

RESEARCH ARTICLE

# Genome-wide association studies on malaria in Sub-Saharan Africa: A scoping review

Morine Akoth<sup>1\*</sup>, John Odhiambo<sup>1</sup>, Bernard Omolo<sup>1,2,3</sup>

**1** Strathmore Institute of Mathematical Sciences, Strathmore University, Ole Sangale Road, Nairobi, Kenya, **2** Division of Mathematics & Computer Science, University of South Carolina-Upstate, Spartanburg, South Carolina, USA, **3** School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, South Africa

\* [makoth@strathmore.edu](mailto:makoth@strathmore.edu)



## Abstract

**Background:** Malaria remains one of the leading causes of death in Sub-Saharan Africa (SSA). The scoping review mapped evidence in research on existing studies on malaria genome-wide association studies (GWAS) in SSA.

**Methods:** A scoping review was conducted to map existing studies in genome-wide association on malaria in SSA, with a review period between 1st January 2000 and 31st December 2024. The searches were made with the last search done in January 2025. The extracted data were analyzed using *R* software and *SRplot*. Relevant studies were identified through electronic searching of Google Scholar, Pubmed, Scopus, and Web of Science databases. Two independent reviewers followed the inclusion-exclusion criteria to extract relevant studies. Data from the studies were collected and synthesized using Excel and Zotero software.

**Results:** We identified 89 studies for inclusion. Most of these studies ( $n = 42$ , 47%) used a case-control study design, while the rest used cross-sectional, cohort, longitudinal, family-based, and experimental study designs. These studies were conducted between 2000 and 2024, with a noticeable increase in publications from 2012. Most studies were carried out in Kenya ( $n = 23$ ), Gambia ( $n = 18$ ), Cameroon ( $n = 15$ ), and Tanzania ( $n = 9$ ), primarily exploring genetic variants associated with malaria susceptibility, resistance, and severity.

**Conclusion:** Many case-control studies in Kenya and Gambia reported genetic variants in malaria susceptibility, resistance, and severity. GWAS on malaria is scarce in SSA, and even fewer studies are model-based. Consequently, there is a pressing need for more genome-wide research on malaria in SSA.

**Keywords:** Genome-wide association studies, malaria, Sub-Saharan Africa, scoping review.

## OPEN ACCESS

**Citation:** Akoth M, Odhiambo J, Omolo B (2025) Genome-wide association studies on malaria in Sub-Saharan Africa: A scoping review. PLoS One 20(5): e0309268. <https://doi.org/10.1371/journal.pone.0309268>

**Editor:** James Colborn, Clinton Health Access Initiative, Global Malaria Program, UNITED STATES OF AMERICA

**Received:** August 28, 2024

**Accepted:** April 02, 2025

**Published:** May 16, 2025

**Copyright:** © 2025 Akoth et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Data availability statement:** All relevant data are within the manuscript and its [Supporting Information](#) files.

**Funding:** The author(s) received no specific funding for this work.

**Competing interests:** The authors have declared that no competing interests exist.

## Introduction

Genome-wide association studies (GWAS) have become essential for identifying genes linked to human diseases, drawing significant interest from researchers worldwide [1]. Studying malaria in Sub-Saharan Africa (SSA) is especially critical, as the disease continues to pose a significant health threat and hinder socio-economic progress [2–6]. The World Health Organization (WHO) report estimated 599 thousand deaths in the year 2020, and 234 million cases in the year 2021 in Africa, accounting for 95% of the global malaria cases [7,8]. GWAS have become powerful tools for understanding the genetic basis of complex diseases, including susceptibility, severity, and resistance to malaria [9–12]. These studies have illuminated the genetic basis of malaria-related traits by examining the entire genome for links between genetic variants and disease traits. This knowledge has paved the way for developing targeted interventions and personalized treatments [13]. In the context of SSA, where genetic diversity is exceptionally high [14], and the malaria burden is felt [9], GWAS holds immense promise for advancing our understanding of malaria epidemiology, pathogenesis, and treatment outcomes. A recent study by Abdellaoui and colleagues [15] reported that GWAS has significant potential, enabling discoveries that impact various fields, including population genetics, complex trait genetics, epidemiology, social science, and medicine.

Most GWAS have been conducted in Europe and Asia [16,17], and Europe has reported bias in large-scale genomic studies. The international consortia for collaboration of genetic studies have left out Africa due to limited data and resources [18]. This has led many African countries to be unrepresented in the research despite the genetic diversity among African populations [14,19,20]. Despite all these, the field of genomics has advanced considerably due to a few current initiatives. Some of these initiatives are the 54Gene, The African Centre of Excellence for Genomics of Infectious Diseases (ACEGID), Inqaba Biotec (Africa's Genomics Company), and The Human Heredity and Health in Africa (H3Africa) Consortium [21]. Ziyaad and colleagues [22], for instance, established the *H3Africa Archive* for African human genomic data management. This effort sought to improve data sharing and accessibility, helping to overcome the challenges of accessing high-throughput genomic technologies.

The primary goal of this scoping review was to map existing malaria GWAS studies in SSA. Despite notable progress in this field, a comprehensive synthesis of study findings is still lacking. This review aimed to highlight existing gaps and provide a foundation for future research recommendations. Previous research has focused on global perspectives, exploring the association of genetic variants with specific phenotypes. This study also looked into GWAS that employed model-based approaches to genetic association while addressing the key issues in malaria GWAS. The scoping review was chosen instead of a systematic review to map existing studies and provide an overview of the current state of malaria GWAS in SSA.

## Methods

### *Study design*

Four databases, namely Google Scholar, PubMed, Scopus, and Web of Science, were systematically searched to identify eligible studies published in English between January 2000 and December 2024. The year of study, study designs, subject areas, and countries of study were mapped and reported. A search strategy was developed to identify relevant literature using the Arksey and O'Malley [23] framework. The search terms used were “Genome-wide association studies”, “GWAS”, “Malaria resistance”, “Malaria”, “Genetic association testing”, and “Sub-Saharan Africa”. All searches included peer-reviewed journal articles.

The study design aimed to conduct a comprehensive search for studies on GWAS in malaria within the SSA region. The Arksey and O'Malley framework has five steps: identifying the research question, identifying relevant studies, selecting studies, charting data, collating, summarizing, and reporting the data. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist is in the S1 checklist [24].

**Identifying research question.** The main research question for the scoping review was: What are the existing genome-wide association studies on malaria in SSA conducted between 2000 and 2024? Table 1 shows the population, concept, and context guide (PCC) used to assess the eligibility of the research question and to guide the selection of studies derived from the Joanna Briggs Institute [25].

**Identifying relevant studies.** Identifying relevant articles required a comprehensive search between 2000 and 2024 in four databases: Google Scholar, Scopus, PubMed, and Web of Science. These are life science journals with biomedical literature. Search strategies used on the four databases are available in the S1 File.

The articles went through title and abstract screening followed by full-text review by two independent reviewers. The two reviewers independently looked at each study to determine eligibility based on predefined inclusion and exclusion criteria. Disagreements between the reviewers were resolved through discussion to reach a consensus.

**Search strategy.** A methodology was devised to examine the existing GWAS on malaria in SSA. Furthermore, the research sought to identify and investigate model-based studies that addressed the concept of heterosis. We searched the literature on malaria GWAS using the mentioned databases. The last search was conducted on January 21, 2025, and included all articles published up to December 31, 2024. A combination of the following keywords was used: "Genome-wide association studies", "Malaria resistance", "Malaria", "Genetic association testing", and "Sub-Saharan Africa". To refine the selection process, a research librarian from Strathmore University provided expert guidance on database selection, search term refinement, and search string construction. All retrieved articles were exported to Excel and Zotero software for screening, and the study selection process adhered to PRISMA-ScR guidelines [24].

**Inclusion and exclusion criteria.** The criteria for inclusion of articles in the scoping review, provided in the S2 File, were as follows: the study must be a GWAS conducted in SSA between January 2000 and December 2024 and focused on malaria, the study must be published in English, and the study must have the full text available, study type included are the manuscripts and theses. The exclusion criteria included studies related to malaria that did not fall under the scope of GWAS, studies conducted in the regions of Algeria, Egypt, Morocco, Tunisia, and Libya, studies investigating non-malarial phenotypes, and systematic reviews, meta-analyses, and other reviews.

**Selecting studies.** A sample of articles was initially reviewed in full to identify and gauge the themes of the studies. Emerging themes were noted, and an Excel spreadsheet was developed to highlight key variables of interest systematically. Two reviewers conducted the data

**Table 1. PCC framework used to determine the eligibility of the research question and to guide the selection of studies on GWAS in malaria.**

Population	General population (adults and children, malaria vector)
Concept	Genome-wide association studies in malaria
Context	Sub-Saharan Africa

<https://doi.org/10.1371/journal.pone.0309268.t001>

extraction process independently, subsequently comparing their findings and reaching a consensus on the key variables to include in the study.

The titles of selected articles from various repositories were filtered and identified, and duplicates were removed using Excel software. Microsoft Excel was the primary data extraction tool employed, while Zotero served as the reference management software for extracting and organizing citation details. Microsoft Excel was also used to manage and chart extracted data. The two reviewers independently evaluated the abstracts of qualified articles based on predetermined inclusion and exclusion criteria and resolved any discrepancies. The database searches, keywords used, and the number of selected articles were noted.

Since this scoping review aimed to map primary research publications, systematic reviews, and review articles pertinent to malaria GWAS were noted during the search process but not included in the synthesis. The data was reported in the [S3 File](#).

**Charting the data.** Two independent reviewers extracted information by manually studying full articles, guided by the PCC framework. During extraction, the data focused on the study population (adults and children, malaria vector), concepts (malaria GWAS), and context (SSA). Information was extracted using the Excel software, including author names, publication dates, article titles, study designs, study country, study areas, genetic modes of inheritance for the model-based studies, genetic variants associated with malaria for some studies, and other significant findings. The PRISMA-ScR guidelines were applied to enhance transparency and reporting of the review process.

