REVIEW ARTICLE

Integrating genomics, epidemiology, and evolutionary dynamics in the study of artemisinin resistance

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ABSTRACT

Background: Artemisinin resistance in *Plasmodium falciparum* jeopardizes global malaria elimination, particularly with recent emergence in Africa.

Objectives: This narrative review synthesizes current evidence on artemisinin resistance to link molecular mechanisms with epidemiological spread, informing public health strategy.

Methods: A narrative literature review was conducted using PubMed, Web of Science, Google Scholar, and African Journals Online (AJOL). Peer-reviewed articles published between 2008 and 2025 were included. The review integrated molecular, genomic, and epidemiological studies focusing on *kelch13* (k13) mutations, genomic surveillance data, and spatiotemporal models of resistance emergence across malaria-endemic regions.

Results: Artemisinin resistance is primarily mediated by *kelch13* gene mutations, which increase phosphatidylinositol-3-phosphate (PI3P) levels and enhance ring-stage survival. It has arisen via multiple independent mutations (a soft selective sweep), with distinct regional patterns: established in Southeast Asia and recently independent emergence in Africa. Notably, *k13* mutations such as C469Y, A675V, and R561H are increasing in prevalence in Uganda, Rwanda, and neighboring regions. Integrated genomic surveillance improves resistance tracking.

Conclusion: Preserving artemisinin efficacy requires coordinated global action, strengthened surveillance, optimized treatment, and robust stewardship. Early genomic signals in Africa provide a critical window for intervention.

Keywords: Artemisinin resistance, *Plasmodium falciparum*, kelch13 gene, genomic surveillance, public health

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Citing this article

Odediji, S.A., Olawuyi, A.O., Amoo, K.O., Amoo-Adeboye, B., Olabanji, S.A., and Adeleke, M.A. Integrating genomics, epidemiology, and evolutionary dynamics in the study of artemisinin resistance. KIU J. Health Sci, 2026: 6(2);

Conflict of Interest: None is declared.

1.0 INTRODUCTION

Artemisinin resistance, first detected in western Cambodia in 2008, poses a major threat to global malaria control [1,2]. Its independent emergence in Africa, with reports from Rwanda, Uganda, and other countries, is of critical concern [3,4]. Understanding the molecular mechanisms, evolutionary dynamics, and public health implications of this resistance is essential for developing effective containment strategies.

The World Health Organization has emphasized this growing threat as resistance spreads geographically [5]. Resistance is strongly linked to mutations in the *Plasmodium falciparum kelch13* gene, impacting cellular stress responses and protein turnover [6,7]. It has arisen through multiple independent genetic events, complicating global surveillance and containment [8,9].

While several reviews have described the molecular basis of artemisinin resistance or its regional epidemiology separately, fewer have explicitly integrated genomic surveillance data with evolutionary theory and public health practice. This review integrates molecular mechanisms, evolutionary origins, and epidemiological patterns to address this gap. It focuses on the urgent implications of Africa's evolving resistance landscape for control policy and practice.

2. MOLECULAR AND GENOMIC BASIS OF ARTEMISININ RESISTANCE

2.1 The Role of *PfKelch13*

Mutations in the *PfKelch13* gene constitute the primary molecular determinant of artemisinin resistance. The *PfKelch13* protein functions as a substrate adaptor in an E3 ubiquitin ligase complex, and resistance-associated mutations impair the parasite's ability to degrade damaged or misfolded proteins [10, 11]. Genome-wide association studies have identified several validated mutations, including C580Y, R539T, Y493H, and I543T, which alter the β-propeller domain of the protein and reduce parasite susceptibility during the early ring stage [12,13]. The major validated and region-specific *PfKelch13* mutations, their geographic distribution, and associated in vitro resistance phenotypes are summarized in Table 1. These mutations allow some parasites to survive initial drug exposure and potentially lead to treatment failure when combined with partner drugs in ACTs [14, 15].

The ring-stage survival assay (RSA) remains the gold standard for in vitro assessment of artemisinin resistance [16,17]. RSA studies demonstrate that *PfKelch13* mutations induce a state of transient growth arrest or quiescence in early ring-stage parasites, allowing survival during the short pharmacokinetic window of artemisinin exposure [18].

2.2 Cellular Stress Responses

Beyond altered protein turnover, resistance is linked to dysregulation of the phosphatidylinositol-3-kinase (PI3K) pathway. Mutations in *PfKelch13* reduce ubiquitination of PfPI3K, leading to elevated levels of phosphatidylinositol-3-phosphate (PI3P) [19]. Increased PI3P enhances vesicular trafficking and strengthens the unfolded protein response (UPR), thereby improving parasite tolerance to oxidative and proteotoxic stress induced by artemisinin activation.

Artemisinins exert their antimalarial effect through heme-mediated cleavage of their endoperoxide bridge, generating cytotoxic radicals that damage parasite proteins [20,21]. Enhanced stress response pathways in resistant parasites mitigate this damage and promote survival.

