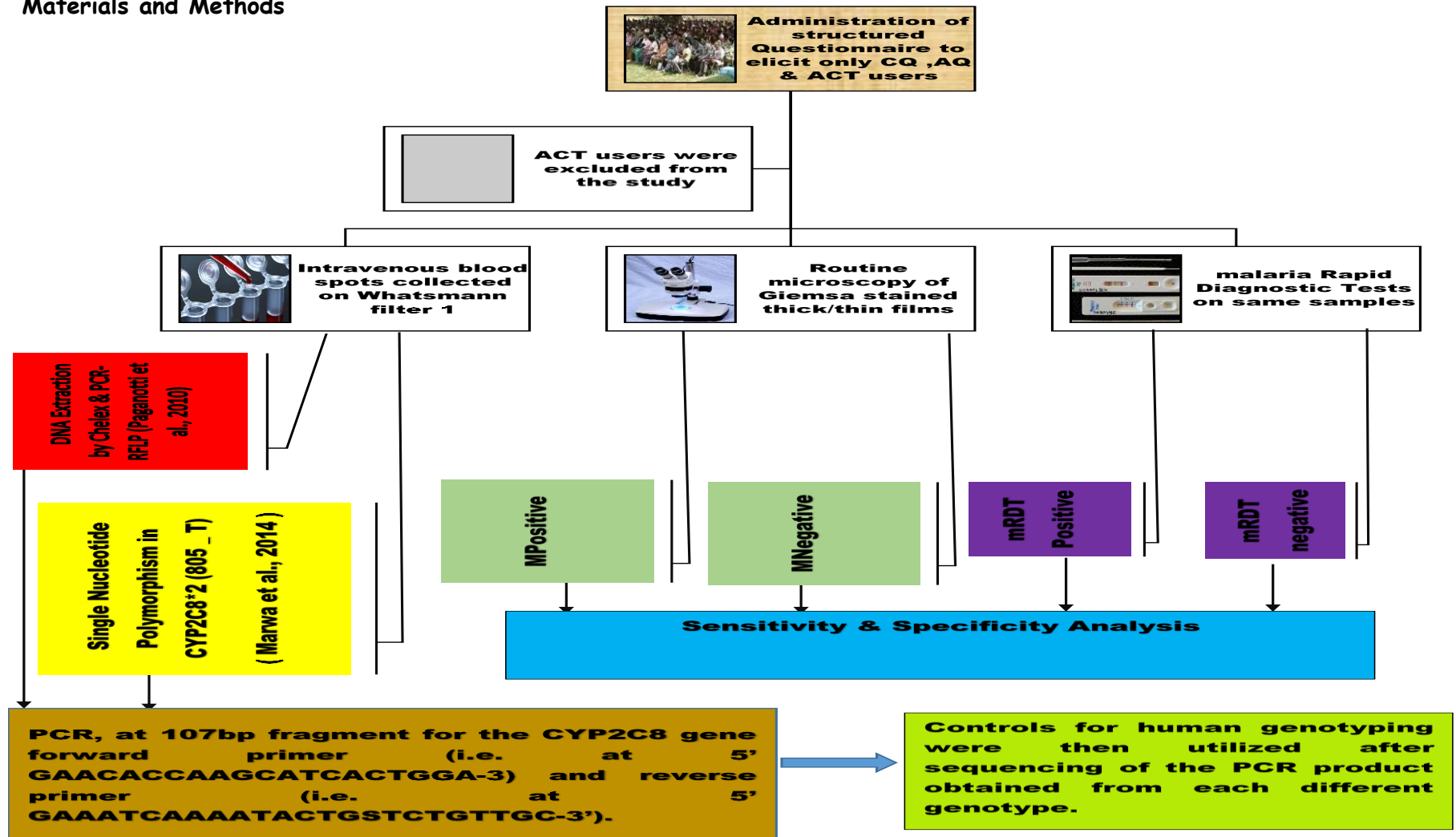
25th April 2019

Background

- Infections arising as a result of *Plasmodium falciparum* is the major cause of malaria-related deaths across sub-Saharan Africa.
- Despite wide documented chloroquine (CQ) and Amodiaquine (AQ) resistance; Africans still rely on therapeutic CQ and AQ-ART medications.
- The increasing failure of these drugs against falciparum malaria constitutes a notable setback in the global malaria elimination efforts.
- The emerging mutations with respect to the drug metabolizer "cytochrome P450 (CYP) 2C8 (CYP2C8)" is a prominent risk factor for the resistant strain of *P. falciparum* in Africa.

