Education and Culture

Erasmus Mundus

CYP2C8 Polymorphisms among malaria patients from Guinea-Bissau

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CBME

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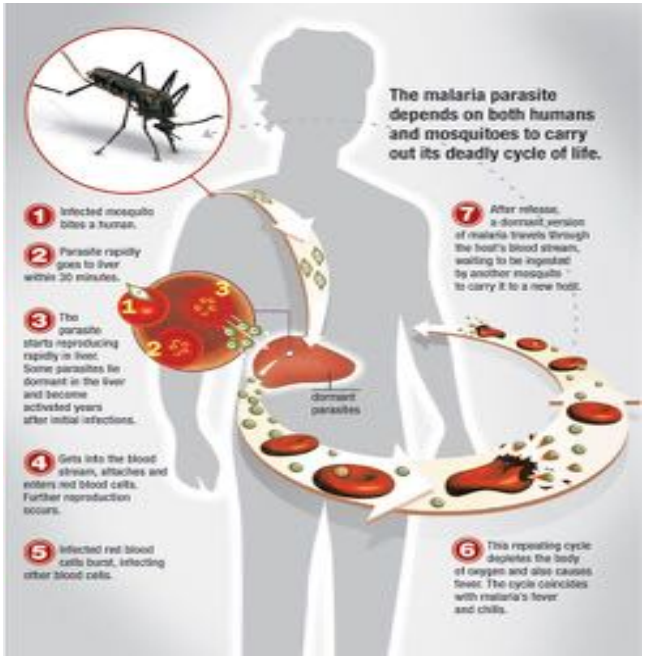
CONTENTS

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).

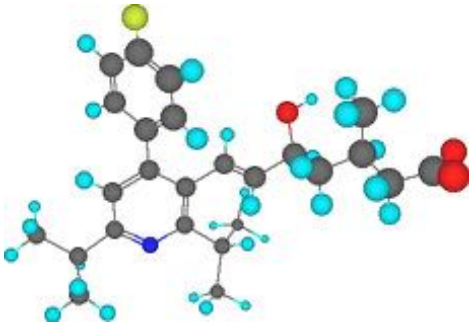


Malaria endemic areas

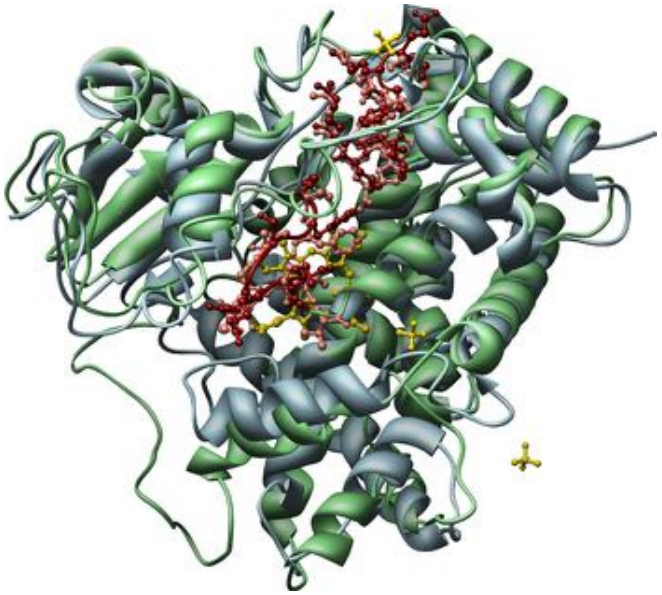
Amodiaquine (AQ) has been recently introduced into artemisinin-based combination therapy for use in malaria control programmes and as a first line treatment for children with uncomplicated malaria (WHO, 2006).

Amodiaquine (AQ) —*CYP2C8*→ N-desethylamodiaquine (DEAQ)

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: *CYP2C8**2**, *CYP2C8**3** and *CYP2C8**4**.