2.3 Polygenic Architecture of Resistance

Although *PfKelch13* mutations are central to resistance, additional loci contribute to the resistance phenotype. Genes such as *fd* (ferredoxin), *arps10* [apicoplast ribosomal protein S10], *mdr2* [multidrug resistance protein 2], and *crt* (chloroquine resistance transporter), form a permissive genetic background that facilitates the emergence and stabilization of resistance [22] This explains why certain PfKelch13 mutations [e.g., C580Y] spread in Southeast Asia but remain rare in Africa, due to regional differences in parasite populations and selective pressures [8, 23]

3. EVOLUTIONARY DYNAMICS OF RESISTANCE

3.1 Emergence and Spread

Artemisinin resistance has emerged through a process known as a "soft selective sweep," characterized by the concurrent rise of multiple resistance-conferring mutations [25]. This contrasts with the "hard selective sweep" observed in other antimalarial resistance events, such as chloroquine resistance, which was driven by the spread of a few dominant haplotypes [26]. The soft selective sweep in artemisinin resistance makes it difficult to track the spread of resistance using traditional molecular markers.

3.2 Regional Variability

In Southeast Asia, the spread of resistance has been rapid and well-documented, with a few mutations, such as C580Y, becoming dominant [12]. In contrast, in Africa, where resistance is emerging, *PfKelch13* mutations

remain diverse and are at lower frequencies [24]. Recent studies in Uganda and Rwanda have confirmed the presence of mutations such as R561H, A675V, and C469Y, suggesting that resistance is becoming established in these regions [27,28]. A comparative overview of dominant resistance mutations, genetic backgrounds, and evolutionary patterns between Southeast Asia and Africa is presented in Table 2**.** This variability in resistance mutations complicates efforts to control resistance and necessitates genome-wide monitoring approaches.

3.3 Fitness Costs and Compensatory Evolution

The persistence of resistance mutations depends partly on their fitness costs in the absence of drug pressure [29]. Many drug resistance mutations impair parasite viability or transmission potential, creating a selective disadvantage when the drug is not present. For k13 mutations, fitness costs appear to be variable and context-dependent [28]. In Southeast Asia, some common mutations [like C580Y] may have relatively low fitness costs, allowing them to persist and spread even in the absence of continuous drug pressure [12]. These regional contrasts in mutation persistence and evolutionary dynamics are further contextualized in Table 2**.**

The concept of compensatory evolution [where secondary mutations arise to offset the fitness costs of primary resistance mutations] is well-established in antimicrobial resistance [30]. While direct evidence for compensatory evolution in artemisinin resistance remains limited, the polygenic nature of resistance suggests that background genes may modulate fitness effects [8]. Additionally, there is concerning evidence that k13 mutations can selectively favor parasites with reduced susceptibility to partner drugs, potentially accelerating the development of multidrug resistance [31]. In Southeast Asia, the convergence of artemisinin resistance with partner drug resistance has led to high treatment failure rates for several ACTs, creating a dire public health situation that may foreshadow challenges for other regions if resistance continues to evolve [31].

4. GENOMIC SURVEILLANCE AND EPIDEMIOLOGY

4.1 Advancements in Surveillance

Genomic surveillance has become a cornerstone of resistance monitoring, enabling near real-time detection of resistance markers, and providing valuable data for public health responses [32]. Compared with traditional therapeutic efficacy studies, genomic approaches are more scalable and informative in low-transmission settings [5]. The interconnections between molecular mechanisms, evolutionary processes, and epidemiological spread discussed here are conceptually illustrated in Figure 1**.**

4.2 Integration into Public Health Strategies

Integrating genomic data into public health strategies is essential for effective malaria control. In Africa, countries like Mozambique have incorporated genomic surveillance into their national malaria control programs, guiding decisions on treatment policies and resource allocation [33]. Expanding such initiatives across the continent is critical to detect and respond to emerging resistance promptly.

5. IMPLICATIONS FOR TREATMENT AND POLICY

The emergence of artemisinin resistance necessitates adaptive treatment strategies, including diversification of first-line therapies, potential rotation of artemisinin-based combination therapies, and careful stewardship to delay resistance to partner drugs [31]. Additionally, the development of novel antimalarial drugs with new mechanisms of action is essential to prevent further resistance emergence [34].

6. LIMITATIONS

Despite the integrative scope of this narrative review, several limitations should be acknowledged. Reliance on published literature may introduce publication bias, particularly in African regions with uneven genomic surveillance, potentially underestimating the true prevalence of emerging kelch13 mutations. Heterogeneity in study designs and sequencing methods limits direct comparability across studies. Furthermore, genomic data alone cannot confirm clinical treatment failure without complementary therapeutic efficacy data. Finally, as a narrative review, it did not follow systematic protocols or exhaustive search methods. Nonetheless, this synthesis captures the dominant evidence and highlights critical knowledge gaps for malaria policy and research in Africa.

