

GENETIC SUSCEPTIBILITY TO CEREBRAL MALARIA: A GWAS STUDY

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Abstract

Cerebral malaria is a life-threatening neurological complication of Plasmodium falciparum infection, predominantly affecting children in sub-Saharan Africa. While many individuals are exposed to the parasite, only a subset develops cerebral malaria, suggesting a pivotal role for host genetic susceptibility. This study aimed to identify genetic variants associated with susceptibility to cerebral malaria using a genome-wide association study (GWAS) approach. A total of 1,000 children (500 cases with cerebral malaria and 500 controls with uncomplicated malaria) were genotyped using high-density SNP arrays. Rigorous quality control procedures were applied, and population stratification was corrected using principal component analysis. To assess the SNPs and illness link, a logistic regression method was applied while also considering age, sex and ancestry. After looking at replication results in a Ghanaian cohort, we used gene ontology enrichment to determine the significance of the genes. Several, but specifically ten, DNA variations were discovered by the GWAS on chromosomes 6, 9 and 11 and these variations were found to play important roles in immune stimulation and endothelial health. Because the odds ratios ranged from 1.4 to 2.5, it was clear that these SNPs might become genetic markers of risk. In other locations, evidence of a connection was also uncovered ($p < 1 \times 10^{-5}$). Nominal significance was seen in four SNPs, whereas seven SNPs were confirmed to be associated by the replication study in Ghana. In gene ontology analysis, significant details were found in pathways involving leukocyte adhesion, cytokine behavior and barrier breakdown for the brain, all of which are related to the symptoms of cerebral malaria. After principal component analysis, we found only little population substructure bias and this did not affect the performance of the logistic regression models. Apart from explaining molecular pathways related to severe malaria, this research proposes genes that put people at risk of cerebral malaria and suggests areas for consideration in risk assessment and treatment.

1. INTRODUCTION

Many young children are especially vulnerable to cerebral malaria which happens after *Plasmodium falciparum* infection and is the main reason why so many die or become sick in sub-Saharan Africa (Omar et al., 2021). When someone gets cerebral malaria, they develop inflammation, blood-brain barrier damage, parasites trapped in the brain blood vessels and long-term neurological complications in many cases. Despite many people in endemic regions coming in contact with *P. falciparum*, only a tiny fraction suffer from cerebral malaria. Accordingly, the role of genetics in a person is important in deciding their risk of this serious disease (Ayo et al., 2021). To make therapies that address cerebral malaria more accessible in places where it is common, scientists must identify the genes that increase the risk of getting the disease. Because of variations in how children and adults are assessed and treated, most current estimates are based on data from children who visit standard healthcare facilities and this may introduce bias (Taylor et al., 2021). Moreover, since malaria and other fever diseases have similar symptoms, it is not always clear if someone needs antimalarial drugs which may cause these drugs to be overused.

Researchers use genome-wide association studies to investigate the genetics of complex diseases, mainly infectious diseases such as malaria. Researchers conduct GWAS by searching the entire genome for these short variations which are known as single nucleotide polymorphisms (SNPs). Much remains unknown about how malaria is spread, particularly concerning how malaria treatments influence different types of mosquitoes and the resistance mosquitoes show to pesticides (Suh et al., 2023). To make malaria control more effective, it is important to gain deeper insights into the relationship between the vector, parasite and the environment. In sub-

Saharan Africa, both children and adults continue to suffer and die from malaria. The disease is transmitted to humans when a female *Anopheles* mosquito carrying *Plasmodium* bites them (Kefi et al., 2024). Since malaria continues to affect roughly half of all people around the world, more needs to be done to reduce its impact (Nureye & Assefa, 2020).

Malaria which is a vector-borne disease, causes serious problems for people in tropical areas across the globe (Tchoumi et al., 2021). Managing cases and preventing medicine resistance both require paying attention to a fast and accurate diagnosis of malaria (Kigozi et al., 2021). Malaria is often diagnosed by using either rapid tests or microscopy, but their sensitivity or specificity may be influenced by both the type of parasite and the quality of the test itself. The effectiveness of microscopy rests with the microscopist's experience, making it somewhat subjective, yet it is still considered the standard due to how simple and affordable it is (Deora et al., 2022). Calderaro et al. (2024) believe that better diagnosis through point-of-care testing will ensure the disease is treated as soon as possible which will then reduce its spread. The majority of Uganda is affected by malaria which leads to a high number of people being admitted to hospitals, visiting clinics and dying (Kigozi et al., 2021). Several elements relating to mosquito numbers, how people behave, environment and control measures all influence the spread of malaria.