A glance at Guinea-Bissau

Source: travelpod.com

A glance at Guinea-Bissau

Source: travelpod.com

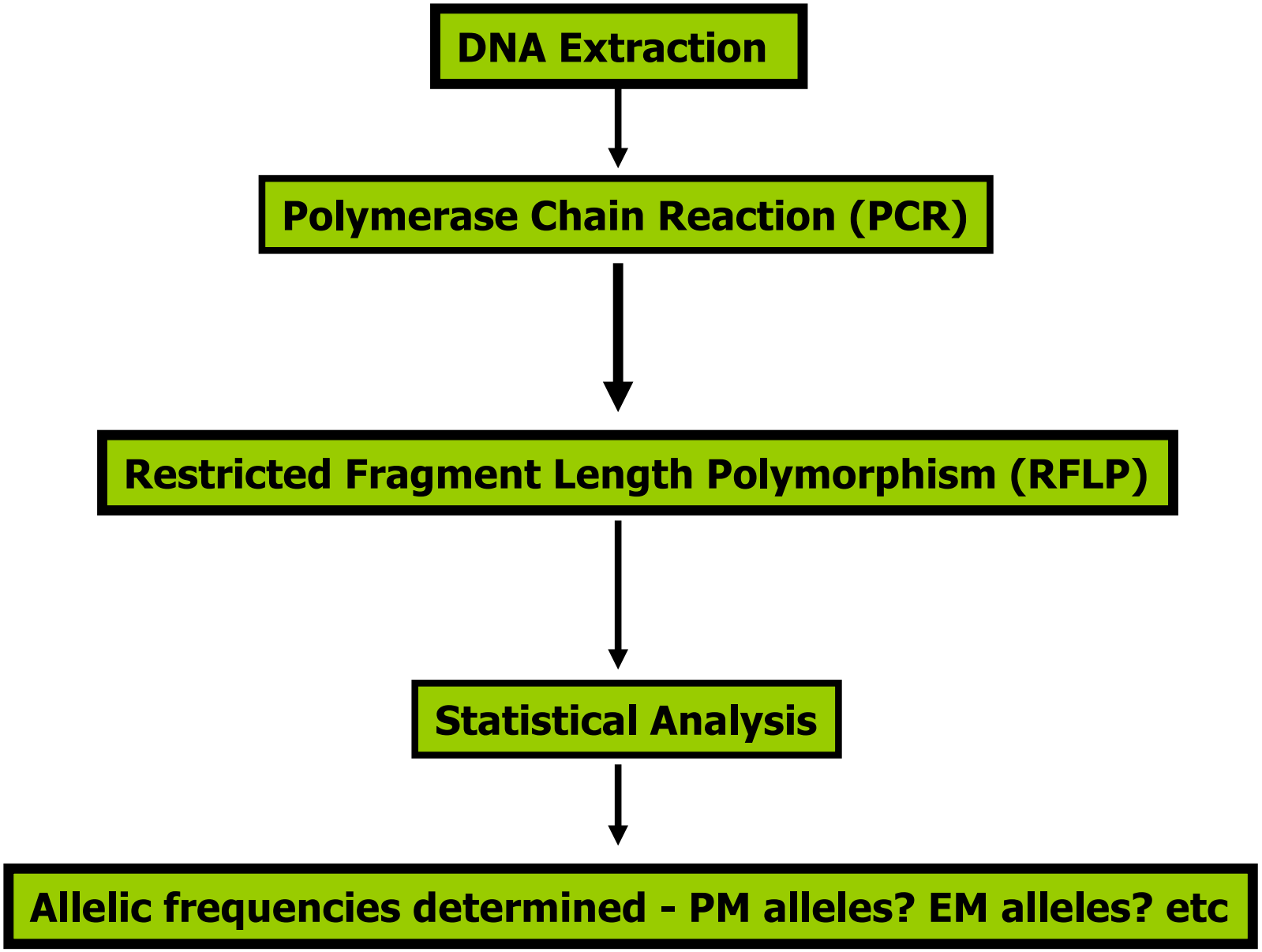
Canchungo hospital, Guinea-Bissau Source: www.kalpana.it

