



Effects of genetic variation in *CYP2C* locus on pharmacokinetics of chlorcycloguanil

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Acknowledgements

Study participants

MRC staff

EDCTP



Objectives



- ❖ To define the prevalence of increased and decreased activity *CYP2C* alleles relevant to treatment of malaria with antimalarial biguanides in The Gambia, West Africa.
- ❖ To assess the effects of both known and newly defined alleles and haplotypes on chlorproguanil and chlorcycloguanil pharmacokinetic parameters such as T_{\max} , C_{\max} and AUC

Methods (1)

- ❖ Bioinformatic analysis of the *CYP2C* gene cluster shows two groups of genetic markers (Figure 1) with a high degree of linkage disequilibrium between markers in each group.

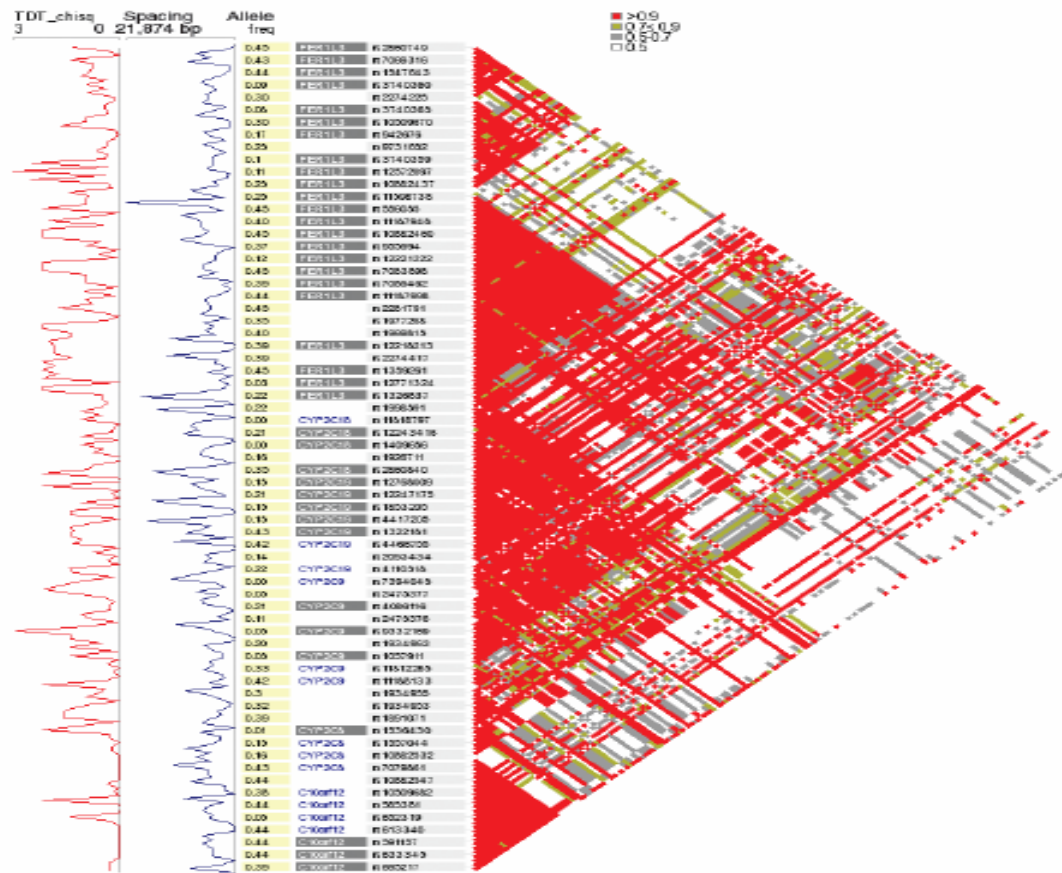


Figure 1 Analysis with marker shows that the *CYP2C* cluster lies in an area of strong linkage disequilibrium (Walton *et al.*, Nature Genetics 2005)