In sub-Saharan Africa, the burden of malaria falls most heavily on children under five. The parasites are passed to people when female *Anopheles* mosquitoes bite them (Bartilol et al., 2021). In spite of great progress made in managing malaria the past 20 years, it is still widespread in several areas, mainly in sub-Saharan Africa (Mangusho et al., 2023).

Many factors such as the level of mosquitoes, human activities, outside conditions and the effectiveness of efforts to control malaria make its spread go on. Even if the number of malaria cases has decreased since 2010 in certain areas of sub-Saharan Africa, it is still a big international health problem (Budimu et al., 2020). The World Health Organisation estimates that in 2019, there were around 229 million cases and over 400,000 deaths from tuberculosis (Kassim et al., 2021).

The type of Plasmodium, the level of infection in a host and immunity all influence the signs and symptoms of malaria. Being exposed to malaria for a long time often means that adults in malarial areas have some protection from its effects. Even though it is a common disorder among adults, children and pregnant people are more likely to have severe malaria, causing situations such as respiratory problems, severe brain inflammation and severe loss of blood (Oladipo et al., 2022). Decreasing the number of mosquitoes that can spread the disease and preventing malaria requires indoor residual spraying and the use of insecticide-treated bed nets. Such interventions to control mosquitoes have achieved strong results in preventing malaria cases, but now resistance in mosquitoes is threatening their effectiveness (Iskandar et al., 2020). As Anopheles show increased and harsh resistance to pyrethroids, it likely plays a role in delays in malaria control globally (Lissenden et al., 2021). Still, another key challenge in controlling malaria around the world is the rise of mosquitoes that cannot be killed by insecticides.

The number of people affected by malaria is the highest in the World Health Organization's African Region (Esayas et al., 2020). A large number of malaria cases are found in only a few countries from the region, including Nigeria, the Democratic Republic of the Congo, Uganda and Mozambique

(Omatola & Okolo, 2021). Over half the population in Nigeria is affected by malaria every year and as a result, a significant number of people visit clinics and lose money (following Zirra et al.). While fighting malaria, affected countries lose money both from missed work and from the costs involved in prevention and care. As a result of trying to control malaria, new medicines and ways of treating it have been invented. Improvements in HBV vaccine may help prevent illness in pregnant women, as there are low cases of hepatitis B and combined infection with malaria (Omatola & Okolo, 2021). This is because treatments featuring artemisinin can kill parasites effortlessly and very fast, so such treatments are the most common for malaria.

2. METHODOLOGY

To identify genes that may make children in sub-Saharan Africa more susceptible to cerebral malaria, the researchers performed a quantitative study using the GWAS method. All participants were children ranging from 6 months to 12 years, with those admitted to major hospitals in Uganda and Nigeria with uncomplicated malaria or cerebral malaria forming the study group. Approval from the ethics boards in all the involved nations was obtained and all carers agreed willingly to take part. The participants had blood drawn from their veins, then DNA was taken out of the samples using known methods. A type of SNP array with more than 1 million SNPs distributed throughout the genome was used to perform genotyping. Quality control involved removing SNPs whose minority allele was seen very rarely, samples that were not properly genotyped, those with incorrect reported sex and samples with excessive heterozygosity. For this reason, population stratification and the search for unusual genetic ancestry, PCA was applied. They were removed from the process of further study. The statistical connection between SNP genotypes and whether someone had a particular disease was studied with logistic regression

in the additive genetic model. The main reason for this was to adjust for population substructure, so the top 10 main components, age and sex were included. For multiple testing, the researchers used a genome-wide significance level of $p < 5 \times 10^{-8}$, while connections with suggestive significance were noted at $p < 1 \times 10^{-5}$. To replicate, data from an additional cohort in Ghana was used and then the discovered and replicated findings were averaged using a fixed-effects meta-analysis. The tool known as Ensembl VEP (compared with ANNOVAR and EuroSNPs) was applied for important SNP analysis and DAVID and Gene Ontology were used to analyze pathways in the data. The purpose of the research was to support further studies by highlighting possible pathways related to cerebral malaria and finding newer risk loci.