RESEARCH OBJECTIVES

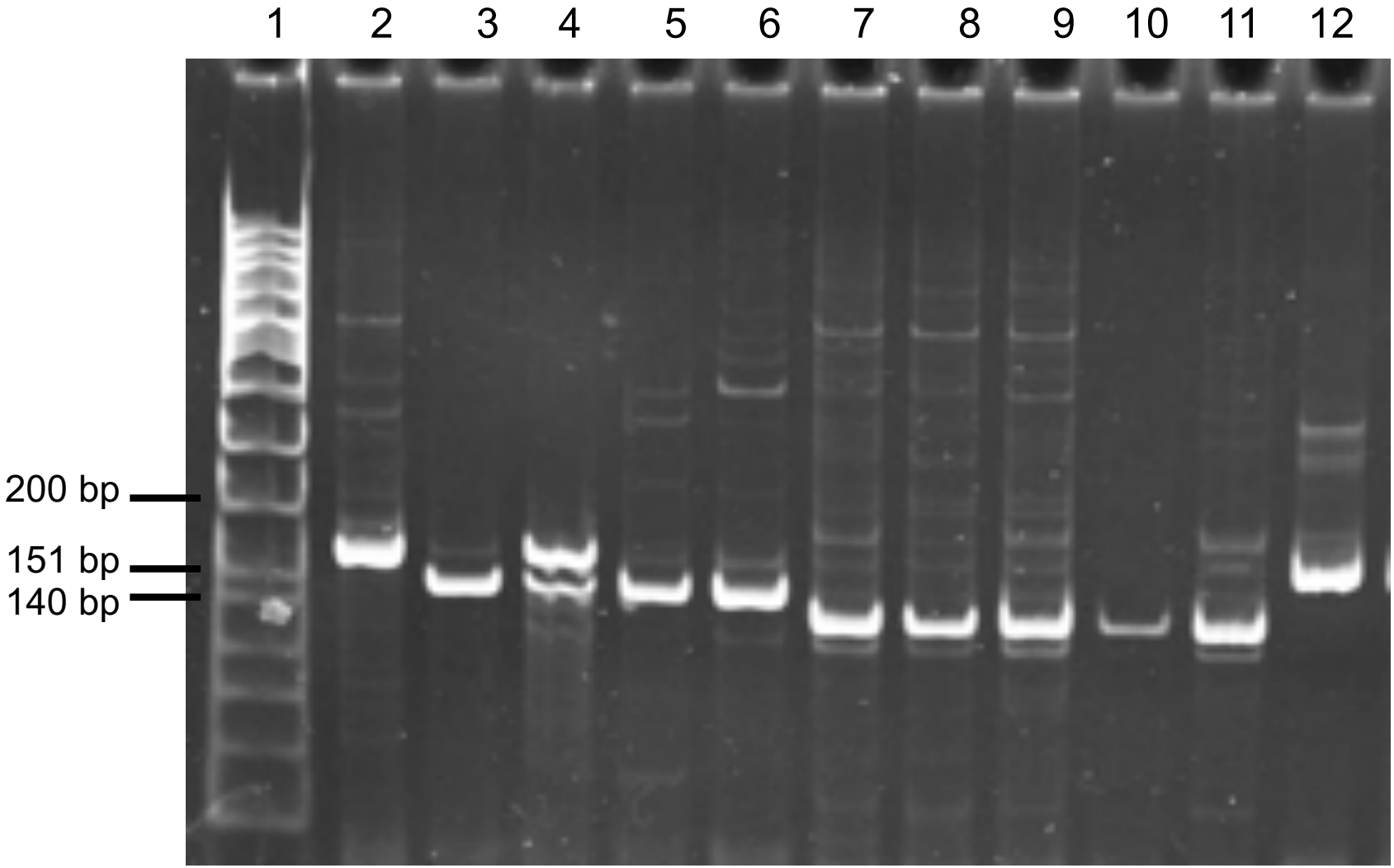
- To **study *CYP2C8* alleles** among malaria patients from Guinea Bissau
- To **assist policy-makers** in the management of malaria in Guinea-Bissau
- To **generate pharmacogenetic data** for the evaluation of treatment and drug dispension
- To **contribute findings** to other databases and bio-banks 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 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

