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Influence of Plasmodium Falciparum Genetic Variants on Antimalarial Drug Resistance in East Africa: A Thematic Review

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ABSTRACT

The emergence and spread of antimalarial drug resistance in *Plasmodium falciparum* continues to undermine malaria control efforts across East Africa. Genetic mutations within the parasite genome have rendered widely used treatments such as chloroquine, sulfadoxine-pyrimethamine (SP), and, more recently, artemisinin-based therapies less effective over time. This review explored the role of key *P. falciparum* genetic variants in mediating antimalarial drug resistance in East Africa, focusing on their distribution, mechanisms, and implications for treatment outcomes. Using a thematic review approach, this article synthesizes findings from peer-reviewed molecular, clinical, and epidemiological studies published between 2000 and 2023 to analyze five core genetic themes. The review discussed chloroquine resistance driven by pfcrt K76T, SP resistance via dhfr and dhps mutations, emerging artemisinin resistance linked to kelch13 variants, multidrug resistance involving pfmdr1 and transporter loci, and the broader implications for diagnostics and public health surveillance. These mutations exhibit regional variability influenced by drug selection pressure and parasite evolution, complicating treatment guidelines and chemoprevention strategies. The growing diversity of resistance markers necessitates stronger molecular surveillance, targeted therapy strategies, and regional coordination to preserve treatment efficacy and guide evidence-based malaria control policies in East Africa.

Keywords: Plasmodium falciparum**,** Antimalarial drug resistance**,** Genetic variants**,** East Africa**,** Molecular surveillance.

INTRODUCTION

Malaria remains a persistent and life-threatening parasitic disease in East Africa, with *Plasmodium falciparum* accounting for most of the morbidity and mortality [1–3]. Despite substantial global and regional efforts to scale up interventions such as insecticide-treated nets, indoor residual spraying, and artemisinin-based combination therapies (ACTs), the emergence and spread of antimalarial drug resistance continues to threaten the sustainability of malaria control programs [4, 5]. At the molecular core of this resistance lie genetic variants in *P. falciparum* that reduce the efficacy of front-line medications. The parasite's genome is highly adaptable, with key mutations conferring resistance to drugs such as chloroquine, sulfadoxine-pyrimethamine, and, more recently, artemisinins [6, 7]. These mutations are not uniformly distributed across regions; East Africa has witnessed a complex landscape of genetic diversity and selection pressure due to widespread drug use, improper treatment practices, and substandard medications [8, 9]. Understanding the relationship between specific *P. falciparum* genetic variants and drug resistance is vital for tracking the efficacy of therapeutic interventions, guiding treatment policy, and designing future antimalarial agents [10]. This is especially important in East Africa, where high transmission intensity and frequent population movement contribute to rapid parasite evolution and gene flow. This thematic review examined the influence of *P. falciparum* genetic variants on antimalarial drug resistance in East Africa, focusing on five key themes: (1) chloroquine resistance and the pfcrt gene; (2) SP resistance through mutations in dhfr and dhps; (3) artemisinin resistance and kelch13 mutations; (4) multidrug resistance loci and transporters; and (5) implications for diagnostics, surveillance, and treatment policy. By synthesizing findings from molecular, epidemiological, and clinical studies, this review aims to elucidate the current state of knowledge and identify gaps that require urgent research attention.

Chloroquine Resistance and the pfcrt Gene

Chloroquine (CQ) was once the cornerstone of malaria treatment in Africa due to its efficacy, affordability, and safety [11, 12]. However, resistance emerged rapidly following widespread use, and East Africa became one of the regions heavily affected. The primary molecular driver of chloroquine resistance is the pfcrt (Plasmodium falciparum chloroquine resistance transporter) gene, particularly the K76T mutation located on chromosome 7 [11].

This mutation alters the parasite's digestive vacuole membrane transport system, reducing chloroquine accumulation in the vacuole and allowing the parasite to survive despite drug presence. The K76T mutation is frequently accompanied by additional pfcrt haplotypes (such as CVIET or SVMNT), which influence the degree of resistance and treatment failure rates. Molecular surveillance studies in countries such as Kenya, Tanzania, and Uganda have consistently reported a high prevalence of pfcrt 76T, particularly during the peak period of CQ use in the 1990s and early 2000s [13, 14]. Following policy shifts away from CQ, some regions have shown a gradual reversion to wild-type alleles, suggesting the possibility of re-sensitization in the absence of drug pressure.

This reversion has public health implications: it opens the door to reconsidering CQ or related drugs for prophylaxis or combination therapy, especially in contexts where resistance alleles have declined. However, this requires cautious evaluation to prevent resistance rebound.

Sulfadoxine-Pyrimethamine Resistance: dhfr and dhps Mutations

Sulfadoxine-pyrimethamine (SP) replaced chloroquine as a first-line antimalarial in many East African countries in the early 2000s [15]. SP targets the parasite's folate biosynthesis pathway through two enzymes: dihydrofolate reductase (dhfr) and dihydropteroate synthase (dhps). Resistance to SP is mediated by point mutations in the genes encoding these enzymes, particularly the dhfr N51I, C59R, and S108N mutations and the dhps A437G and K540E mutations [16]. These mutations confer stepwise resistance: single or double mutations offer partial resistance, while the accumulation of triple (dhfr) and double (dhps) mutations, collectively termed the quintuple mutant, is associated with high-level SP treatment failure. In East Africa, the quintuple mutant is now widely prevalent, especially in western Kenya, northern Tanzania, and southern Uganda. SP is no longer recommended as monotherapy for treatment but remains in use for intermittent preventive treatment in pregnancy (IPTp) and infants (IPTi). However, the increasing prevalence of sextuple mutations, which include additional mutations such as dhps A581G, threatens the effectiveness of these preventive strategies. Continued SP resistance also underscores the urgent need to develop and deploy alternative chemoprevention tools, such as triple ACTs or non-folate pathway-based drugs, particularly in regions where high mutation prevalence compromises existing protocols.