**Collating, summarizing and reporting results.** Emerging themes related to GWAS in malaria were summarized. A descriptive analysis of peer-reviewed papers that addressed the research question was performed. The search covered various aspects, including the year of publication, the number of publications in different countries in SSA, the different study designs used, the categorization of subject areas into distinct categories such as susceptibility, severity, and resistance to malaria, the methodologies used to evaluate genetic association, drug resistance, population diversity, and host-parasite interactions. Discrepancies in extraction were resolved through discussion. Most primary authors explicitly specified the study designs in their publications. However, when the study designs were not stated, the review team carefully discussed the methodologies and context provided in the articles to determine and assign an appropriate study design classification.

Tables and graphs were employed where appropriate to represent the findings visually. R software was used to summarize and categorize the data. *SRplot* platform, a data visualization and graphing tool ([26]), was also utilized to create the figures in compliance with the required standards. The scoping review results were used to identify knowledge gaps on malaria GWAS in SSA. The data and materials linked to this study are now available through the Open Science Framework (OSF) repository at <https://doi.org/10.17605/OSF.IO/DFK5G>.

## Results

A total of 631 studies were found in four electronic databases (Google Scholar (n=531), PubMed (n=34), Web of Science (n=8), and Scopus (n=58)). After removing 82 duplicate and 395 ineligible records for various reasons (not within the population, not malaria GWAS, and not published in English), 154 unique records underwent title and abstract screening. Of these, 53 records were irrelevant and excluded (16 non-GWAS, 12 non-malaria phenotypes, one not from the human population, 25 Systematic reviews and meta-analysis, and other reviews), leaving 101 reports for full-text retrieval. However, seven records were inaccessible or only had abstracts published, leaving 94 full-text reports for eligibility assessment by at

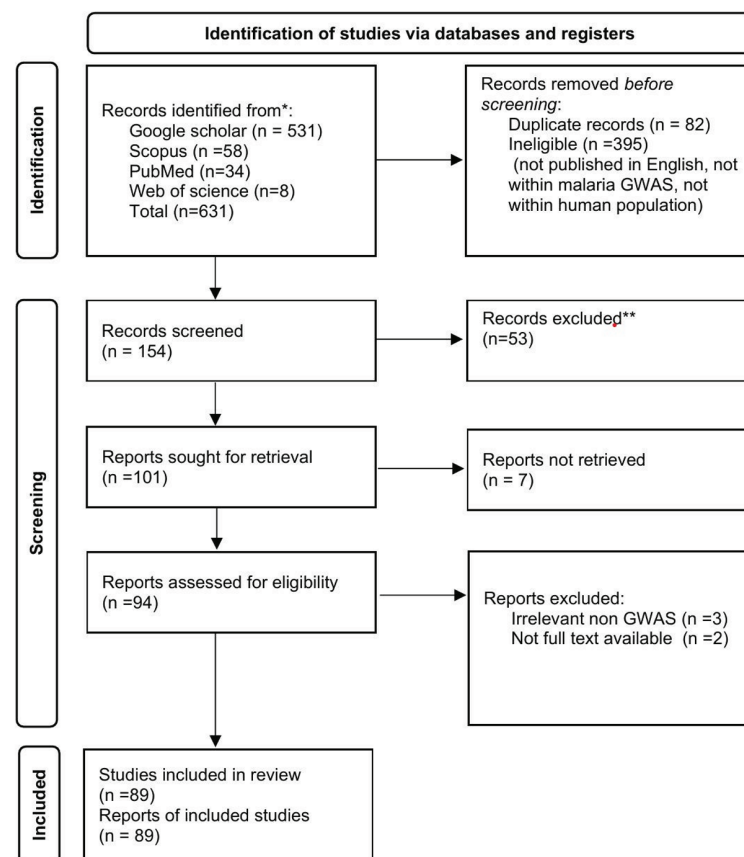
least two reviewers. After full-text screening, five more records were excluded, and 89 studies were included in this scoping review. The study selection process is shown in Fig 1 [27].

### Study designs

The predominant study design among the included investigations was case-control studies ( $n = 42, 47\%$ ) [8,10,28–67], cohort studies ( $n = 16, 18\%$ ) [68–83], cross-sectional ( $n = 23, 24\%$ ) [60,74,79,84–103], longitudinal studies ( $n = 3, 3\%$ ) [96,104,105] and family-based studies ( $n = 4, 5\%$ ) [35,106–108] (Fig 2). Other study designs include computational and laboratory-based experimental designs ( $n = 3, 3\%$ ) [93,109,110].

### Study areas

Most GWAS on malaria focused on identifying genetic variants associated with susceptibility, resistance, and severity of malaria [8,10,28,29,31–39,42,43,45–52,54–59,65–67,69,71–75, 77,78,81,82,84,86,92,95,96,105,108,110]. Furthermore, considerable research had been conducted on methodological approaches to genetic association testing, malaria drug resistance

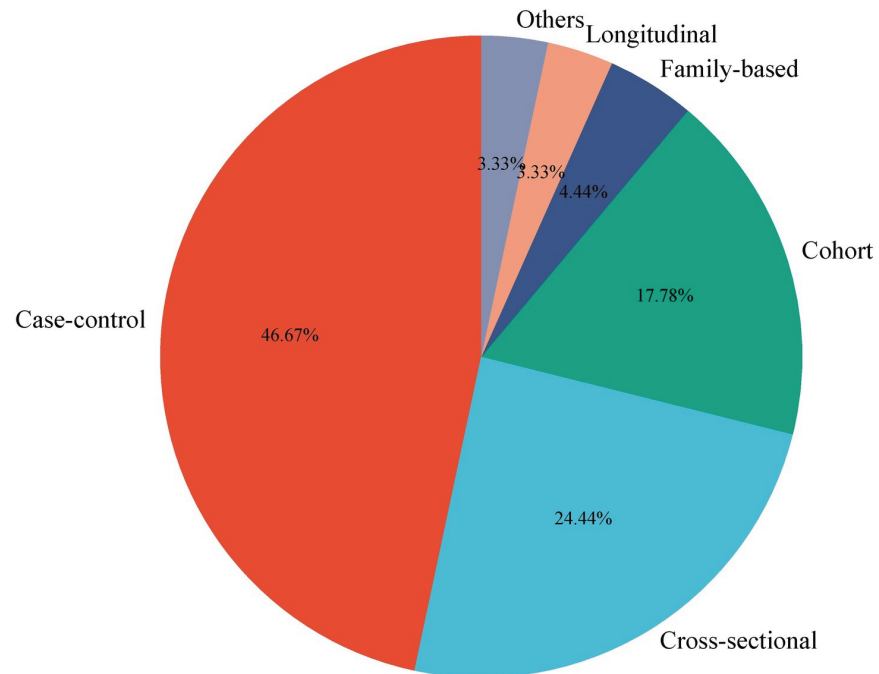


\* Number of records identified from each database.

\*\* Records excluded: not malaria phenotypes, not SSA populations, systematic reviews and meta-analysis and other reviews.

**Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) on malaria GWAS in SSA.**

<https://doi.org/10.1371/journal.pone.0309268.g001>



**Fig 2. Different study designs used in malaria GWAS.**

<https://doi.org/10.1371/journal.pone.0309268.g002>

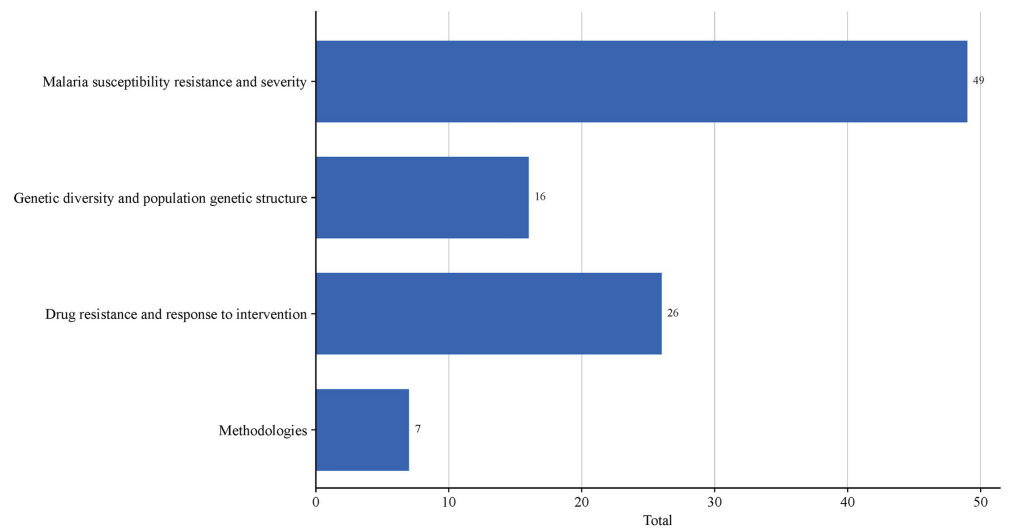
patterns exhibited by malaria parasites, and the effectiveness of vaccine interventions [33,41, 44,47,52–54,63,64,68,79,80,83,87,88,90,93,94,97,101–104,106,107,109]. Other areas of study included host-parasite interactions, population diversity and structures, genetic variation and evolutionary insights such as gene flow and natural selection [8,17,32,60,62,67,73,74,76,86,89, 96,98–100,108] and Mendelian randomization [91,92] (Fig 3).

### ***Year of study and spatial distribution of studies***

Studies reported were published between 2000 and 2024, with a noticeable increase in publications from 2012, as shown in Fig 4.