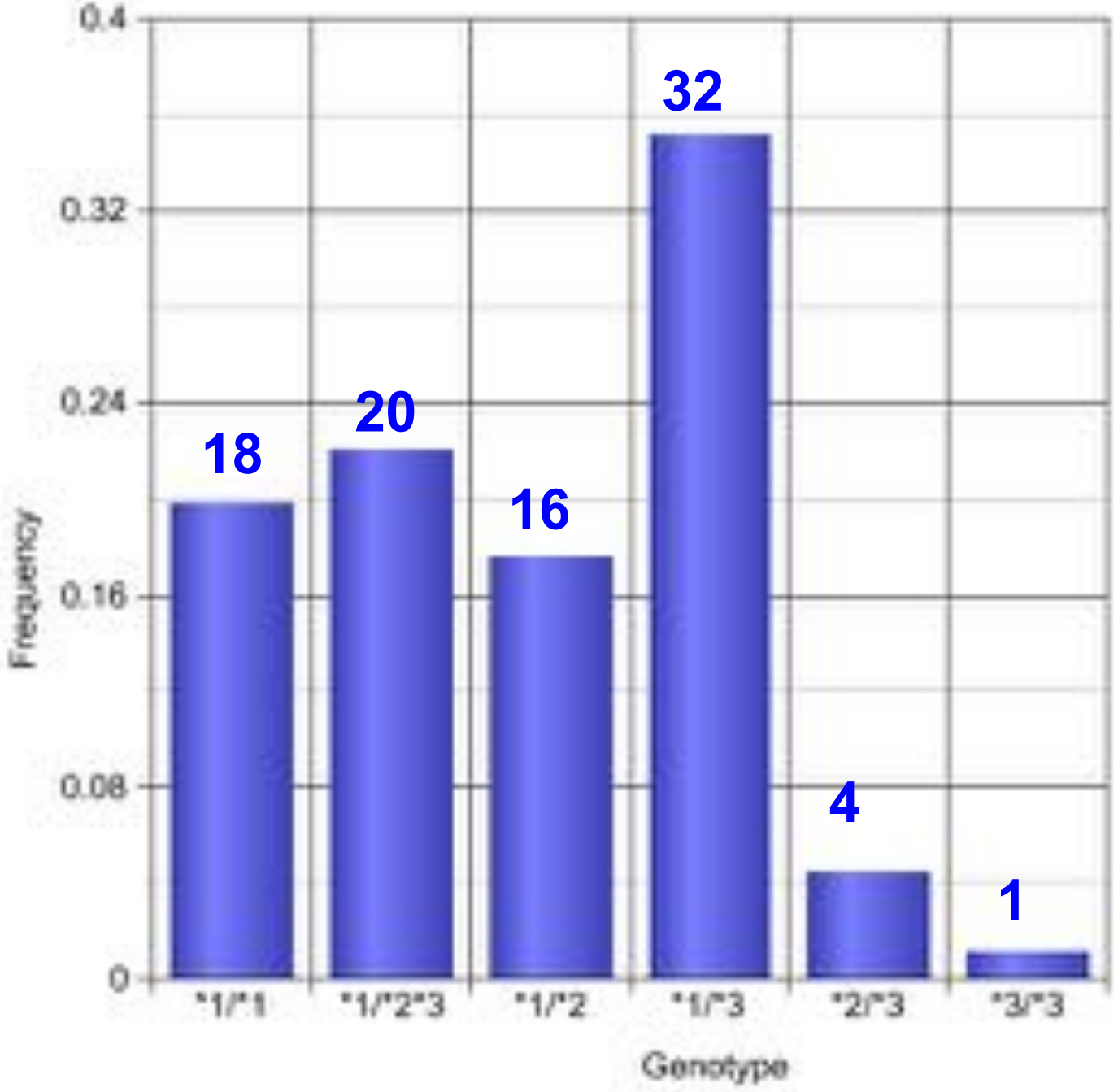
CYP2C8 allele frequencies obtained:

*CYP2C8*2* = 0.2418

*CYP2C8*3* = 0.3242

*CYP2C8*4* = not detected

Distribution of *CYP2C8* genotypes among GB subjects



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**

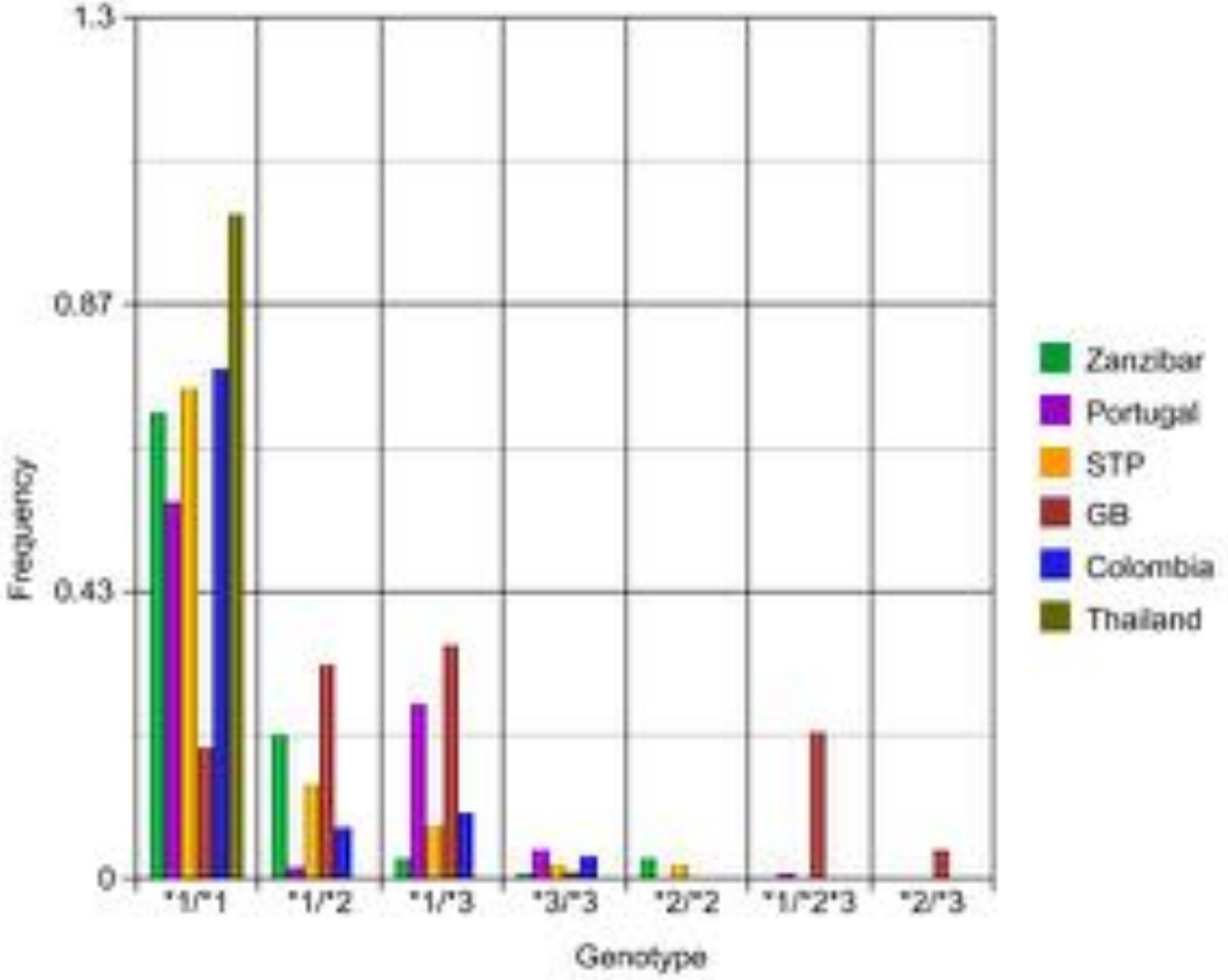
Comparison of *CYP2C8* allele frequencies between malaria patients from Guinea-Bissau and Zanzibar