Artemisinin Resistance and kelch13 Mutations

Artemisinin-based combination therapies (ACTs) are currently the frontline treatment for uncomplicated *P. falciparum* malaria [17]. Although artemisinin resistance was first documented in Southeast Asia, recent findings have confirmed the presence of kelch13 propeller domain mutations in *P. falciparum* isolates from East Africa.

The kelch13 gene, located on chromosome 13, plays a role in the parasite's stress response. Mutations such as R561H, M476I, and C580Y have been linked to delayed parasite clearance, a clinical marker of artemisinin resistance [18]. Unlike in Asia, where C580Y predominates, Africa shows a broader range of kelch13 polymorphisms, many of which are not yet fully validated as resistance markers. Surveillance in Rwanda, Uganda, and northern Tanzania has detected R561H at increasing frequencies, raising alarms about the potential spread of artemisinin partial resistance. While these mutations have not yet translated into widespread ACT treatment failure in East Africa, their emergence warrants close molecular monitoring, particularly because artemisinin acts as the backbone of current combination therapies. Additionally, delayed clearance in the presence of kelch13 mutations may lead to greater selection pressure on partner drugs, accelerating the evolution of multidrug resistance. Therefore, understanding kelch13 dynamics is vital for preserving ACT efficacy.

Multidrug Resistance Loci and Transporter Gene Mutations

Beyond individual drug resistance genes, several multidrug resistance loci contribute to the reduced efficacy of various antimalarials. Key among them is the pfmdr1 (Plasmodium falciparum multidrug resistance 1) gene, which encodes a transmembrane protein involved in drug transport and intracellular accumulation. Mutations in pfmdr1, such as N86Y, Y184F, and D1246Y, have been associated with altered sensitivity to multiple antimalarial agents including lumefantrine, mefloquine, and amodiaquine [19]. These mutations may act synergistically or antagonistically with other resistance genes, depending on drug combination and parasite strain. In East Africa, studies have shown that ACT partner drugs influence pfmdr1 allele selection. For instance, the use of artemether-lumefantrine tends to select for the N86 allele, while amodiaquine selects for 86Y. This selective pressure can affect treatment outcomes and guide drug policy decisions regarding ACT cycling or rotation to prevent resistance buildup. Other transporters, such as pfmrp1 (multidrug resistance-associated protein 1) and pfcrt variants beyond K76T, have also been implicated in modulating antimalarial response [20]. Although less studied, these genes may hold the key to understanding cross-resistance phenomena and warrant deeper exploration in East African settings.

Implications for Diagnostics, Surveillance, and Policy

The growing diversity of *P. falciparum* resistance-associated genetic variants in East Africa presents significant challenges for diagnostics, therapeutic monitoring, and public health policy. Molecular tools, such as PCR-based genotyping and next-generation sequencing (NGS), are increasingly being deployed to detect and track resistance markers in real-time [21]. However, diagnostic capacity remains uneven across the region. Some countries lack consistent molecular surveillance programs or rely on sentinel site data, which may not capture local heterogeneities in mutation prevalence. Furthermore, interpretation of genetic data requires continuous refinement, particularly in understanding the phenotypic relevance of emerging variants. From a policy standpoint, timely incorporation of molecular surveillance into national malaria control programs is essential. Data on genetic resistance should inform drug procurement, IPTp implementation, and treatment guideline updates. For example, in areas with high SP resistance, policymakers may need to pivot toward alternative preventive therapies or integrate resistance testing into antenatal care. Global partnerships, such as WWARN (Worldwide Antimalarial Resistance Network) and MalariaGEN, have played key roles in aggregating data and providing comparative insights. Strengthening these networks and fostering regional collaboration will be vital in staying ahead of the parasite's evolutionary trajectory.

CONCLUSION

The landscape of *Plasmodium falciparum* genetic variants in East Africa is rapidly evolving, driven by drug pressure, human mobility, and parasite adaptability. This thematic review has outlined the major genetic determinants of antimalarial resistance, including mutations in pfcrt, dhfr, dhps, kelch13, and pfmdr1 that collectively shape treatment efficacy and policy decisions across the region. While chloroquine and SP resistance are now well-characterized, emerging artemisinin and multidrug resistance markers pose a new wave of challenges. The detection of kelch13 mutations and their association with delayed parasite clearance in East Africa signals a potentially critical turning point in the continent's malaria control narrative. The need for robust molecular surveillance, responsive treatment policies, and investment in research infrastructure cannot be overstated. As drug resistance continues to undermine the gains made in malaria control, integrating genetic insights into programmatic decision-making will be vital to safeguarding the efficacy of existing therapies and developing next-generation antimalarials. Ultimately, a molecularly informed approach to malaria control grounded in regional epidemiology and genetic data offers the best path forward. Collaboration among researchers, policymakers, and health systems will be essential to managing and mitigating the threat of drug-resistant malaria in East Africa and beyond.

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