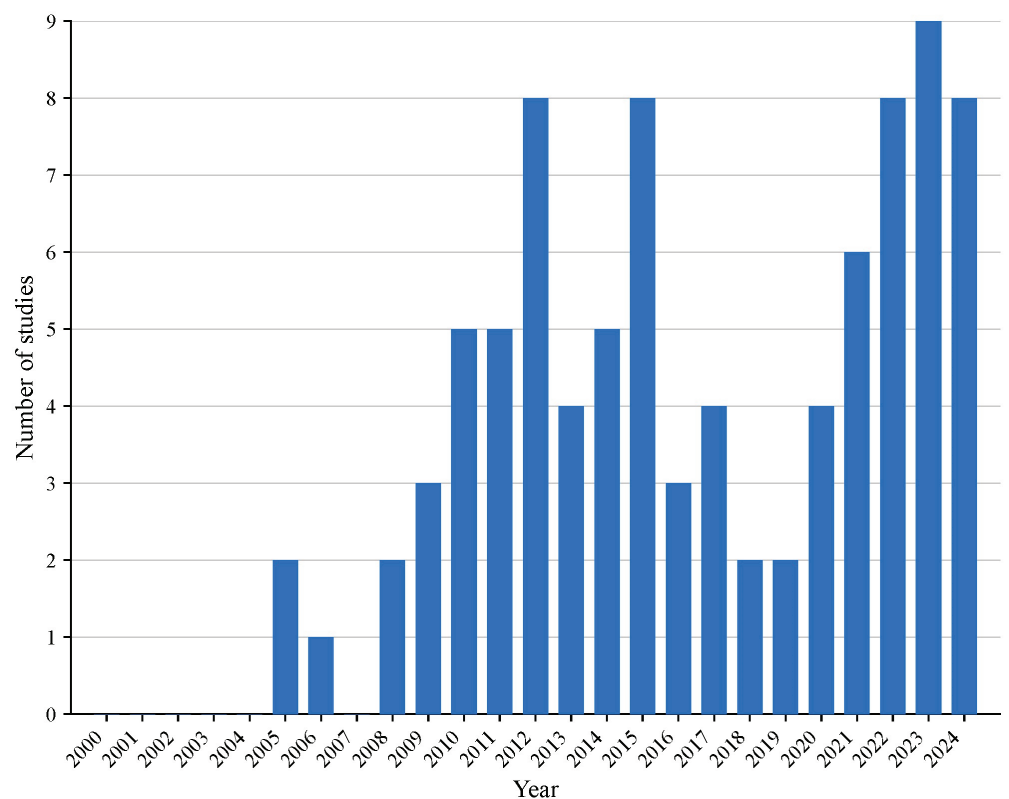
The study covered 21 different locations across various countries in SSA, with Kenya having the highest number of articles (n=23) [32,36,37,41,42,47,50,51,56,62,65,73,78,81,82,90, 91,93,94,104,105,109,110] as shown in Fig 5. Other countries included Gambia (n=18) [28, 32,35,36,39,41,43,44,46,53,54,56,65,66,73,91,108,109], Cameroon (n=15) [30,36,41,56,64,68, 70,76,77,82,85,91,98,101,102], Tanzania (n=9) [36,38,41,56,72,75,77,90,91], Ghana (n=7) [10, 52,56,60,100,103,109], Malawi (n=9) [36,41,56,62,65,73,74,87,93], Burkina Faso (n=11) [36, 37,41,56,69,76,82,95,97–99], Uganda (n=4) [47,60,62,87], South Africa (n=1) [65], Togo (n=2) [89,103], Mali (n=6) [41,49,57,84,95,97], Benin (n=7) [48,83,87,88,92,96,103], Ethiopia (n=3) [77,80,86], Ivory Coast (n=4) [45,76,98,103], Mozambique (n=3) [40,55,58], Nigeria (n=8) [36,41,54,56,76,82,98,109], Guinea (n=1) [100], Botswana (n=1) [77], Senegal (n=8) [8, 59,67,76,79,93,98,107], Sudan (n=1) [108], and Democratic republic of Congo (n=3) [76, 90,98]. There were no malaria GWAS in some SSA regions, such as Rwanda, Somalia, Chad, Namibia, Sierra Leone, Niger, Mauritania, Angola, Madagascar, and Burundi.

The research areas were further categorized into four distinct geographical regions, namely, Western Africa, Southern Africa, Eastern Africa, and Central Africa, as shown in Fig 6.



**Fig 3. Different research areas in malaria GWAS in SSA.**

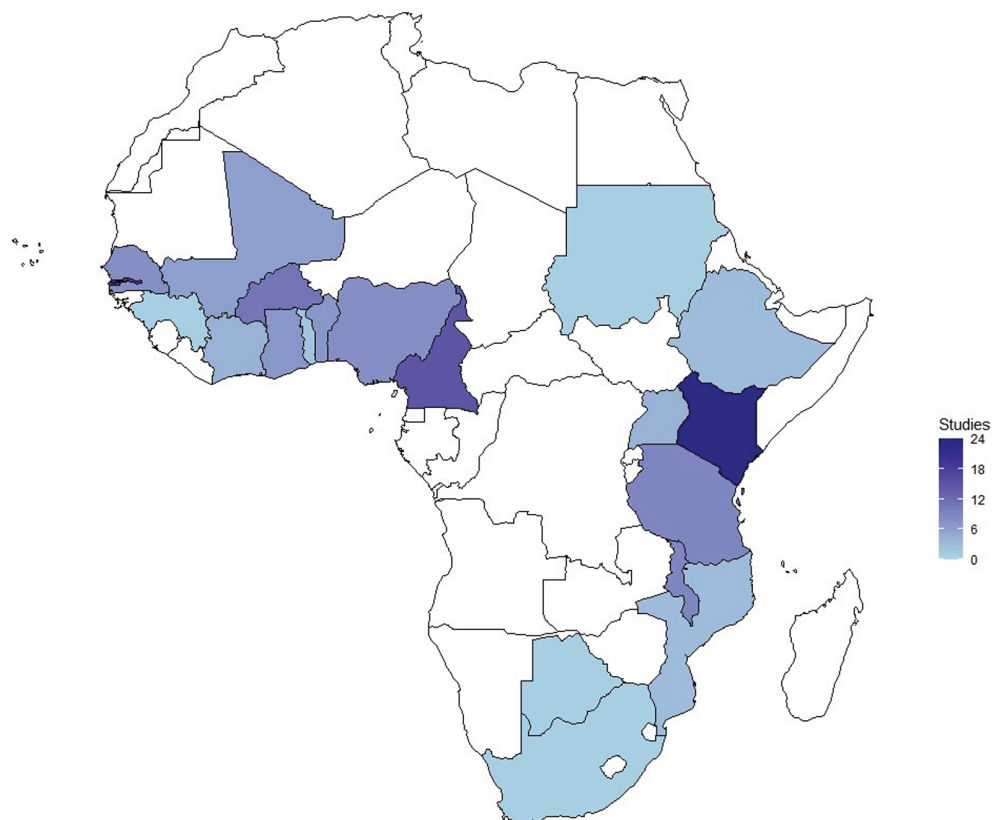
<https://doi.org/10.1371/journal.pone.0309268.g003>



**Fig 4. Number of articles in malaria GWAS in SSA published between 2000 and 2024.**

<https://doi.org/10.1371/journal.pone.0309268.g004>





**Fig 5. SSA countries conducting GWAS in malaria mapped with publications.** The map was created using public domain data from Natural Earth (<https://www.naturalearthdata.com/>).

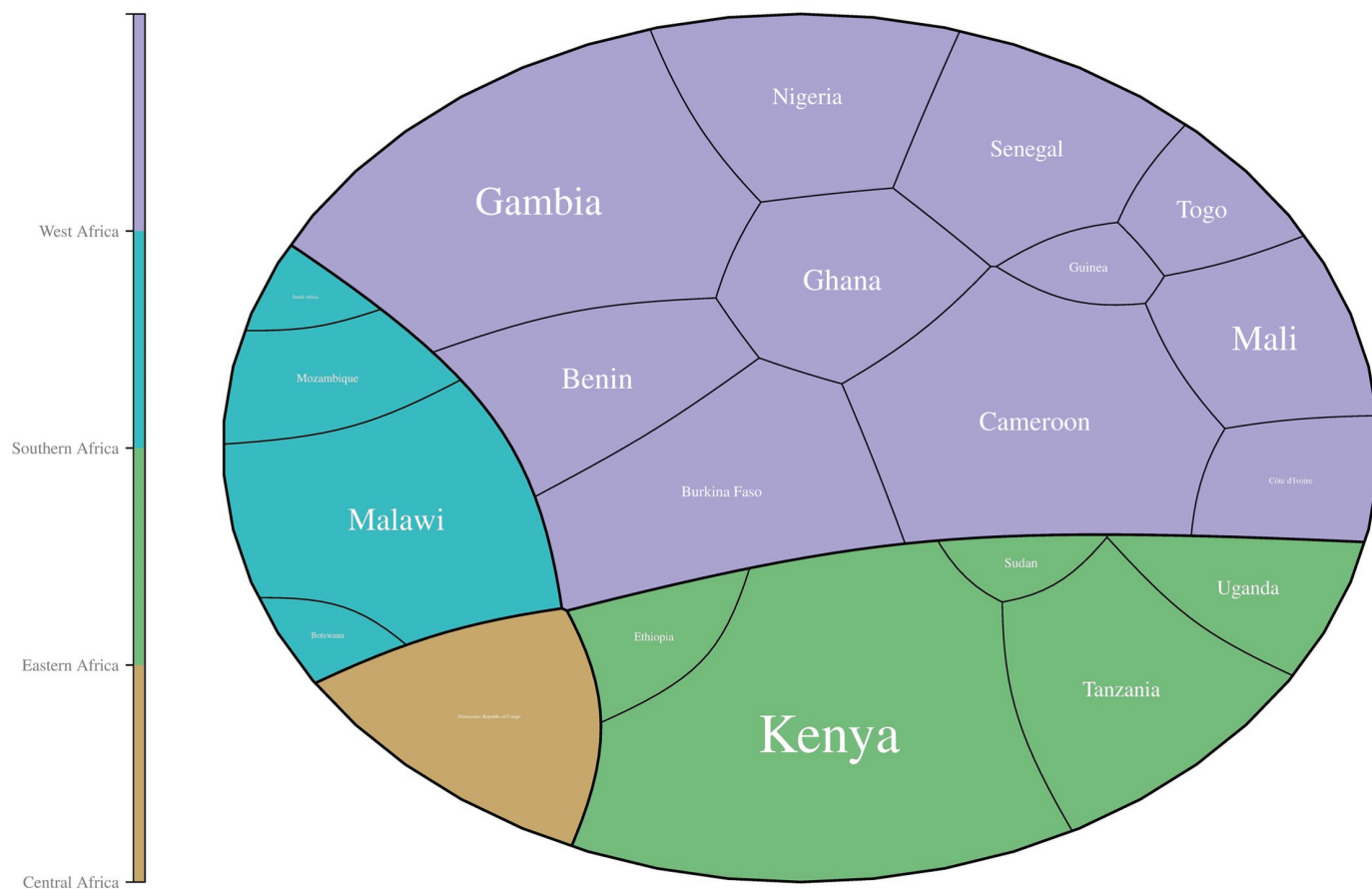
<https://doi.org/10.1371/journal.pone.0309268.g005>

Many articles were mapped in the Western Africa region, with Gambia having the highest number of articles (n=18).