- Recent studies further revealed that drug resistant strains are often characterized with the genetic defective variant (CYP2C8*2).
- With the aforementioned, we investigated and determined the occurrence and allele frequencies of CYP2C8*2 amongst residents in malaria high transmission zone of North-Central Nigeria.

Materials and Methods



Results

Table 1: Characteristics of samples taken for CYP2C8*2 analysis.

Factor	No examined (%)	Allele frequency (%)		p-value
		Mutants	Wild Type	
Total no examined	385	75 (19.5)	310 (80.5)	
Gender				0.814
Male	175 (45.5)	35 (46.7)	140 (45.2)	
Female	210 (54.5)	40 (53.3)	170 (54.8)	
Age group				0.003
0-5	100 (26.0)	20 (26.7)	80 (25.8)	
6-15	90 (23.4)	10 (13.3)	80 (25.8)	
16-25	50 (13.0)	20 (26.7)	30 (9.7)	
26-35	35 (9.1)	5 (6.7)	30 (9.7)	
36-45	60 (15.6)	10 (13.3)	50 (16.1)	
>45	50 (13.0)	10 (13.3)	40 (12.9)	
Ethnic group				0.102
Yoruba	195 (50.6)	45 (60.0)	150 (48.4)	
Hausa	40 (10.4)	10 (13.3)	30 (9.7%)	
Igbo	45 (11.7)	5 (6.7)	40 (12.9)	
Others*	105 (29.9)	15 (20.0)	90 (29.0)	

*Idoma (30, 7.8%), Fulani (10, 2.6%), Nupe (40, 10.4%), Igala (10, 2.6%) and Benue/Igede (15, 3.9%).

Table 2: Genotypes for CYP2C8*2 and T allele frequency among the studied Ethnic groups

CYP2C8*2 (rs11572103, A > T)					
Ethnic groups	Genotype frequencies				Allele frequency
	N	AA	AT	TT	T
Yoruba	195	0.862	0.133	0.005	1 in 8
Hausa	40	0.709	0.266	0.025	1 in 4
Igbo	45	0.724	0.254	0.022	1 in 4
Others*	105	0.814	0.176	0.010	1 in 6

Idoma (30, 7.8%), Fulani (10, 2.6%), Nupe (40, 10.4%), Igala (10, 2.6%) and Benue/Igede (15, 3.9%). AA – homozygous wild-type; AT – heterozygous carrier; TT – homozygous mutant; T – Phenotype

Discussion

- Investigation on defective CYP2C8*2 is essential to evaluate emergence of antimalarial drug resistance markers in *P. falciparum* populations among the three major Nigerian ethnic groups.
- In this study, a non-negligible frequency of 19.5% of autosomal recessive CYP2C8*2 mutants was obtained among malaria patients.
- This outcome is similar to the report of Adehin et al., (2016) in South-west Nigeria. However, this study reported a lower prevalence CYP2C8*2 status when compared with several early reports in African populations [Marwa et al., 2014; Paganotti et al., 2010; Bains 2013].
- This suggests that mutations in specific *P.f.* genes may confer resistance to antimalarial drugs, climaxing into sustained drug pressure.

Conclusion

- The current increasing knowledge in genomic revolution is gradually improving our understanding of reasons why individuals and populations differ in their susceptibility to multiple diseases.

- The occurrence of inter-ethnic differences in the frequencies of clinically relevant CYP450 variants is the real reason populations do not maintain the stable allele frequencies predicted by the Hardy-Weinberg equilibrium.
- A remarkable inter-ethnic differences in autosomal recessive CYP2C8*2 allele were observed in this study.
- By implication, there appears to be a gradual incursion of genetic drift for poor CQ and AQ-ART metabolizers among the inhabitants.

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