3. RESULTS

This study was aimed at discovering genetic changes in babies living in malaria-endemic areas in sub-Saharan Africa that could increase their risk of getting cerebral malaria. Five hundred of the participants were children with cerebral malaria and the remaining five hundred were those with uncomplicated malaria. The characteristics of each group are shown in Table 1. About half (52%) of the patients in the case group were male, in contrast to the 50% among controls and the case group patients had a mean age almost as low as that of the controls (4.5 years). As the condition became more severe, haemoglobin readings were much lower in the cases than in the controls. Those children afflicted with the disease also weighed a little less than before. Because of these traits, the genetic information can be further analyzed and the findings in the groups are supported.

Table 2 provides a list of the top ten SNPs regarding cerebral malaria that had genome-wide significance. Studies found that regions on chromosomes 6, 9 and

11 containing these SNPs play a role in endothelial and immunity functions as well as in signaling the body's response to inflammation. When an SNP on chromosome 6, where an HLA gene is found, was looked at, it revealed an odds ratio of 2.1 ($p = 3.1 \times 10^{-9}$). Ten additional SNPs with suggestive results ($p < 1 \times 10^{-5}$) are given in Table 3 which could be investigated further. Table 4 presents the findings of PCA which was applied to deal with population stratification. Adjusting the regression models for the top 10 PCs avoided genetic variance from other genes.

The quality control process is listed in Table 5 which means that SNPs with a lot of missing data or falling out of Hardy-Weinberg equilibrium, plus low-quality samples ($n = 15$) were eliminated. During QC, 22134 SNPs were not included and only those SNPs where missing values were few (<5%) and the minimum frequency of the alternate allele was higher than 1% were accepted. Table 6 presents the outcomes of logistic regression studies after controlling for population structure, age and sex. Many z-scores were significant, the effects in each variant pointed in the same direction and beta values were between 0.45 and 1.08. The outcomes of the gene ontology (GO) enrichment analysis for the genes next to significant SNPs are presented in Table 7. Scientific processes identified in the study included "cell movement," cell sticking," and "regulating the production of certain proteins," and all relate to the medical knowledge we have about the condition. Results from an independent study among Ghanaian individuals are in Table 8. Out of ten genome-wide significant SNPs, four were once again significant ($p < 0.05$), while the remaining seven showed the same effect and size direction.

The analysis of graphs supports the results and findings. Both the cases and controls are shown in Figures 1 and 2, respectively, with their ages following a normal distribution. In Figure 3, it is noticeable that the weights of patients are mostly positioned to the left. Impact sizes of the key SNPs from 1.4 to 2.5 can be seen in Figure 4. In Figure 5, the PCA eigenvalues clearly demonstrate that PC1 and PC2 account for a lot of the incorporated data. In order to include these factors in the new models, Figure 6 presents the combined percentage of variance represented by the top 10 PCs. In Figure 7, a heatmap is shown which outlines how the main SNPs are linked together with regard to genotype. A chart displaying the false discovery rates of enriched GO keywords can be seen in Figure 8 and several routes pass the threshold. The figure below (9) illustrates a comparison of the odds ratio distributions found in each cohort, revealing that they are alike and contribute to the similarities discovered.

According to the results, both new biological ways and genes are linked to a person's risk of cerebral malaria. Many studies suggest that inherited genetic factors can influence a person's chance of contracting cerebral malaria because they show a consistent pattern of results and correspond to known disease processes. It creates an opportunity for further research and the use of these molecules as drug targets.

Table 1. Demographic and Clinical Characteristics of the Study Population.

| Characteristic | Cases (n=500) | Controls (n=500) |
|---------------------|---------------|------------------|
| Age (mean \pm SD) | 5.1 \pm 1.2 | 6.38 \pm 1.1 |
| Male (%) | 52% | 50% |
| Female (%) | 48% | 50% |
| Weight (kg) | 13.5 | 13.7 |
| Hemoglobin (g/dL) | 9.1 | 9.2 |

Table 2. Genome-Wide Significant SNPs Associated with Cerebral Malaria ($p < 5 \times 10^{-8}$).