### ***Genetic variants and malaria***

Most studies focused on genetic variants associated with susceptibility, severity, and resistance to malaria (n=49). Table 2 shows some single nucleotide polymorphisms (SNPs) and genes associated with malaria protection and severity. Five studies [29,38,66,84,106] had genetic modes of inheritance on variants associated with malaria severity and protection. The studies are model-based, with heterosis as one of the genetic inheritance modes related to severe or mild malaria phenotypes. Ranvehall et al. [29] found SNP rs334 to be significantly associated with resistance to severe malaria. Manjurano et al. [38] reported the G6PD gene with heterozygous advantage effect, which has a deficiency known to protect against severe malaria in the Tanzanian populations. Maiga et al. [84] reported some of the regions of the genome under heterozygous advantage with significant SNPs associated with severe malaria. Other genetic models reported in the studies were the additive, recessive, and dominant modes.





**Fig 6. Polygon areas proportional to the number of studies conducted in SSA in different regions of Western Africa, Eastern Africa, Southern Africa, and Central Africa.**

<https://doi.org/10.1371/journal.pone.0309268.g006>

**Table 2. Associated SNPs and genes with protection and severe malaria with underlying genetic models in the studies**

Author	Genetic model	Associated SNPs/ Genes	Malaria outcome
Jallow et al. 2009 [66]	Heterosis	rs10890361, rs316414, rs10249420	Severe
	Additive	rs5488069, rs2046784, rs2949632	Severe
	Dominant	rs10192428, rs12405994, rs16957052	Severe
	recessive	rs1384057, rs11013140, rs17728971	Severe
Maiga et al. 2014 [84]	Heterosis	rs4898389, rs7879049	Severe
	Additive	rs2515905, rs1050828	Severe
	Dominant	rs915942	Severe
	Recessive	rs915941, rs1050828	
Manjurano et al. 2015 [38]	Heterosis	G6PD376, rs762515, rs2515905	Protection
Ravenshall et al. 2018 [29]	Heterosis	rs334, rs9296359, rs113449872	Severe
	Additive	rs149085856, rs17624383, rs2967790, rs144312177	Severe
	Recessive	rs3832816, rs8109875, rs6682413	Severe
Milet et al. 2016 [106]	Dominant	rs16942900, rs3821869, rs12946796, rs10905522	Protection
	Additive	rs10757705, rs17640520, rs6675815, rs11679441, rs453079	Protection
	Recessive	rs971990, rs7694946, rs7123288	Protection

<https://doi.org/10.1371/journal.pone.0309268.t002>

## Discussion

This scoping review aimed to identify existing malaria GWAS in SSA. A search was performed on Google Scholar, Pubmed, Scopus, and Web of Science, and the results are highlighted in Fig 1. It included 89 articles, with most studies covering susceptibility, resistance, and severity of malaria, where genetic variants associated with malaria have been discovered and provided vital information. The research showed increasing articles over time (Fig 4). In over 24 years, publications in malaria GWAS have consistently increased. The upward trend indicates that GWAS is increasingly recognized as a valuable tool for understanding the genetic factors that impact malaria susceptibility, resistance, and severity in SSA. A recent study by Abdellaoui et al. [15] reported an upward trend in GWAS publications worldwide between 2007 and 2022. Our findings reflect this trend in malaria GWAS in SSA, with a notable increase in research articles in 2012.

Most studies were conducted in Kenya and Gambia (Fig 5). The other countries with articles in malaria GWAS included Ghana, Cameroon, Tanzania, Burkina Faso, Benin, Uganda, Malawi, South Africa, Ethiopia, Ivory Coast, Senegal, Guinea, Congo, Mali, Sudan, Nigeria, Togo, Mozambique, and Botswana. Despite being malaria-prone regions, some countries had no studies reported on the subject area. These included Zambia, Rwanda, Somalia, Chad, Namibia, Sierra Leone, Niger, Eritrea, Liberia, Burundi, Central African Republic, and Lesotho. A review by Damena et al. [111] reported that malaria GWAS was conducted in specific regions due to genetic diversity across different countries. Regions with more significant heterogeneity in association signals were studied more frequently. The availability of resources also played an essential role in determining study locations within particular countries. Fig 6 further highlights the number of studies per region classified as Western, Eastern, Southern, and Central Africa. Many studies were reported in the Western region, with Gambia having the highest number of publications in the area. Previous studies have uncovered more than 3 million genetic variants from African populations, some considered novel [18]. The diverse genetic variants have been observed among different ethnic communities; hence, the potential to use knowledge to understand disease mechanisms and drug targets in clinical practices [17, 112]. Gouveia and colleagues [60] reported a high genetic diversity in Eastern Africa, while Ndo et al. [76] reported similar results in Western Africa. Although Africa is the continent with the highest genetic diversity, it has hosted only 2% of worldwide GWAS [18]. Studies on genetic diversity have shown that most GWAS focus mainly on European populations, as highlighted in studies such as Sirugo et al. (2019) [113] and Melzer et al. (2020) [114]. Despite Africa's significant genetic diversity, GWAS have not adequately been conducted in SSA.

Most study designs were case-control, accounting for 47% of the articles (Fig 2). Case-control studies have been used to investigate disease risk factors and outcomes. They are less costly and less time-consuming than other study designs. The study design has been used in GWAS due to its efficiency and practicality in identifying genetic variants associated with complex diseases [115,116]. In contrast to linkage studies, which require large sample sizes, case-control studies can detect genes that contribute only a minor fraction to the overall likelihood of a disease [117]. Heightened sensitivity is crucial in unraveling complex genetic associations. In addition, cohort, cross-sectional, longitudinal, family-based, and experimental study designs were reported.

Many studies have explored the genetic basis of malaria, focusing on susceptibility, severity, resistance to malaria, and associated genetic variants (Fig 3). Some GWAS have identified SNPs and genes linked to malaria outcomes under different genetic models (Table 2). Jallow et al. [66] reported the strongest association signals across dominant, trend, recessive, and heterozygous advantage models, reinforcing the complexity of genetic influences

on malaria susceptibility. These findings align with broader GWAS evidence indicating that disease risk is modulated by multiple inheritance patterns [118]. The role of heterozygote advantage in malaria resistance has been documented in some studies [3,118], and findings by Maiga et al. [84]. Manjurano et al. [38] further support the findings. Manjurano et al. [38] reported that female heterozygotes showed protective effects, suggesting the influence of sex-specific genetic mechanisms, which require further investigation. Similarly, other SNPs have been associated with malaria susceptibility under additive and recessive models, consistent with Ravenhall et al. [29] findings in the Tanzanian population. Some studies have consistently identified genetic variants following a heterotic mode of inheritance, linking them to malaria severity and protection [29,38,66,84]. Similarly, Milet et al. [106] reported SNPs associated with malaria protection under additive, recessive, and dominant models in Senegalese children, reinforcing the genetic diversity underlying malaria resistance. These findings emphasize the complex genetic basis of malaria susceptibility, indicating that multiple genetic loci and inheritance patterns interact to affect disease outcomes [9,73]. The consistency of these results across diverse African populations underscores the need for further replication studies to validate these associations and enhance disease risk prediction.

Additionally, investigating drug resistance patterns, refining methodological tools, and evaluating intervention effectiveness highlights the broad scope of GWAS. For example, studies by Milet et al. [106] looked at the GWAS of antibody response to malaria vaccines, and studies by Ali et al. [70] investigated the prevalence of drug resistance mutations among children in Cameroon. Several studies have used various statistical techniques, including Bayesian modeling [54] and generalized linear models [83], to explore genetic associations with malaria. Similar GWAS in other regions or those that address different phenotypes in SSA have adopted diverse methodologies [28,119–124], to investigate genetic associations with the respective phenotype. In addition, a range of GWAS software tools, such as *IMPUTE2* as a framework used to impute genotypes, *beagle* [109] and *R* [122], have been used to assess genetic correlations and explore associated genetic loci. A few studies on host-parasite interactions and evolutionary insights were also reported.

A key limitation of this scoping review is the relatively small number of GWAS studies focusing on malaria in SSA. This is mainly due to the region's limited resources, infrastructure, and research funding, which reduced the number of studies available for inclusion. We extended our literature search to cover over 24 years to increase the number of articles. Secondly, the vast genetic diversity in SSA presents a significant challenge, as many studies fail to capture the genetic variations across different ethnic communities adequately. In addition, many countries within SSA reported fewer or no studies, which could lead to bias.

