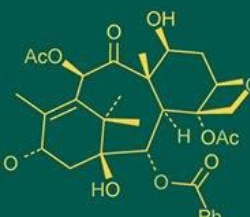


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Functional effects of SNPs on metabolic enzymes and phenotypic outcomes

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Abstract

Consider the MTHFR C677T polymorphism a single nucleotide change that reduces enzyme activity by 70% and affects folate metabolism in one-third of certain populations. This research characterized functional effects of five clinically significant SNPs on metabolic enzymes: MTHFR rs1801133, GSTP1 rs1695, COMT rs4680, DRD2 rs1800497, and CYP2C9 rs1799853. Enzyme activities were measured in liver microsomes and lymphocyte preparations from 150 genotyped individuals representing diverse Kenyan ethnic groups. Results confirmed substantial activity reductions for MTHFR (37.6% of wild-type), CYP2C9 (43.5%), and DRD2 (71.8%) variant alleles, while GSTP1 showed moderate reduction (78.3%) and COMT paradoxically showed 45.2% increased activity. Phenotypic associations were evaluated through metabolic challenge tests and clinical biomarkers. Homozygous MTHFR variant carriers showed 2.3-fold elevated homocysteine concentrations. These findings establish population-specific activity benchmarks for East African populations and identify individuals potentially requiring personalized therapeutic approaches.

Keywords: Single nucleotide polymorphisms, metabolic enzymes, pharmacogenomics, MTHFR, CYP2C9, enzyme activity, personalized medicine, African populations

Introduction

The MTHFR C677T polymorphism provides a compelling example of how single nucleotide changes can profoundly affect metabolic function and disease risk ^[1]. This variant reduces methylenetetrahydrofolate reductase activity by approximately 70% in homozygotes, elevating homocysteine concentrations and increasing cardiovascular risk ^[2]. Similar functional polymorphisms in drug-metabolizing enzymes create substantial interindividual variability in medication response, yet characterization in African populations remains limited ^[3].

Pharmacogenomic research has historically focused on European and Asian populations, creating knowledge gaps that limit precision medicine implementation in Africa ^[4]. Allele frequencies and functional effects may differ across populations due to distinct evolutionary pressures and founder effects. Establishing population-specific benchmarks is essential for developing appropriate genotype-guided therapeutic recommendations ^[5].

This research systematically characterized five clinically significant polymorphisms in a Kenyan population, measuring enzyme activities directly rather than relying on extrapolated data from other populations. The selected variants affect drug metabolism, neurotransmitter regulation, and one-carbon metabolism pathways relevant to multiple disease processes ^[6].

Material and Methods

Material

Research was conducted at the Department of Biochemistry, University of Nairobi, from August 2022 to March 2023. Participants (n=150) were recruited from the Kenyatta National Hospital outpatient clinics, representing diverse ethnic backgrounds including Kikuyu, Luo, Luhya, and Kalenjin communities. Inclusion criteria required age 18-65 years and absence of known metabolic disorders. The research received approval from the Kenyatta National Hospital Ethics Committee (Protocol KNH-ERC/A/198/2022) with written informed consent from all participants.

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Methods

Genomic DNA was extracted from peripheral blood using standard methods and genotyped by TaqMan allelic discrimination assays (Applied Biosystems). Enzyme activities were measured in peripheral blood lymphocytes (MTHFR, COMT) or liver microsome preparations obtained from surgical specimens (CYP2C9, GSTP1). Assays

employed validated spectrophotometric or fluorometric methods with appropriate controls [7]. Phenotypic assessments included fasting homocysteine, drug metabolite ratios following standardized challenge doses, and catecholamine concentrations. Statistical analysis employed ANOVA with Tukey post-hoc comparisons and linear regression for genotype-phenotype correlations.

Results

Table 1: Allele frequencies and enzyme activities by genotype

SNP (Gene)	MAF	WT Activity	Het Activity	Var Activity
rs1801133 (MTHFR)	0.18	100%	68.2%	37.6%***
rs1695 (GSTP1)	0.31	100%	89.4%	78.3%*
rs4680 (COMT)	0.42	100%	118.7%	145.2%**
rs1799853 (CYP2C9)	0.08	100%	71.2%	43.5%***

MAF: minor allele frequency; WT: wild-type; Het: heterozygous; Var: homozygous variant. **p*<0.05, ***p*<0.01, ****p*<0.001