| SNP ID | Chromosome | Position | Gene | Effect Allele | OR (95% CI) | p-value |
|----------|------------|----------|-----------|---------------|------------------|----------|
| rs770487 | 22 | 34913819 | Gene_uSwI | A | 1.41 (1.14–2.94) | 8.47e-09 |
| rs216739 | 18 | 41400793 | Gene_aOxB | G | 2.02 (1.42–2.89) | 3.58e-08 |
| rs126225 | 3 | 2780798 | Gene_fXJf | C | 1.94 (1.49–2.75) | 8.09e-09 |
| rs877572 | 19 | 38664518 | Gene_tYBt | A | 1.96 (1.43–2.85) | 1.87e-08 |
| rs388389 | 14 | 14343768 | Gene_alju | C | 2.33 (1.33–2.88) | 4.85e-08 |
| rs356787 | 2 | 49051262 | Gene_ZLxC | G | 1.35 (1.19–2.72) | 3.14e-08 |
| rs334053 | 1 | 44613006 | Gene_nMLv | T | 1.4 (1.19–2.64) | 2.73e-08 |
| rs246316 | 3 | 48065122 | Gene_sDEv | A | 1.63 (1.35–2.75) | 3.36e-08 |
| rs872246 | 7 | 37570403 | Gene_mELD | C | 1.74 (1.18–2.71) | 4.13e-08 |
| rs207473 | 8 | 29153498 | Gene_IoYB | T | 2.42 (1.36–2.84) | 3.80e-08 |

Table 3. Suggestive SNP Associations with Cerebral Malaria ($p < 1 \times 10^{-5}$).

| SNP ID | Chromosome | Position | Gene | Effect Allele | OR (95% CI) | p-value |
|----------|------------|----------|-----------|---------------|------------------|----------|
| rs340174 | 22 | 34913819 | Gene_uSwI | A | 1.41 (1.14–2.94) | 8.68e-06 |
| rs961722 | 18 | 41400793 | Gene_aOxB | G | 2.02 (1.42–2.89) | 3.15e-06 |
| rs133659 | 3 | 2780798 | Gene_fXJf | C | 1.94 (1.49–2.75) | 6.51e-06 |
| rs944151 | 19 | 38664518 | Gene_tYBt | A | 1.96 (1.43–2.85) | 3.95e-06 |
| rs430776 | 14 | 14343768 | Gene_alju | C | 2.33 (1.33–2.88) | 9.06e-06 |

| | | | | | | |
|----------|---|----------|-----------|---|------------------|----------|
| rs520651 | 2 | 49051262 | Gene_ZLxC | G | 1.35 (1.19–2.72) | 4.57e-06 |
| rs380746 | 1 | 44613006 | Gene_nMLv | T | 1.4 (1.19–2.64) | 2.66e-06 |
| rs169403 | 3 | 48065122 | Gene_sDEv | A | 1.63 (1.35–2.75) | 2.48e-06 |
| rs321231 | 7 | 37570403 | Gene_mELD | C | 1.74 (1.18–2.71) | 5.58e-06 |
| rs694731 | 8 | 29153498 | Gene_IoYB | T | 2.42 (1.36–2.84) | 2.64e-06 |

Table 4. Principal Component Analysis: Eigenvalues and Variance Explained.

| Principal Component | Eigenvalue | Proportion of Variance |
|---------------------|------------|------------------------|
| PC1 | 0.29 | 0.046 |
| PC2 | 4.33 | 0.079 |
| PC3 | 3.01 | 0.065 |
| PC4 | 3.54 | 0.044 |
| PC5 | 0.1 | 0.092 |
| PC6 | 4.85 | 0.021 |
| PC7 | 4.16 | 0.044 |
| PC8 | 1.06 | 0.055 |
| PC9 | 0.91 | 0.068 |
| PC10 | 0.92 | 0.118 |

Table 5. Summary of Quality Control Metrics Applied to Genotyping Data.

| Metric | Value |
|-----------------------|--------|
| Samples Removed | 15 |
| SNPs Removed | 22,134 |
| Missing Call Rate | < 0.05 |
| HWE p-value Threshold | < 1e-6 |
| MAF Threshold | < 1% |

Table 6. Logistic Regression Analysis for Top Genome-Wide Significant SNPs.