6. CONCLUSION

Artemisinin resistance represents a complex, evolving threat that spans molecular biology, evolutionary dynamics, and public health practice. Integrating genomic surveillance with epidemiological data offers a powerful framework for early detection and response. African malaria programs must act now to contain resistance before treatment failures become widespread.

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Conflict of interests

The authors declare that they have no competing interests

Acknowledgments

The authors gratefully acknowledge Engr R.A Odediji , Mrs M. Odediji and Mrs Oyebanji-Olawuyi Mariam for their technical and logistics support.

Consent for publication

All authors consent to publication of this article

Availability of data and material

The datasets generated and/or analyzed during the current study are available from the corresponding

author on reasonable request.

Funding
The authors declare that they received no funding for this work.

Authors' Contributions

- Conception and design of the study:Saheed A. Odediji and Monsuru A. Adeleke
- Research framework: Saheed A. Odediji, Surakat A. Olabanji, Abdullahi O. Olawuyi
- Literature search and data collection: Abdullahi O. Olawuyi, Saheed A. Odediji, and Surakat A. Olabanji,
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Statements and Declarations

This study has not been published before or is not under consideration for publication elsewhere. Its publication is permitted by all authors and after acceptance for publication, it will not be submitted for publication anywhere else, in English or in any other language, without written approval. No use of artificial intelligence tools in manuscript preparation.

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TABLES AND FIGURE

Tables

Table 1: Major Validated and Associated *PfKelch13* Mutations and Their Geographic Distribution

Mutation	Classification	Primary Region[s)	In Vitro RSA Survival	Clinical Impact
C580Y	Validated	Southeast Asia, Africa	5-20%	Delayed clearance
R539T	Validated	Southeast Asia	10-25%	Delayed clearance
Y493H	Validated	Southeast Asia	5-15%	Delayed clearance
I543T	Validated	Southeast Asia	5-15%	Delayed clearance
C469Y	Validated	Africa [Uganda)	5-15%	Delayed clearance
A675V	Validated	Africa [Uganda)	5-15%	Delayed clearance
R561H	Validated	Africa [Rwanda)	5-15%	Delayed clearance

Note: Data compiled from [5) and [24). RSA = Ring-stage survival assay.

Table 2: Evolutionary Features of Artemisinin Resistance in Major Geographic Regions

Evolutionary Feature	Southeast Asia	Africa
Primary Selection Pattern	Soft selective sweep with multiple independent mutations	Mainly standing variation with localized soft sweeps
Dominant *PfKelch13* Mutations	C580Y, R539T, Y493H	Region-specific: C469Y, A675V [Uganda), R561H [Rwanda)
Genetic Background	Permissive haplotypes pre-dating artemisinin use	Diverse backgrounds; permissiveness under investigation
Transmission Intensity	Low to moderate	High in most regions
Gene Flow	Limited between countries	Extensive within regions
Current Status	High prevalence in GMS; multiple *PfKelch13* mutations fixed	Emerging foci with increasing frequency

Note: Data compiled from [12) and [4). GMS = Greater Mekong Subregion.

Figures

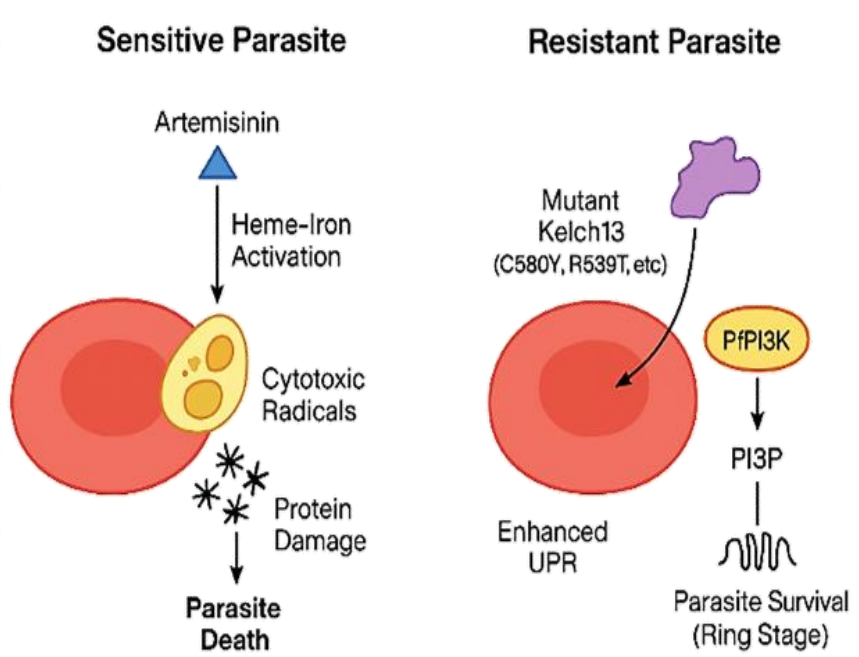

Figure 1: Conceptual framework integrating molecular, epidemiological, and evolutionary dimensions of artemisinin resistance [24, 29).