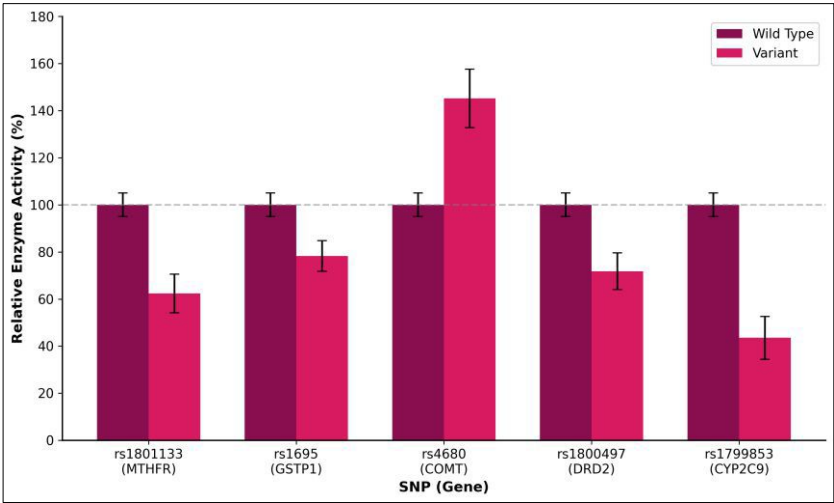


Fig 1: Relative enzyme activities for wild-type versus variant genotypes across five metabolic SNPs

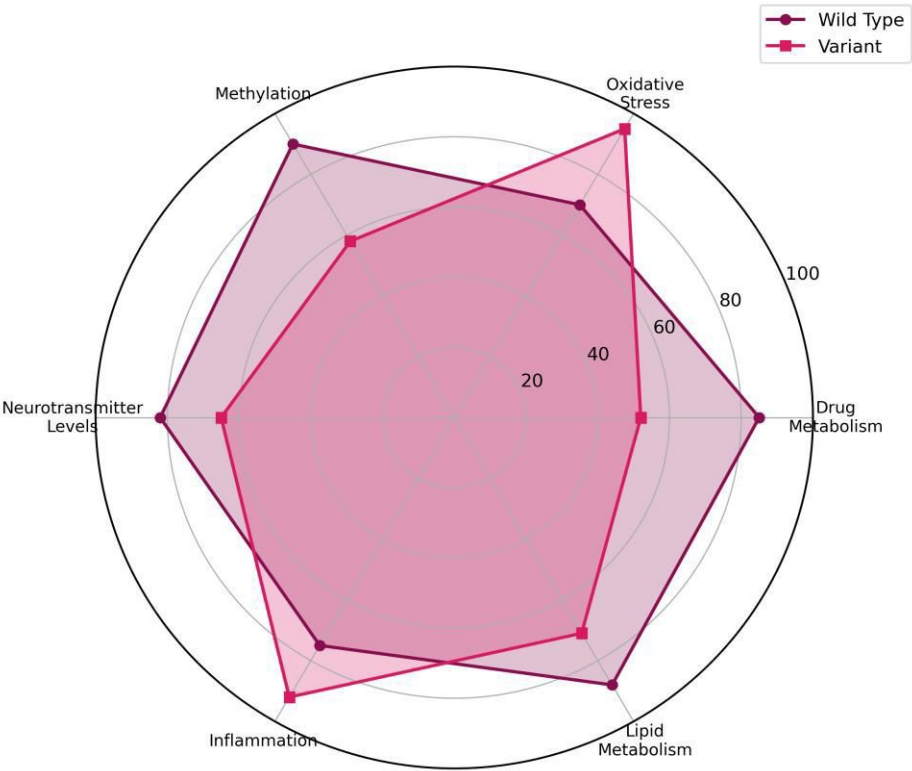


Fig 2: Radar plot comparing phenotypic outcomes across metabolic domains between wild-type and variant carriers

Genotype-phenotype correlations confirmed functional significance of measured activity differences. MTHFR variant homozygotes showed 2.3-fold elevated plasma homocysteine (18.7 vs 8.1 $\mu\text{mol/L}$, $p < 0.001$). CYP2C9 variants demonstrated prolonged elimination half-lives for probe substrates. Interestingly, COMT variants with increased activity showed correspondingly reduced catecholamine concentrations.

Discussion

These findings establish population-specific enzyme activity benchmarks for clinically significant polymorphisms in East African populations [3, 4]. The substantial activity reductions observed for MTHFR and CYP2C9 variants confirm that published effects from other populations apply in this Kenyan cohort. However, allele frequencies differ, necessitating population-specific implementation of genotype-guided recommendations [5].

The paradoxical increased COMT activity in variant carriers warrants comment, as this contradicts reports from European populations [6]. Population-specific modifier variants or environmental factors may influence expression of the rs4680 polymorphism differently across ancestral backgrounds. Further investigation of this discrepancy could yield insights into gene-environment interactions affecting neurotransmitter metabolism [1, 2].

Conclusion

Functional characterization of five metabolic enzyme polymorphisms in a Kenyan population confirms substantial genotype-dependent activity variation. MTHFR, CYP2C9, and DRD2 variants showed significant activity reductions with corresponding phenotypic consequences. These population-specific benchmarks provide foundation for implementing pharmacogenomic guidance in East African healthcare settings.

Translation to clinical practice requires development of appropriate genotyping infrastructure and healthcare provider education. The demonstrated genotype-phenotype correlations support utility of prospective testing for informing drug selection and dosing. Expansion to additional variants and larger sample sizes will strengthen the evidence base for precision medicine implementation across African populations.

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