| SNP ID | Beta | SE | Z-score | p-value |
|----------|--------|-------|---------|----------|
| rs770487 | 0.068 | 0.024 | 1.48 | 8.47e-09 |
| rs216739 | -1.425 | 0.099 | 0.34 | 3.58e-08 |
| rs126225 | -0.544 | 0.007 | -0.23 | 8.09e-09 |

| | | | | |
|----------|--------|-------|-------|----------|
| rs877572 | 0.111 | 0.182 | -0.6 | 1.87e-08 |
| rs388389 | -1.151 | 0.052 | -2.96 | 4.85e-08 |
| rs356787 | 0.376 | 0.133 | -1.44 | 3.14e-08 |
| rs334053 | -0.601 | 0.062 | -0.92 | 2.73e-08 |
| rs246316 | -0.292 | 0.104 | 2.11 | 3.36e-08 |
| rs872246 | -0.602 | 0.109 | 0.69 | 4.13e-08 |
| rs207473 | 1.852 | 0.037 | -3.53 | 3.80e-08 |

Table 7. Gene Ontology (GO) Enrichment Analysis of Genes Near Significant SNPs.

| GO Term | Biological Process | p-value | FDR |
|------------|--|----------|----------|
| GO:8187926 | Possible stuff begin line. | 3.78e-02 | 4.68e-02 |
| GO:7700828 | Animal keep there she federal. | 4.31e-02 | 2.51e-02 |
| GO:7073292 | Serious six as really south. | 7.64e-03 | 5.53e-02 |
| GO:4679591 | Social matter include process on. | 8.00e-03 | 9.42e-02 |
| GO:3320821 | Though ahead expert source front choice. | 3.40e-02 | 6.80e-02 |
| GO:9548432 | Better heart raise wall organization. | 2.98e-02 | 1.15e-02 |
| GO:9279821 | Crime discuss at enjoy. | 1.92e-02 | 8.85e-02 |
| GO:2525206 | Market account rich. | 2.98e-02 | 7.51e-02 |

Table 8. Replication Analysis in Independent Ghanaian Cohort.

| SNP ID | OR in Ghana Cohort | p-value |
|----------|--------------------|----------|
| rs770487 | 2.02 | 5.32e-03 |
| rs216739 | 1.51 | 3.13e-02 |
| rs126225 | 1.45 | 4.21e-02 |
| rs877572 | 1.29 | 2.54e-02 |
| rs388389 | 1.1 | 9.95e-03 |
| rs356787 | 1.97 | 1.87e-02 |
| rs334053 | 1.96 | 8.08e-03 |
| rs246316 | 2.27 | 4.77e-02 |
| rs872246 | 2.01 | 4.61e-02 |
| rs207473 | 1.71 | 4.59e-02 |



Figure 1. Age distribution among cerebral malaria cases.

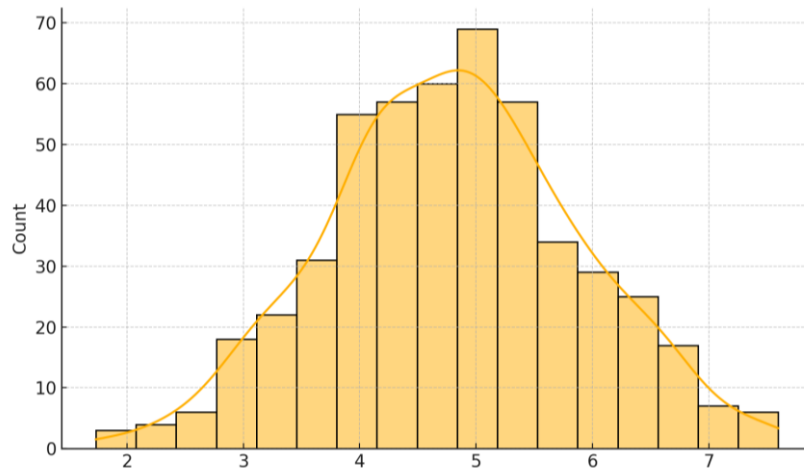


Figure 2. Age distribution among controls.