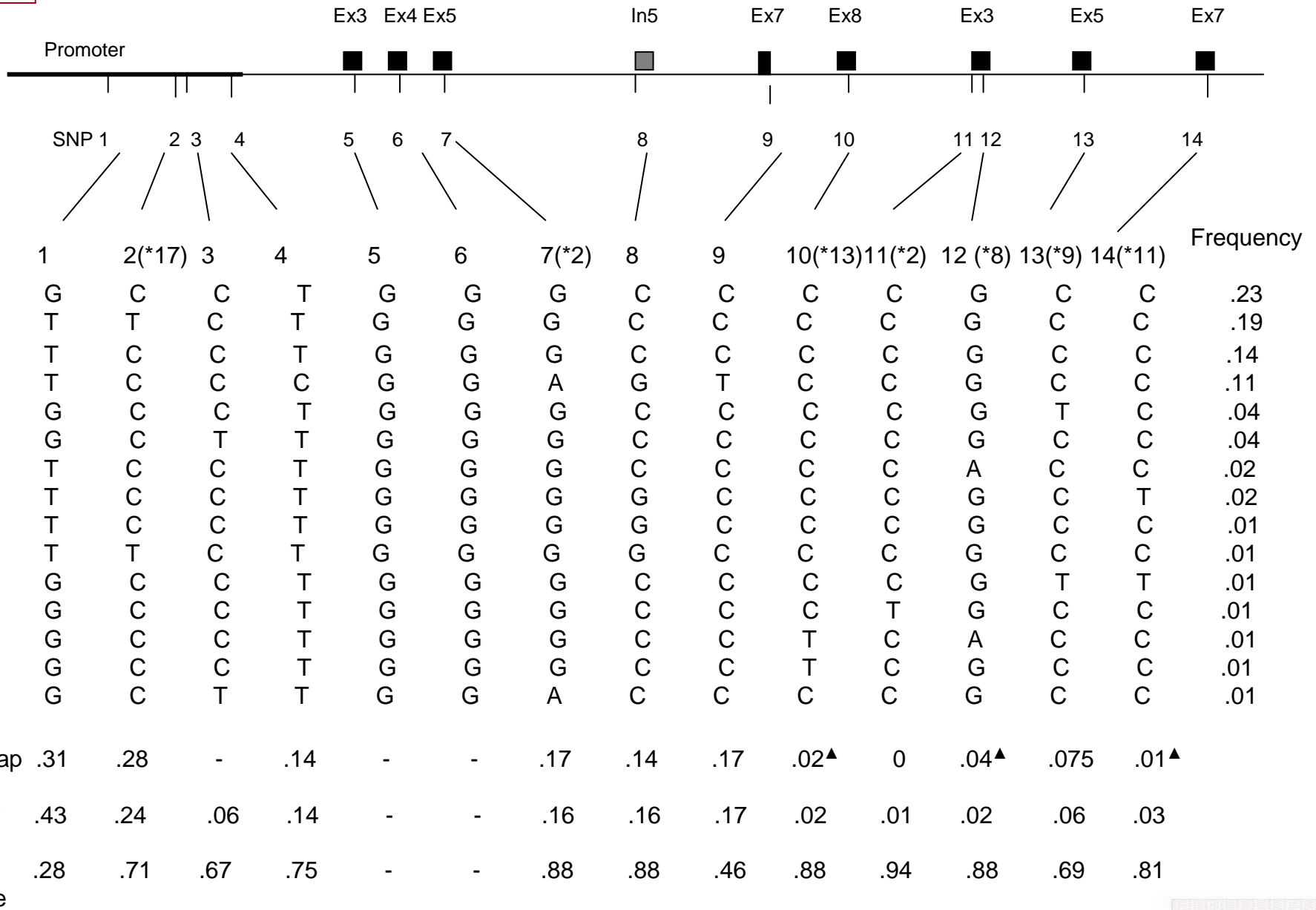
Methods (2)



- ❖ We selected 14 loci to genotype by allele specific and real-time PCR
- ❖ Study subjects were 43 adult participants who underwent detailed pharmacokinetic studies on Lapdap
- ❖ DNA was extracted and allele specific primers designed using Primer3 software
- ❖ Primers tested in a preliminary ARMS PCR run using control DNA samples from Sukuta in the Gambia
- ❖ *CYP2C19* SNPs available on the Taqman platform were assessed using ABI 7500 real-time PCR system.
- ❖ Haplotypes were assembled using a Bayesian algorithm implemented in the Phase 2.2 computer program and analysed for association using MARKER
- ❖ *CYP2C19**17 is a gain of function mutation and the *2 is a loss of function mutation