### ***Identified gaps in the review***

The gaps identified in this study highlight the significantly fewer malaria GWAS than other studies globally. A study review by Abdellaoui and colleagues reported the existing GWAS between 2007 and 2022. In their findings, thousands of GWAS studies were reported, with a noticeable increase starting from 2011 [15]. However, malaria GWAS have remained limited in SSA, with the few existing studies conducted primarily in the continent's western region. The global trend in GWAS has not been reflected in SSA.

Existing research has mainly focused on genetic variants associated with malaria susceptibility, severity, and resistance. Many of these studies have not examined the effects of different genetic modes of inheritance adopted in malaria research. This scoping review reported about 6% of model-based studies. Yet, certain genetic modes of inheritance, such as heterosis, in the previous studies have been linked with malaria resistance in patients with sickle cell

anemia [118]. The impact of genetic modes of inheritance and the heterotic conditions on malaria and other phenotypes is yet to be explored.

Various genetic association tests, including the allelic test, MAX test, and Cochran-Armitage Trend Test (CATT), have been used to assess the relationship between genetic variants and malaria. In a previous study, the allelic test was reported to lose power when the genetic variant exhibited heterosis [125]; hence, the simulation study, under the SNP, showed that accounting for heterotic effects could enhance the power of the test, underscoring the need for model selection before genetic association testing.

## Conclusion

The findings in genetic studies on malaria in SSA highlight the significant efforts to deepen our understanding of malaria, including increasing publications, various methodological approaches, research on a diverse population, and the study of malaria GWAS in different geographic locations. However, despite the considerable genetic diversity observed in SSA, global representation in research still needs to be achieved. There is also a lot of untapped potential to develop novel methodologies and discover more genetic loci related to susceptibility, resistance, and severity of malaria.

The African Genome Variation project and the Africa BioGenome projects, among other projects, have enabled genetic studies in SSA by discovering millions of genetic variants [126,127]. Such projects provide platforms for collaborations and partnerships among African scientists through biodiversity genomics.

## Supporting information

**S1 Checklist. PRISMA-ScR Checklist.**

(DOC)

**S1 File. Search strategy.**

(DOC)

**S2 File. Inclusion and exclusion criteria.**

(XLSX)

**S3 File. Systematic reviews meta-analysis, and other reviews.**

(PDF)

## Acknowledgments

The authors acknowledge the support of Strathmore University during the conduct of this research.

## Author contributions

**Conceptualization:** Bernard Omolo.

**Formal analysis:** Morine Akoth, Bernard Omolo.

**Investigation:** Morine Akoth, Bernard Omolo.

**Methodology:** Morine Akoth.

**Supervision:** John Odhiambo, Bernard Omolo.

**Writing – original draft:** Morine Akoth.

**Writing – review & editing:** Morine Akoth, Bernard Omolo.

## References

1. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature*. 2007;447(7145):661–78. <https://doi.org/10.1038/nature05911> PMID: 17554300
2. Kwiatkowski DP. How malaria has affected the human genome and what human genetics can teach us about malaria. *Am J Hum Genet*. 2005;77(2):171–92. <https://doi.org/10.1086/432519> PMID: 16001361
3. Hedrick PW. Resistance to malaria in humans: the impact of strong, recent selection. *Malar J*. 2012;11:349. <https://doi.org/10.1186/1475-2875-11-349> PMID: 23088866
4. Snow RW, Guerra CA, Noor AM, Myint HY, Hay SI. The global distribution of clinical episodes of *Plasmodium falciparum* malaria. *Nature*. 2005;434(7030):214–7. <https://doi.org/10.1038/nature03342> PMID: 15759000
5. Bhatt S, Weiss DJ, Cameron E, Bisanzio D, Mappin B, Dalrymple U, et al. The effect of malaria control on *Plasmodium falciparum* in Africa between 2000 and 2015. *Nature*. 2015;526(7572):207–11. <https://doi.org/10.1038/nature15535> PMID: 26375008
6. Oriero EC, Amenga-Etego L, Ishengoma DS, Amambua-Ngwa A. *Plasmodium malariae*, current knowledge and future research opportunities on a neglected malaria parasite species. *Crit Rev Microbiol*. 2021;47(1):44–56.
7. World Health Organization. World malaria report 2022. Geneva: World Health Organization; 2022.
8. Thiam A, Nisar S, Adjemout M, Gallardo F, Ka O, Mbengue B, et al. ATP2B4 regulatory genetic variants are associated with mild malaria. *Malar J*. 2023;22(1):68. <https://doi.org/10.1186/s12936-023-04503-8> PMID: 36849945
9. Malaria Genomic Epidemiology Network. Insights into malaria susceptibility using genome-wide data on 17,000 individuals from Africa, Asia and Oceania. *Nat Commun*. 2019;10(1):5732.
10. Timmann C, Thye T, Vens M, Evans J, May J, Ehmen C, et al. Genome-wide association study indicates two novel resistance loci for severe malaria. *Nature*. 2012;489(7416):443–6. <https://doi.org/10.1038/nature11334> PMID: 22895189
11. Bryc K, Auton A, Nelson MR, Oksenberg JR, Hauser SL, Williams S, et al. Genome-wide patterns of population structure and admixture in West Africans and African Americans. *Proc Natl Acad Sci U S A*. 2010;107(2):786–91. <https://doi.org/10.1073/pnas.0909559107> PMID: 20080753
12. Williams TN, Mwangi TW, Roberts DJ, Alexander ND, Weatherall DJ, Wambua S, et al. An immune basis for malaria protection by the sickle cell trait. *PLoS Med*. 2005;2(5):e128. <https://doi.org/10.1371/journal.pmed.0020128> PMID: 15916466
13. Timmann C, Evans JA, König IR, Kleensang A, Rüschendorf F, Lenzen J, et al. Genome-wide linkage analysis of malaria infection intensity and mild disease. *PLoS Genet*. 2007;3(3):e48. <https://doi.org/10.1371/journal.pgen.0030048> PMID: 17381244
14. Campbell MC, Tishkoff SA. African genetic diversity: implications for human demographic history, modern human origins, and complex disease mapping. *Annu Rev Genomics Hum Genet*. 2008;9:403–33. <https://doi.org/10.1146/annurev.genom.9.081307.164258> PMID: 18593304
15. Abdellaoui A, Yengo L, Verweij KJH, Visscher PM. 15 Years of GWAS discovery: realizing the promise. *Am J Hum Genet*. 2023;110(2):179–94. <https://doi.org/10.1016/j.ajhg.2022.12.011> PMID: 36634672
16. Visscher PM, Wray NR, Zhang Q, Sklar P, McCarthy MI, Brown MA, et al. 10 years of GWAS discovery: biology, function, and translation. *Am J Hum Genet*. 2017;101(1):5–22.
17. Bien SA, Wojcik GL, Hodonsky CJ, Gignoux CR, Cheng I, Matise TC, et al. The future of genomic studies must be globally representative: perspectives from PAGE. *Annu Rev Genomics Hum Genet*. 2019;20:181–200. <https://doi.org/10.1146/annurev-genom-091416-035517> PMID: 30978304
18. Bentley AR, Callier S, Rotimi CN. Diversity and inclusion in genomic research: why the uneven progress? *J Community Genet*. 2017;8(4):255–66. <https://doi.org/10.1007/s12687-017-0316-6> PMID: 28770442
19. Oni-Orisan A, Mavura Y, Banda Y, Thornton TA, Sebro R. Embracing genetic diversity to improve black health. *N Engl J Med*. 2021;384(12):1163–7. <https://doi.org/10.1056/NEJMms2031080> PMID: 33567186