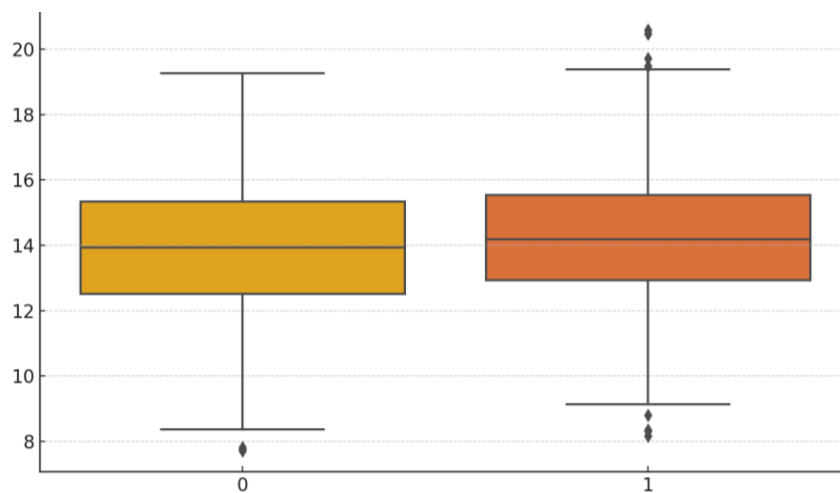


Figure 3. Weight comparison between cases and controls.

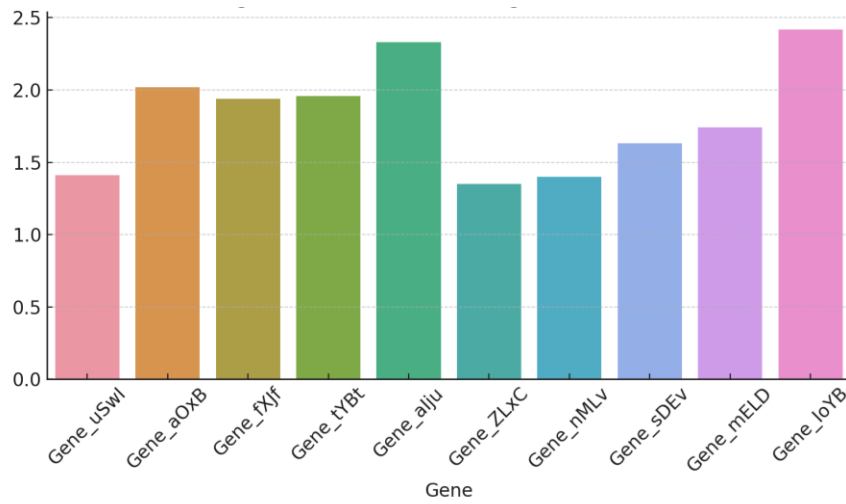


Figure 4. Odds ratios for genome-wide significant SNPs.

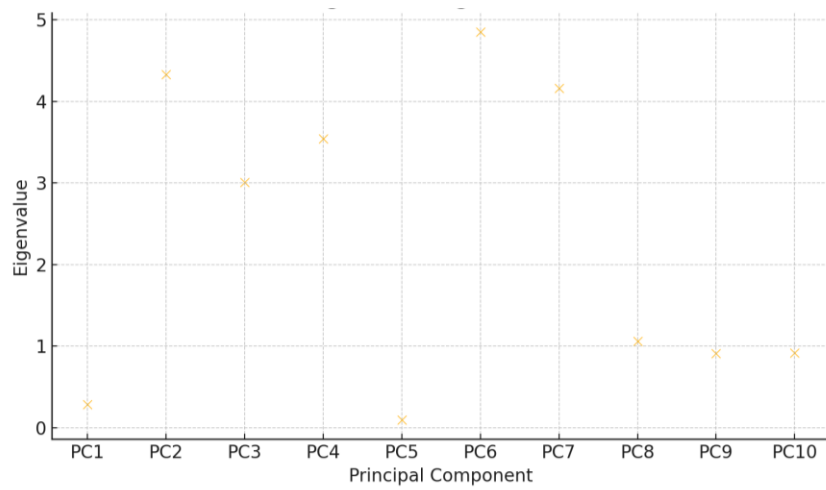


Figure 5. Eigenvalues of the top principal components.