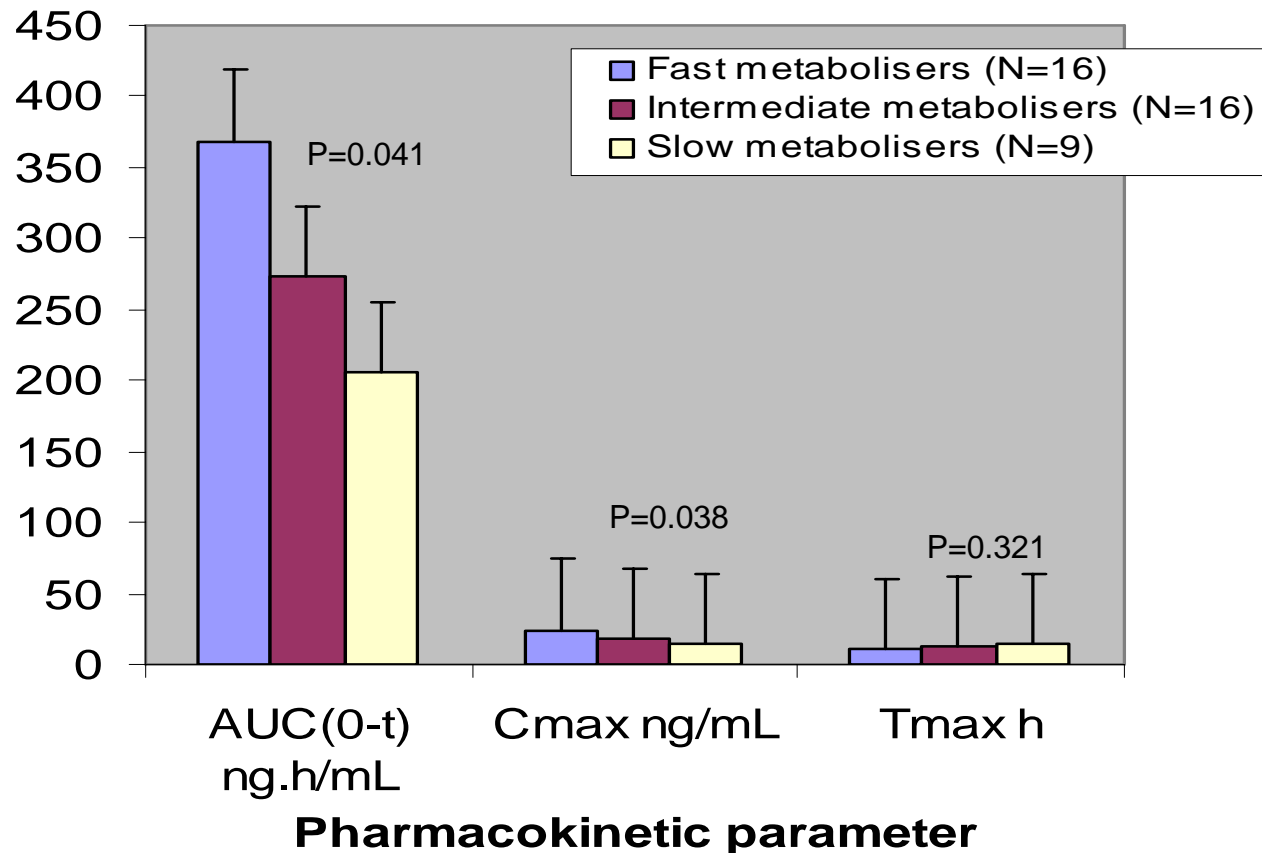
CYP2C19

CYP2C9



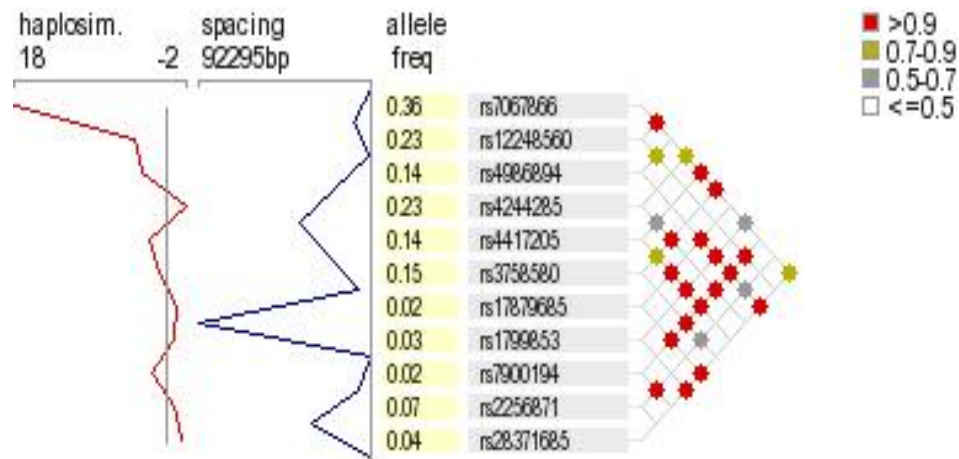
Allele and haplotype frequencies of CYP2C alleles in Gambians

Effects of genetic variants of CYP2C19 on antimalarial pharmacokinetics





Haplotype block of *CYP2C19* and *CYP2C9* alleles generated using the program Marker.



The alleles exhibit very strong LD with high D' -values >0.9 .



Discussion & Conclusions



- ❖ Slow metabolising alleles and fast metabolising alleles have a frequency of 14% and 24% respectively in the adult population in The Gambia
- ❖ The allele frequencies in the Gambia are similar to frequencies established in West African Yorubas in the HapMap project and in Europeans
- ❖ The presence of *fast metabolising alleles* cause significant increase in AUC and Cmax of chlorcycloguanil ($P < 0.05$)
- ❖ *CYP2C9* effects cannot be discounted because of strong linkage disequilibrium among *CYP2C* alleles



Future Perspectives



- ❖ Work is in progress to select more markers in the *CYP2C* cluster. Novel polymorphisms in the population will be identified by sequencing and the new alleles will be biochemically characterised
- ❖ We will determine whether the genetic differences that we have shown in pharmacokinetics of chlorcycloguanil translate to clinical effectiveness of antimalarial treatment in a randomised controlled trial of a chlorproguanil/dapsone combination for mild malaria in children (n=417)