20. Pfennig A, Petersen LN, Kachambwa P, Lachance J. Evolutionary genetics and admixture in african populations. *Genome Biol Evol.* 2023;15(4):evad054. <https://doi.org/10.1093/gbe/evad054> PMID: 36987563
21. Omotoso OE, Teibo JO, Atiba FA, Oladimeji T, Adebesin AO, Babalghith AO. Bridging the genomic data gap in Africa: implications for global disease burdens. *Global Health.* 2022;18(1):103. <https://doi.org/10.1186/s12992-022-00898-2> PMID: 36494695
22. Parker Z, Maslamoney S, Meintjes A, Botha G, Panji S, Hazelhurst S, et al. Building infrastructure for African human genomic data management. *Data Sci J.* 2019;18. <https://doi.org/10.5334/dsj-2019-047>
23. Westphaln KK, Regoeczi W, Masotya M, Vazquez-Westphaln B, Lounsbury K, McDavid L, et al. From Arksey and O'Malley and beyond: customizations to enhance a team-based, mixed approach to scoping review methodology. *MethodsX.* 2021;8:101375. <https://doi.org/10.1016/j.mex.2021.101375> PMID: 34430271
24. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): checklist and explanation. *Ann Intern Med.* 2018;169(7):467–73. <https://doi.org/10.7326/M18-0850> PMID: 30178033
25. Peters MD, Marnie C, Tricco AC, Pollock D, Munn Z, Alexander L, et al. Updated methodological guidance for the conduct of scoping reviews. *JBI Evid Synth.* 2020;18(10):2119–26.
26. Tang D, Chen M, Huang X, Zhang G, Zeng L, Zhang G, et al. SRplot: a free online platform for data visualization and graphing. *PLoS One.* 2023;18(11):e0294236. <https://doi.org/10.1371/journal.pone.0294236> PMID: 37943830
27. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Int J Surg.* 2021;88:105906. <https://doi.org/10.1016/j.ijsu.2021.105906> PMID: 33789826
28. Loley C, König IR, Hothorn L, Ziegler A. A unifying framework for robust association testing, estimation, and genetic model selection using the generalized linear model. *Eur J Hum Genet.* 2013;21(12):1442–8. <https://doi.org/10.1038/ejhg.2013.62> PMID: 23572026
29. Ravenhall M, Campino S, Sepúlveda N, Manjurano A, Nadjm B, Mtove G, et al. Novel genetic polymorphisms associated with severe malaria and under selective pressure in North-eastern Tanzania. *PLoS Genet.* 2018;14(1):e1007172. <https://doi.org/10.1371/journal.pgen.1007172> PMID: 29381699
30. Esoh KK, Apinjoh TO, Amambua-Ngwa A, Nyanjom SG, Chimusa ER, Amenga-Etego L, et al. Genome-wide association study identifies novel candidate malaria resistance genes in Cameroon. *Hum Mol Genet.* 2023;32(12):1946–58. <https://doi.org/10.1093/hmg/ddad026> PMID: 36752565
31. Manjurano A, Sepúlveda N, Nadjm B, Mtove G, Wangai H, Maxwell C, et al. USP38, FREM3, SDC1, DDC, and LOC727982 gene polymorphisms and differential susceptibility to severe malaria in Tanzania. *J Infect Dis.* 2015;212(7):1129–39.
32. Malaria Genomic Epidemiology Network, Band G, Rockett KA, Spencer CCA, Kwiatkowski DP. A novel locus of resistance to severe malaria in a region of ancient balancing selection. *Nature.* 2015;526(7572):253–7. <https://doi.org/10.1038/nature15390> PMID: 26416757
33. Barnes C, Plagnol V, Fitzgerald T, Redon R, Marchini J, Clayton D, et al. A robust statistical method for case-control association testing with copy number variation. *Nat Genet.* 2008;40(10):1245–52.
34. Schuldt K, Ehmen C, Sievertsen J, Evans J, May J, Ansong D, et al. Lack of association of CD55 receptor genetic variants and severe malaria in Ghanaian children. *G3 (Bethesda).* 2017;7(3):859–64. <https://doi.org/10.1534/g3.116.036475> PMID: 28104671
35. Ackerman H, Usen S, Jallow M, Sisay-Joof F, Pinder M, Kwiatkowski D. A comparison of case-control and family-based association methods: the example of sickle-cell and malaria. *Ann Hum Genet.* 2005;69(5):559–65.
36. Fry AE, Auburn S, Diakite M, Green A, Richardson A, Wilson J, et al. Variation in the ICAM1 gene is not associated with severe malaria phenotypes. *Genes Immun.* 2008;9(5):462–9. <https://doi.org/10.1038/gene.2008.38> PMID: 18528404
37. Leffler EM, Band G, Busby GBJ, Kivinen K, Le QS, Clarke GM, et al. Resistance to malaria through structural variation of red blood cell invasion receptors. *Science.* 2017;356(6343):eaam6393. <https://doi.org/10.1126/science.aam6393> PMID: 28522690
38. Manjurano A, Sepulveda N, Nadjm B, Mtove G, Wangai H, Maxwell C, et al. African glucose-6-phosphate dehydrogenase alleles associated with protection from severe malaria in heterozygous females in Tanzania. *PLoS Genet.* 2015;11(2):e1004960. <https://doi.org/10.1371/journal.pgen.1004960> PMID: 25671784
39. Shah SS, Rockett KA, Jallow M, Sisay-Joof F, Bojang KA, Pinder M, et al. Heterogeneous alleles comprising G6PD deficiency trait in West Africa exert contrasting effects on two major clinical



- presentations of severe malaria. *Malar J.* 2016;15(1):1–8.
40. Sikora M, Ferrer-Admetlla A, Laayouni H, Menendez C, Mayor A, Bardaji A, et al. A variant in the gene FUT9 is associated with susceptibility to placental malaria infection. *Hum Mol Genet.* 2009;18(16):3136–44. <https://doi.org/10.1093/hmg/ddp240> PMID: 19460885
  41. Tai KY, Dhaliwal J, Balasubramaniam V. Leveraging Mann-Whitney U test on large-scale genetic variation data for analysing malaria genetic markers. *Malar J.* 2022;21(1):79. <https://doi.org/10.1186/s12936-022-04104-x> PMID: 35264165
  42. Gilchrist JJ, Kariuki SN, Watson JA, Band G, Uyoga S, Ndila CM, et al. BIRC6 modifies risk of invasive bacterial infection in Kenyan children. *Elife.* 2022;11:e77461. <https://doi.org/10.7554/eLife.77461> PMID: 35866869
  43. Yuan J, Cheng KC-C, Johnson RL, Huang R, Pattaradilokrat S, Liu A, et al. Chemical genomic profiling for antimalarial therapies, response signatures, and molecular targets. *Science.* 2011;333(6043):724–9. <https://doi.org/10.1126/science.1205216> PMID: 21817045
  44. Howey R, Cordell HJ. Imputation without doing imputation: a new method for the detection of non-genotyped causal variants. *Genet Epidemiol.* 2014;38(3):173–90.
  45. Courtin D, Argiro L, Jamonneau V, N'dri L, N'guessan P, Abel L, et al. Interest of tumor necrosis factor- $\alpha$  -308 G/A and interleukin-10 -592 C/A polymorphisms in human African trypanosomiasis. *Infect Genet Evol.* 2006;6(2):123–9. <https://doi.org/10.1016/j.meegid.2005.03.002> PMID: 15894515
  46. Sabeti P, Usen S, Farhadian S, Jallow M, Doherty T, Newport M, et al. CD40L association with protection from severe malaria. *Genes Immun.* 2002;3(5):286–91. <https://doi.org/10.1038/sj.gene.6363877> PMID: 12140747
  47. Watson JA, Ndila CM, Uyoga S, Macharia A, Nyutu G, Mohammed S, et al. Improving statistical power in severe malaria genetic association studies by augmenting phenotypic precision. *Elife.* 2021;10:e69698. <https://doi.org/10.7554/eLife.69698> PMID: 34225842
  48. Idaghdour Y, Quinlan J, Goulet J-P, Berghout J, Gbeha E, Bruat V, et al. Evidence for additive and interaction effects of host genotype and infection in malaria. *Proc Natl Acad Sci U S A.* 2012;109(42):16786–93. <https://doi.org/10.1073/pnas.1204945109> PMID: 22949651
  49. Toure O, Konate S, Sissoko S, Niangaly A, Barry A, Sall AH, et al. Candidate polymorphisms and severe malaria in a Malian population. *PLoS One.* 2012;7(9):e43987. <https://doi.org/10.1371/journal.pone.0043987> PMID: 22957039
  50. Willcocks LC, Carr EJ, Niederer HA, Rayner TF, Williams TN, Yang W, et al. A defunctioning polymorphism in FCGR2B is associated with protection against malaria but susceptibility to systemic lupus erythematosus. *Proc Natl Acad Sci U S A.* 2010;107(17):7881–5. <https://doi.org/10.1073/pnas.0915133107> PMID: 20385827
  51. Opi DH, Swann O, Macharia A, Uyoga S, Band G, Ndila CM, et al. Two complement receptor one allele have opposing associations with cerebral malaria and interact with  $\alpha$ -thalassemia. *Elife.* 2018;7:e31579.
  52. Tindana P, Bull S, Amenga-Etego L, de Vries J, Aborigo R, Koram K, et al. Seeking consent to genetic and genomic research in a rural Ghanaian setting: a qualitative study of the MalariaGEN experience. *BMC Med Ethics.* 2012;13:15. <https://doi.org/10.1186/1472-6939-13-15> PMID: 22747883
  53. Sallah N, Carstensen T, Wakeham K, Bagni R, Labo N, Pollard MO, et al. Whole-genome association study of antibody response to Epstein-Barr virus in an African population: a pilot. *Glob Health Epidemiol Genom.* 2017;2:e18. <https://doi.org/10.1017/gheg.2017.16> PMID: 29868224
  54. Clark TG, Campino SG, Anastasi E, Auburn S, Teo YY, Small K, et al. A Bayesian approach using covariance of single nucleotide polymorphism data to detect differences in linkage disequilibrium patterns between groups of individuals. *Bioinformatics.* 2010;26(16):1999–2003. <https://doi.org/10.1093/bioinformatics/btq327> PMID: 20554688
  55. Sikora M, Laayouni H, Menendez C, Mayor A, Bardaji A, Sigauque B, et al. A targeted association study of immunity genes and networks suggests novel associations with placental malaria infection. *PLoS One.* 2011;6(9):e24996. <https://doi.org/10.1371/journal.pone.0024996> PMID: 21949827
  56. Constantinescu A-E, Hughes DA, Bull CJ, Fleming K, Mitchell RE, Zheng J, et al. A genome-wide association study of neutrophil count in individuals associated to an African continental ancestry group facilitates studies of malaria pathogenesis. *Hum Genomics.* 2024;18(1):26. <https://doi.org/10.1186/s40246-024-00585-w> PMID: 38491524
  57. Damena D, Barry A, Morrison R, Gaoussou S, Mahamar A, Attaher O, et al. A novel locus in CSMD1 gene is associated with increased susceptibility to severe malaria in Malian children. *Front Genet.* 2024;15:1390786. <https://doi.org/10.3389/fgene.2024.1390786> PMID: 38854427



