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CYP2C8 Polymorphisms among malaria patients from Guinea-Bissau

Yvonne Khoo J-Lyn
Supervised by Prof. Dr. Vera Ribeiro
European Joint Master in Water and Coastal Management
Universidade do Algarve
Portugal
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INTRODUCTION

Malaria is one of the major public health problems in more than 90 countries, inhabited by a total of some 2.4 billion people, representing about 40% of the world’s population (WHO, 2004).
Malaria endemic areas
Amodiaquine (AQ) has been recently introduced into artemisinin-based combination therapy for use in malaria control programmes and as a first line treatment for children with uncomplicated malaria (WHO, 2006).
Besides amodiaquine, CYP2C8 also metabolizes several therapeutically important drugs and endogenous substances including:

- paclitaxel
- verapamil
- rosiglitazone
- cerivastatin
- amiodarone
- dapsone
- all-trans-retinoic acid
- arachidonic acid
CYP2C8 is mainly expressed in the liver, as well as in various extrahepatic tissues such as the vascular smooth muscles (Klose et al., 1999; Fleming, 2001).

The main CYP2C8 polymorphisms known code for the amino acid changes I269F, R139K, K399R and I264M.

These SNPs define 3 main non-wild-type alleles: $\text{CYP2C8}^*2$, $\text{CYP2C8}^*3$ and $\text{CYP2C8}^*4$. 
A glance at Guinea-Bissau

Source: travelpod.com
A glance at Guinea-Bissau

Source: travelpod.com
Canchungo hospital, Guinea-Bissau  Source: www.kalpana.it
RESEARCH OBJECTIVES

• To study CYP2C8 alleles among malaria patients from Guinea Bissau

• To assist policy-makers in the management of malaria in Guinea-Bissau

• To generate pharmacogenetic data for the evaluation of treatment and drug dispersion

• To contribute findings to other databases and bio-banks within and outside Europe

• To allow further comparisons with other populations previously characterized in the Center for Molecular and Structural Biomedicine, Universidade do Algarve, Portugal
MATERIALS AND METHODS

Subjects: 91 randomly selected malaria patients from Guinea-Bissau
DNA Extraction

Polymerase Chain Reaction (PCR)

Restricted Fragment Length Polymorphism (RFLP)

Statistical Analysis

Allelic frequencies determined - PM alleles? EM alleles? etc
RESULTS

Lane 1: φX174 DNA/HinfI Marker; Lane 2: Homozygous mutant for the CYP2C8*2 allele; Lane 3, 5, 6: Homozygous wild-type for the CYP2C8*2 allele; Lane 4: Heterozygous for CYP2C8*2 allele; Lanes 7 to 11: Homozygous wild-type bands for the CYP2C8*4 variant; Lane 12: PCR amplicon used to generate the RFLPs
RESULTS

CYP2C8 allele frequencies obtained:

CYP2C8*2 = 0.2418

CYP2C8*3 = 0.3242

CYP2C8*4 = not detected
Distribution of CYP2C8 genotypes among GB subjects

- *1/*1: 18
- *1/*2: 20
- *1/*3: 32
- *2/*3: 4
- *3/*3: 1
DISCUSSION

- Comparison of **CYP2C8 genotypes** with other populations
- Comparison of **CYP2C8 allele frequencies** with other populations
- Comparison of **CYP2C8 allele frequencies** between malaria patients from GB and Zanzibar
Comparison of CYP2C8 allele frequencies between malaria patients from Guinea-Bissau and Zanzibar

- Higher prevalence of the CYP2C8*3 allele in West Africa

Comparison with Asian and Oceanic CYP2C8 allele frequencies

- Significant differences not detected
CYP2C8 genotype comparison with 5 other populations
Comparison of CYP2C8 allele frequencies with other populations

[Graph showing comparative allele frequencies across different populations, with Guinea-Bissau highlighted.]
CONCLUSION

• Highest frequency of CYP2C8 variant alleles ever recorded in a population of African descent.

• High occurrence of CYP2C8*2 and CYP2C8*3 alleles among malaria patients in Guinea-Bissau.

• This implies a high incidence of CYP2C8 poor metabolizer alleles among malaria patients in Guinea-Bissau who may be at a greater risk of adverse effects compared to other populations previously characterized.
FUTURE RECOMMENDATIONS

- Further investigation taking into account the effects of CYP2C8 metabolism on the pharmacokinetics of antimalarials
- Study of polymorphisms in healthy subjects
BIBLIOGRAPHY


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*Mu**to obrigada*