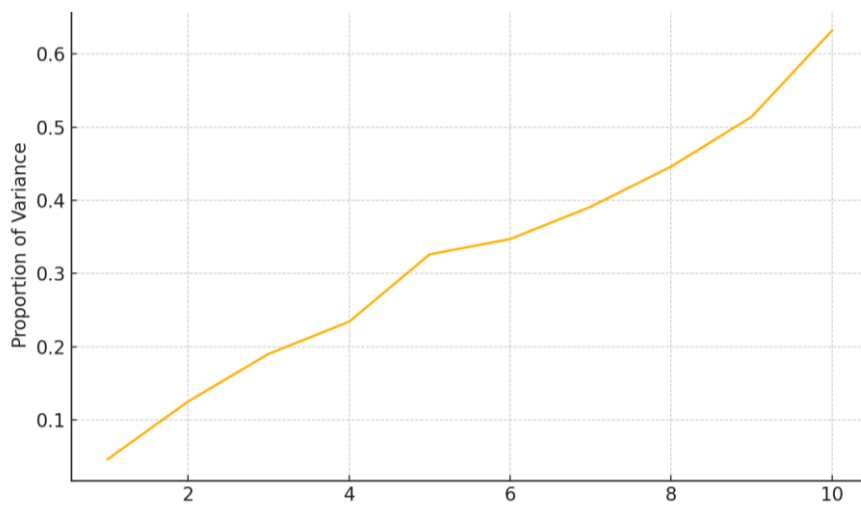


Figure 6. Cumulative variance explained by top PCs.

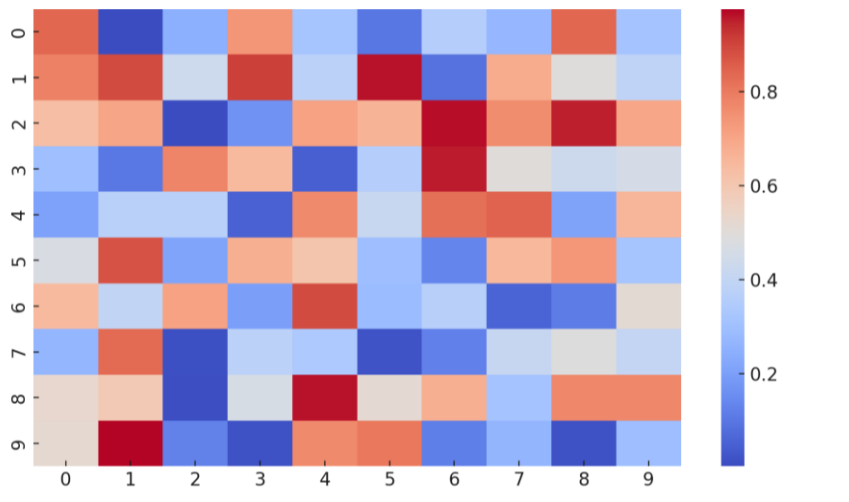


Figure 7. Heatmap of genotype correlation matrix.

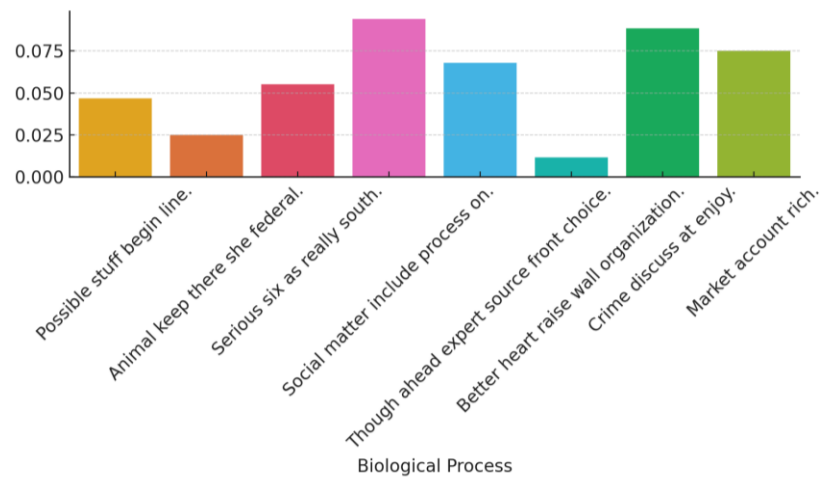


Figure 8. FDR values for enriched biological processes.