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

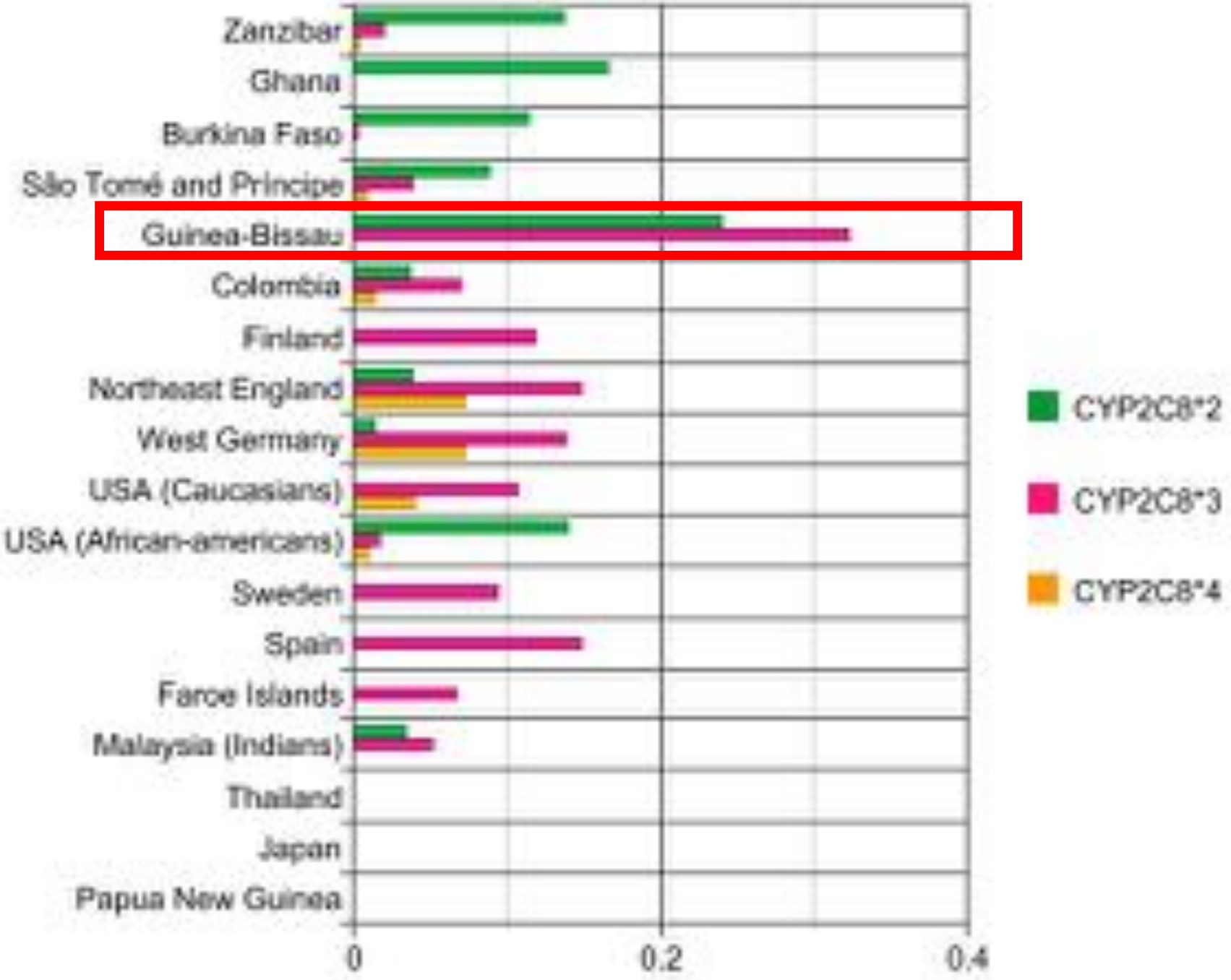
Comparison with Asian and Oceanic *CYP2C8* allele frequencies

- Significant differences not detected

CYP2C8 genotype comparison with 5 other populations



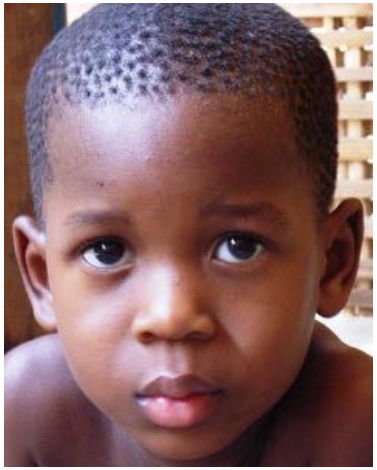
Comparison of *CYP2C8* allele frequencies with other populations