58. Brown N, da Silva C, Webb C, Matias D, Dias B, Cancio B, et al. Antimalarial resistance risk in Mozambique detected by a novel quadruplex droplet digital PCR assay. *Antimicrob Agents Chemother*. 2024:e00346-24.
59. Adjemout M, Gallardo F, Torres M, Thiam A, Mbengue B, Dieye A, et al. From genome-wide association studies to functional variants: ARL14 cis-regulatory variants are associated with severe malaria. *J Infect Dis*. 2024;jiae159.
60. Gouveia MH, Bergen AW, Borda V, Nunes K, Leal TP, Ogwang MD, et al. Genetic signatures of gene flow and malaria-driven natural selection in sub-Saharan populations of the “endemic Burkitt Lymphoma belt”. *PLoS Genet*. 2019;15(3):e1008027. <https://doi.org/10.1371/journal.pgen.1008027> PMID: 30849090
61. Ndila CM, Nyirongo V, Macharia AW, Jeffreys AE, Rowlands K, Hubbart C, et al. Haplotype heterogeneity and low linkage disequilibrium reduce reliable prediction of genotypes for the - $\alpha$  3.71 form of  $\alpha$ -thalassaemia using genome-wide microarray data. *Wellcome Open Res*. 2021;5:287. <https://doi.org/10.12688/wellcomeopenres.16320.2> PMID: 34632085
62. Tomlinson S. Genomic introgression events in the *Anopheles gambiae* complex. Liverpool School of Tropical Medicine; 2021.
63. Apinjoh TO, Ouattara A, Titanji VP, Djimde A, Amambua-Ngwa A. Genetic diversity and drug resistance surveillance of *Plasmodium falciparum* for malaria elimination: is there an ideal tool for resource-limited sub-Saharan Africa? *Malar J*. 2019; 18(1):1-12.
64. Kum KE. Genetic diversity and markers of symptomatic malaria susceptibility in three malaria-endemic regions of Cameroon. JKUAT-COHES; 2021.
65. Kabongo EN. Functional genome-wide association study in susceptibility and resistance of Malaria. 2021.
66. Jallow M, Teo YY, Small KS, Rockett KA, Deloukas P, Clark TG, et al. Genome-wide and fine-resolution association analysis of malaria in West Africa. *Nat Genet*. 2009;41(6):657–65.
67. Nisar S, Torres M, Thiam A, Pouvelle B, Rosier F, Gallardo F, et al. Identification of ATP2B4 regulatory element containing functional genetic variants associated with severe malaria. *Int J Mol Sci*. 2022;23(9):4849.
68. Weetman D, Wilding CS, Steen K, Morgan JC, Simard F, Donnelly MJ. Association mapping of insecticide resistance in wild *Anopheles gambiae* populations: major variants identified in a low-linkage disequilibrium genome. *PLoS One*. 2010;5(10):e13140. <https://doi.org/10.1371/journal.pone.0013140> PMID: 20976111
69. Mitri C, Markianos K, Guelbeogo WM, Bischoff E, Gneme A, Eiglmeier K, et al. The kdr-bearing haplotype and susceptibility to *Plasmodium falciparum* in *Anopheles gambiae*: genetic correlation and functional testing. *Malar J*. 2015;14:391. <https://doi.org/10.1186/s12936-015-0924-8> PMID: 26445487
70. Ali IM, Evehe M-SB, Netongo PM, Atogho-Tiedeu B, Akindeh-Nji M, Ngora H, et al. Host candidate gene polymorphisms and associated clearance of *P. falciparum* amodiaquine and fansidar resistance mutants in children less than 5 years in Cameroon. *Pathog Glob Health*. 2014;108(7):323–33. <https://doi.org/10.1179/2047773214Y.0000000159> PMID: 25388906
71. Johnson MK, Clark TD, Njama-Meya D, Rosenthal PJ, Parikh S. Impact of the method of G6PD deficiency assessment on genetic association studies of malaria susceptibility. *PLoS One*. 2009;4(9):e7246. <https://doi.org/10.1371/journal.pone.0007246> PMID: 19789650
72. Manjurano A, Clark TG, Nadjm B, Mtove G, Wangai H, Sepulveda N, et al. Candidate human genetic polymorphisms and severe malaria in a Tanzanian population. *PLoS One*. 2012;7(10):e47463. <https://doi.org/10.1371/journal.pone.0047463> PMID: 23144702
73. Damena D, Chimusa ER. Genome-wide heritability analysis of severe malaria resistance reveals evidence of polygenic inheritance. *Hum Mol Genet*. 2020;29(1):168-76.
74. Shah Z, Naung MT, Moser KA, Adams M, Buchwald AG, Dwivedi A, et al. Whole-genome analysis of Malawian *Plasmodium falciparum* isolates identifies possible targets of allele-specific immunity to clinical malaria. *PLoS Genet*. 2021;17(5):e1009576. <https://doi.org/10.1371/journal.pgen.1009576> PMID: 34033654
75. Rubach MP, Mukemba J, Florence S, John B, Crookston B, Lopansri BK, et al. Plasma *Plasmodium falciparum* histidine-rich protein-2 concentrations are associated with malaria severity and mortality in Tanzanian children. *PLoS One*. 2012;7(5):e35985. <https://doi.org/10.1371/journal.pone.0035985> PMID: 22586457
76. Ndo C, Antonio-Nkondjio C, Cohuet A, Ayala D, Kengne P, Morlais I, et al. Population genetic structure of the malaria vector *Anopheles nili* in sub-Saharan Africa. *Malar J*. 2010;9:161. <https://doi.org/10.1186/1475-2875-9-161> PMID: 20540796
77. McQuillan MA, Verhulst S, Hansen ME, Beggs W, Meskel DW, Belay G, et al. Association between telomere length and *Plasmodium falciparum* malaria endemicity in sub-Saharan Africans. *Am J Hum Genet*. 2024;111(5):927-38.

78. Anyona SB, Cheng Q, Wasena SA, Osata SW, Guo Y, Raballah E, et al. Entire expressed peripheral blood transcriptome in pediatric severe malarial anemia. *Nat Commun*. 2024;15(1):5037. <https://doi.org/10.1038/s41467-024-48259-4> PMID: 38866743
79. Park DJ, Lukens AK, Neafsey DE, Schaffner SF, Chang H-H, Valim C, et al. Sequence-based association and selection scans identify drug resistance loci in the *Plasmodium falciparum* malaria parasite. *Proc Natl Acad Sci U S A*. 2012;109(32):13052–7. <https://doi.org/10.1073/pnas.1210585109> PMID: 22826220
80. St Jean PL, Koh GCKW, Breton JJ, Espino FEJ, Hien TT, Krudsood S, et al. Pharmacogenetic assessment of tafenoquine efficacy in patients with *Plasmodium vivax* malaria. *Pharmacogenet Genomics*. 2020;30(7):161–5. <https://doi.org/10.1097/FPC.0000000000000407> PMID: 32433338
81. Wendler JP, Okombo J, Amato R, Miotto O, Kiara SM, Mwai L, et al. A genome wide association study of *Plasmodium falciparum* susceptibility to 22 antimalarial drugs in Kenya. *PLoS One*. 2014;9(5):e96486. <https://doi.org/10.1371/journal.pone.0096486> PMID: 24809681
82. Shah SS, Macharia A, Makale J, Uyoga S, Kivinen K, Craik R, et al. Genetic determinants of glucose-6-phosphate dehydrogenase activity in Kenya. *BMC Med Genet*. 2014;15:93. <https://doi.org/10.1186/s12881-014-0093-6> PMID: 25201310
83. Milet J, Courtin D, Garcia A, Perdry H. Mixed logistic regression in genome-wide association studies. *BMC Bioinformatics*. 2020;21(1):536. <https://doi.org/10.1186/s12859-020-03862-2> PMID: 33228527
84. Maiga B, Dolo A, Campino S, Sepulveda N, Corran P, Rockett KA, et al. Glucose-6-phosphate dehydrogenase polymorphisms and susceptibility to mild malaria in Dogon and Fulani, Mali. *Malar J*. 2014; 13(1):1–12.
85. Esoh KK, Apinjoh TO, Nyanjom SG, Wonkam A, Chimusa ER, Amenga-Etego L, et al. Fine scale human genetic structure in three regions of Cameroon reveals episodic diversifying selection. *Sci Rep*. 2021;11(1):1039.
86. Shenkutie TT, Nega D, Hailu A, Kepple D, Witherspoon L, Lo E, et al. Prevalence of G6PD deficiency and distribution of its genetic variants among malaria-suspected patients visiting Metehara health centre, Eastern Ethiopia. *Malar J*. 2022;21(1):260. <https://doi.org/10.1186/s12936-022-04269-5> PMID: 36076204
87. Riveron JM, Ibrahim SS, Mulamba C, Djouaka R, Irving H, Wondji MJ, et al. Genome-wide transcription and functional analyses reveal heterogeneous molecular mechanisms driving pyrethroids resistance in the major malaria vector *Anopheles funestus* across Africa. *G3 (Bethesda)*. 2017;7(6):1819–32. <https://doi.org/10.1534/g3.117.040147> PMID: 28428243
88. Witzig C, Wondji CS, Strode C, Djouaka R, Ranson H. Identifying permethrin resistance loci in malaria vectors by genetic mapping. *Parasitology*. 2013;140(12):1468–77. <https://doi.org/10.1017/S0031182013000024> PMID: 23448678
89. Kassegne K, Komi Koukoura K, Shen H-M, Chen S-B, Fu H-T, Chen Y-Q, et al. Genome-wide analysis of the malaria parasite *Plasmodium falciparum* isolates from togo reveals selective signals in immune selection-related antigen genes. *Front Immunol*. 2020;11:552698. <https://doi.org/10.3389/fimmu.2020.552698> PMID: 33193320
90. Njoroge H, Van't Hof A, Oruni A, Pipini D, Nagi SC, Lynd A, et al. Identification of a rapidly-spreading triple mutant for high-level metabolic insecticide resistance in *Anopheles gambiae* provides a real-time molecular diagnostic for antimalarial intervention deployment. *Mol Ecol*. 2022;31(16):4307–18. <https://doi.org/10.1111/mec.16591> PMID: 35775282
91. Hamilton F, Mitchell RE, Constantinescu A, Hughes D, Cunningham A, Ghazal P, et al. The effect of interleukin-6 signaling on severe malaria: a Mendelian randomization analysis. *Int J Infect Dis*. 2023;129:251–9. <https://doi.org/10.1016/j.ijid.2023.02.008> PMID: 36801374
92. Traore M, Sangare H, Diabate O, Diawara A, Cissé C, Nashiru O, et al. Causal effect of severe and non-severe malaria on dyslipidemia in African Ancestry individuals: a Mendelian randomization study. *Ann Hum Genet*. 2024. <https://doi.org/10.1111/ahg.12555> PMID: 38488696
93. Van Tyne D, Park DJ, Schaffner SF, Neafsey DE, Angelino E, Cortese JF, et al. Identification and functional validation of the novel antimalarial resistance locus PF10\_0355 in *Plasmodium falciparum*. *PLoS Genet*. 2011;7(4):e1001383. <https://doi.org/10.1371/journal.pgen.1001383> PMID: 21533027
94. Wang X, Afrane YA, Yan G, Li J. Constructing a genome-wide LD map of wild *A. gambiae* using next-generation sequencing. *Biomed Res Int*. 2015;2015:238139. <https://doi.org/10.1155/2015/238139> PMID: 26421280
95. Redmond SN, Eiglmeier K, Mitri C, Markianos K, Guelbeogo WM, Gneme A, et al. Association mapping by pooled sequencing identifies TOLL 11 as a protective factor against *Plasmodium falciparum* in *Anopheles gambiae*. *BMC Genomics*. 2015;16:779. <https://doi.org/10.1186/s12864-015-2009-z> PMID: 26462916