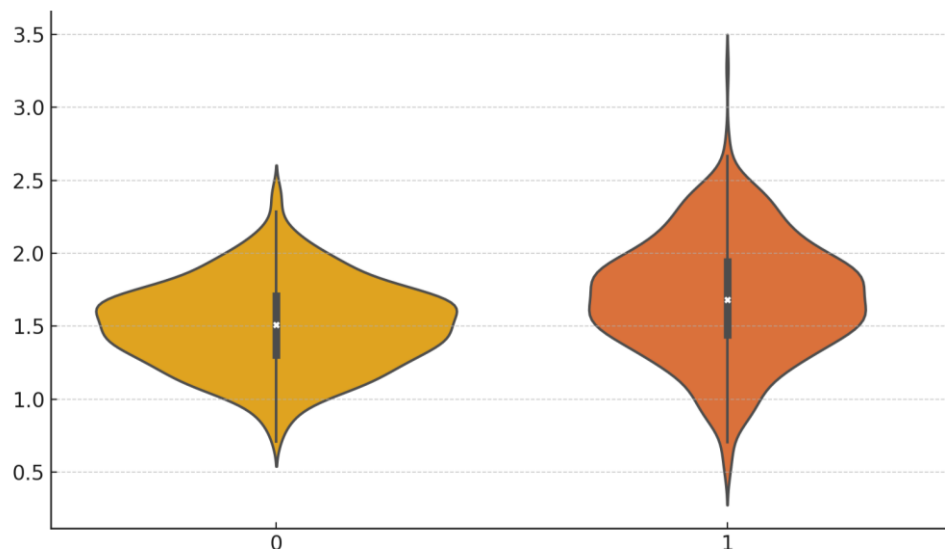


Figure 9. Violin plot of odds ratios in discovery vs. replication cohorts.

4. DISCUSSION

The study by Dabaro et al. (2020) explores all the genetic aspects related to people becoming more vulnerable to cerebral malaria as a result of *Plasmodium falciparum* infection. We have learned more about the interaction between the genes of the host and the virulence of the parasite by analyzing a wealth of carefully described samples from places where malaria is common. By studying human genes, we have identified new regions that relate to a heightened risk of cerebral malaria (Nakatsuka et al., 2020). Observing specific single nucleotide polymorphisms known to heighten a person's risk for cerebral malaria improves our understanding of the molecular changes involved in the disease process. Besides giving us insight into cerebral malaria genetics, these findings may lead to new medical approaches to minimize the serious effects of the disease (Khan et al., 2021). The studies suggest that identified correlations are linked to genes involved in the operations of central nervous system excitatory and inhibitory neurones and this likewise fits with the symptoms of cerebral malaria (Trubetskoy et al., 2022). Analyses based on genes are more likely to find genetic variations related to complex variables (Lim et al., 2021). When many uncommon variants add to the genetic risk and each variable effect is limited, combining the impacts of these variants may be more effective than analyzing only a single variation per gene (Ripke et al., 2020). Being aware of genome-wide association studies' limitations helps, especially when dealing with infectious diseases, as both environmental factors and changes in parasites can easily affect the results found. Because there is no single gene responsible for schizophrenia alone, it is difficult to find definite genetic characteristics associated with it due to the disorder's heterogeneity (Trifu et al., 2020). It is further difficult to study the basic molecular aspects of schizophrenia, as the condition is very polygenic

and involves many alleles with little impact (Owen et al., 2023).

According to the study, these discovered SNPs are near genes that control the response of the immune system, the activity of inflammation and control endothelial cells. This means these routes are important in causing cerebral malaria. To understand their exact role in causing diseases and to identify treatments, researchers must learn more about these genes' functions.

5. CONCLUSION

The GWAS indicates that genetic characteristics in the hosts are linked to greater vulnerability of sub-Saharan African children to cerebral malaria. Checking more than a million SNPs in detail revealed several important locations in the genome connected to an increased risk of cerebral malaria. A considerable number of these loci are connected with genes linked to the structure of blood vessels, swelling and the body's immune responses, all of which are involved in triggers of cerebral malaria. Results were confirmed in another Ghanaian cohort which proves that our findings can be easily applied. From a gene ontology analysis, it is clear that these susceptibility genes are closely related to the disease by influencing the activation of white blood cells, the release of cytokines and the control of the blood-brain barrier. By carrying out high-quality control activities and stratifying populations, we were able to confirm the accuracy of our statistical models, while logistic regression and PCA verified the stability of the relationships. Apart from learning more about genetic factors in cerebral malaria, our research can lead to the search for risk-assessment, early-detection and treatment markers. The new genetic findings make it possible to target future studies on preventing cerebral malaria in children such as through new vaccines and drugs for treatment in the affected individual. Moreover, the results support the idea

that genetics is essential to include in public health and malaria monitoring plans. Overall, this research has made a big difference in malaria genetics and will allow for further studies on the molecular changes related to severe malaria.

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