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

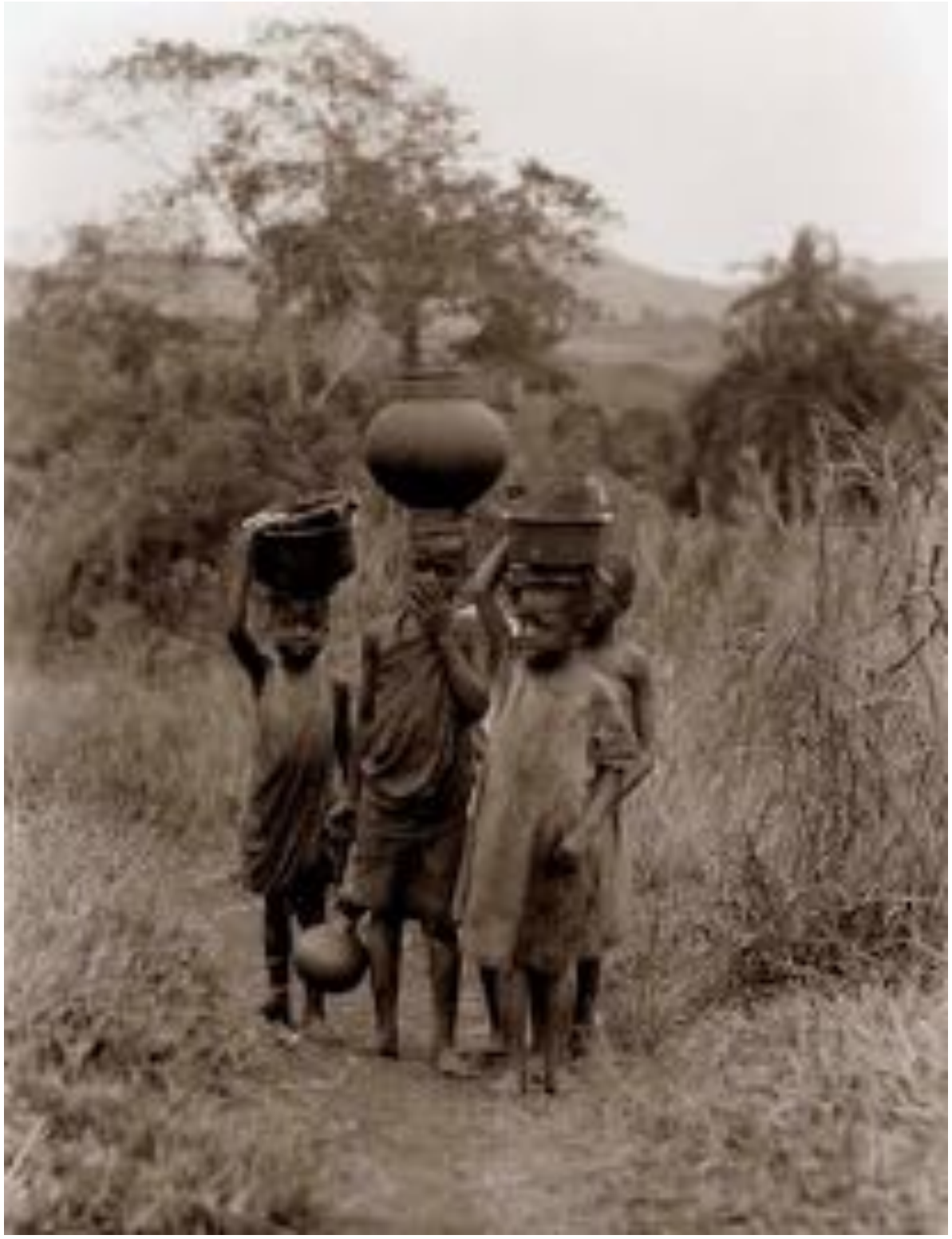
Bradley, D.J., 1974. Chapter in Human Rights in Health. Ciba Foundation Symposium **23:** 81–98.

Cavaco, I., Stromberg-Norklit, J., Kaneko, A., Msellem, M.I., Dahoma, M., Ribeiro, V.L., Bjorkman, A. and Gil, J.P., 2005. *CYP2C8* polymorphism frequencies among malaria patients in Zanzibar. *Eur J Clin Pharmacol* **61:** 15–18

Cavaco, I., Piedade, R., Gil, J.P. and Ribeiro, V., 2006. *CYP2C8* polymorphism among the Portuguese. *Clin Chem Lab Med* **44:** 168–170.

Kofoed, P.E., 2006. Treatment of uncomplicated malaria in Guinea-Bissau. PhD Thesis. Karolinska Institutet, Stockholm, Sweden.

WHO, 2006. WHO Guidelines for the treatment of malaria. WHO Press, Geneva.



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Muito obrigada