96. Henry B, Volle G, Akpovi H, Gineau L, Roussel C, Ndour PA, et al. Splenic clearance of rigid erythrocytes as an inherited mechanism for splenomegaly and natural resistance to malaria. *EBioMedicine*. 2022;82:104167. <https://doi.org/10.1016/j.ebiom.2022.104167> PMID: 35843175
97. Auburn S, Campino S, Miotto O, Djimde AA, Zongo I, Manske M, et al. Characterization of within-host *Plasmodium falciparum* diversity using next-generation sequence data. *PLoS One*. 2012;7(2):e32891. <https://doi.org/10.1371/journal.pone.0032891> PMID: 22393456
98. Mu J, Awadalla P, Duan J, McGee KM, Joy DA, McVean GAT, et al. Recombination hotspots and population structure in *Plasmodium falciparum*. *PLoS Biol*. 2005;3(10):e335. <https://doi.org/10.1371/journal.pbio.0030335> PMID: 16144426
99. Crawford JE, Riehle MM, Markianos K, Bischoff E, Guelbeogo WM, Gnome A, et al. Evolution of GOUNDRY, a cryptic subgroup of *Anopheles gambiae* sl, and its impact on susceptibility to *Plasmodium* infection. *Mol Ecol*. 2016;25(7):1494–510.
100. Mobegi VA, Duffy CW, Amambua-Ngwa A, Loua KM, Laman E, Nwakanma DC, et al. Genome-wide analysis of selection on the malaria parasite *Plasmodium falciparum* in West African populations of differing infection endemicity. *Mol Biol Evol*. 2014;31(6):1490–9. <https://doi.org/10.1093/molbev/msu106> PMID: 24644299
101. Sofeu-Feugaing DD, Nkengeh Ajongfac F, Nyuylam Moyeh M, Obejumo Apinjohn T, Essende ME, Talla Kouam GD, et al. Status of the multidrug resistance-1 gene of *Plasmodium falciparum* in four malaria epidemiological strata, two decades after the abolition of chloroquine as first-line treatment for uncomplicated malaria in Cameroon. *J Trop Med*. 2023;2023:6688380. <https://doi.org/10.1155/2023/6688380> PMID: 37426306
102. Apinjohn TO, Ajonina MU, Abera D, Chi HF, Tata RB, Mugri RN, et al. Genomic analysis of *Plasmodium falciparum* isolates across different altitudinal zones along the slope of Mount Cameroon. *Front Malar*. 2023;1:1075755.
103. Lucas ER, Nagi SC, Egyir-Yawson A, Essandoh J, Dadzie S, Chabi J, et al. Genome-wide association studies reveal novel loci associated with pyrethroid and organophosphate resistance in *Anopheles gambiae* and *Anopheles coluzzii*. *Nat Commun*. 2023;14(1):4946. <https://doi.org/10.1038/s41467-023-40693-0> PMID: 37587104
104. Borrmann S, Straimer J, Mwai L, Abdi A, Rippert A, Okombo J, et al. Genome-wide screen identifies new candidate genes associated with artemisinin susceptibility in *Plasmodium falciparum* in Kenya. *Sci Rep*. 2013;3:3318. <https://doi.org/10.1038/srep03318> PMID: 24270944
105. Olewe PK, Awandu SS, Munde EO, Anyona SB, Raballah E, Amolo AS, et al. Hemoglobinopathies, merozoite surface protein-2 gene polymorphisms, and acquisition of Epstein Barr virus among infants in Western Kenya. *BMC Cancer*. 2023;23(1):566. <https://doi.org/10.1186/s12885-023-11063-2> PMID: 37340364
106. Milet J, Sabbagh A, Migot-Nabias F, Luty AJF, Gaye O, Garcia A, et al. Genome-wide association study of antibody responses to *Plasmodium falciparum* candidate vaccine antigens. *Genes Immun*. 2016;17(2):110–7. <https://doi.org/10.1038/gene.2015.59> PMID: 26741287
107. Loucoubar C, Grant AV, Bureau J-F, Casademont I, Bar NA, Bar-Hen A, et al. Detecting multi-way epistasis in family-based association studies. *Brief Bioinform*. 2017;18(3):394–402. <https://doi.org/10.1093/bib/bbw039> PMID: 27178992
108. Elzein A. Genomic, patterns of selection and differentiation in African populations and implications for mapping disease association. Open University (UK); 2009.
109. Howie B, Marchini J, Stephens M. Genotype imputation with thousands of genomes. *G3 (Bethesda)*. 2011;1(6):457–70. <https://doi.org/10.1534/g3.111.001198> PMID: 22384356
110. Li J, Wang X, Zhang G, Githure JI, Yan G, James AA. Genome-block expression-assisted association studies discover malaria resistance genes in *Anopheles gambiae*. *Proc Natl Acad Sci USA* 2013;110(51):20675–80.
111. Damena D, Denis A, Golassa L, Chimusa ER. Genome-wide association studies of severe *P. falciparum* malaria susceptibility: progress, pitfalls and prospects. *BMC Med Genomics*. 2019;12(1):120. <https://doi.org/10.1186/s12920-019-0564-x> PMID: 31409341
112. Stewart C, Pepper MS. Cystic fibrosis on the African continent. *Genet Med*. 2016;18(7):653–62. <https://doi.org/10.1038/gim.2015.157> PMID: 26656651
113. Sirugo G, Williams SM, Tishkoff SA. The missing diversity in human genetic studies. *Cell*. 2019;177(1):26–31. <https://doi.org/10.1016/j.cell.2019.02.048> PMID: 30901543
114. Melzer D, Pilling LC, Ferrucci L. The genetics of human ageing. *Nat Rev Genet*. 2020;21(2):88–101. <https://doi.org/10.1038/s41576-019-0183-6> PMID: 31690828
115. Ziegler A, Sun YV. Study designs and methods post genome-wide association studies. Springer; 2012.

116. Zondervan KT, Cardon LR. Designing candidate gene and genome-wide case-control association studies. *Nat Protoc.* 2007;2(10):2492–501. <https://doi.org/10.1038/nprot.2007.366> PMID: 17947991
117. Bellivier F. Genetic association studies. In: Leboyer M, Bellivier F, editors. *Psychiatric genetics. Methods in Molecular Medicine™*, vol 77. Humana Press. <https://doi.org/10.1385/1-59259-348-8:127>
118. Hedrick PW. Population genetics of malaria resistance in humans. *Heredity (Edinb).* 2011;107(4):283–304. <https://doi.org/10.1038/hdy.2011.16> PMID: 21427751
119. Li Z, Wang S, Lin X. Variable selection and estimation in generalized linear models with the seamless L0 penalty. *Can J Stat.* 2012;40(4):745–69. <https://doi.org/10.1002/cjs.11165> PMID: 23519603
120. Zintzaras E, Santos M. Performance of MAX test and degree of dominance index in predicting the mode of inheritance. *Stat Appl Genet Mol Biol.* 2012;11(4). <https://doi.org/10.1515/1544-6115.1804>
121. Hothorn LA, Hothorn T. Order-restricted scores test for the evaluation of population-based case-control studies when the genetic model is unknown. *Biom J.* 2009;51(4):659–69. <https://doi.org/10.1002/bimj.200800203> PMID: 19650055
122. Zang Y, Fung WK, Zheng G, et al. Simple algorithms to calculate the asymptotic null distributions of robust tests in case-control genetic association studies in R. *J Stat Softw* 2010;33(8):1–24. <https://doi.org/10.18637/jss.v033.i08>
123. González JR, Carrasco JL, Dudbridge F, Armengol L, Estivill X, Moreno V. Maximizing association statistics over genetic models. *Genet Epidemiol.* 2008;32(3):246–54.
124. Zheng G, Joo J, Yang Y. Pearson's test, trend test, and MAX are all trend tests with different types of scores. *Ann Hum Genet* 2009;73(2):133–40.
125. Omolo B, Zhang H, Karmaus W. Cautions of Using Allele-Based Tests Under Heterosis. *Int J Stat Med Res.* 2013;2(1):47.
126. Gurdasani D, Carstensen T, Tekola-Ayele F, Pagani L, Tachmazidou I, Hatzikotoulas K, et al. The African Genome Variation Project shapes medical genetics in Africa. *Nature.* 2015;517(7534):327–32. <https://doi.org/10.1038/nature13997> PMID: 25470054
127. Sharaf A, Ndiribe CC, Omotoriogun TC, Abueg L, Badaoui B, Markey FJB, et al. Open institute of the African BioGenome Project: bridging the gap in African biodiversity genomics and bioinformatics. *Nat Biotechnol.* 2023;41(9):1348–54. <https://doi.org/10.1038/s41587-023-01933-2> PMID: 37699986.