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REVIEW ARTICLE

Adaptive Genetic Traits in Human Populations: Evolutionary Responses to Malaria

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Abstract
Malaria continues to be a significant health concern in tropical and subtropical areas. The disease is caused by *Plasmodium* parasites and spread through mosquito bites. This review investigates the genetic adaptations that humans have developed over time as a response to malaria. Notable adaptations include hemoglobinopathies (sickle cell trait, thalassemias, hemoglobin C), enzyme disorders (G6PD deficiency, pyruvate kinase deficiency), and membrane protein variations (Duffy antigen negativity, hereditary ovalocytosis). These traits disrupt the malaria parasite's life cycle or enhance immune responses, thereby protecting against severe disease. However, they also introduce health risks, such as chronic anemia and complications with certain medications. Future research focuses on gene-editing technologies and new treatments to improve malaria management while addressing these associated health challenges.

Keywords: Malaria, Genetic adaptations, Population genetics

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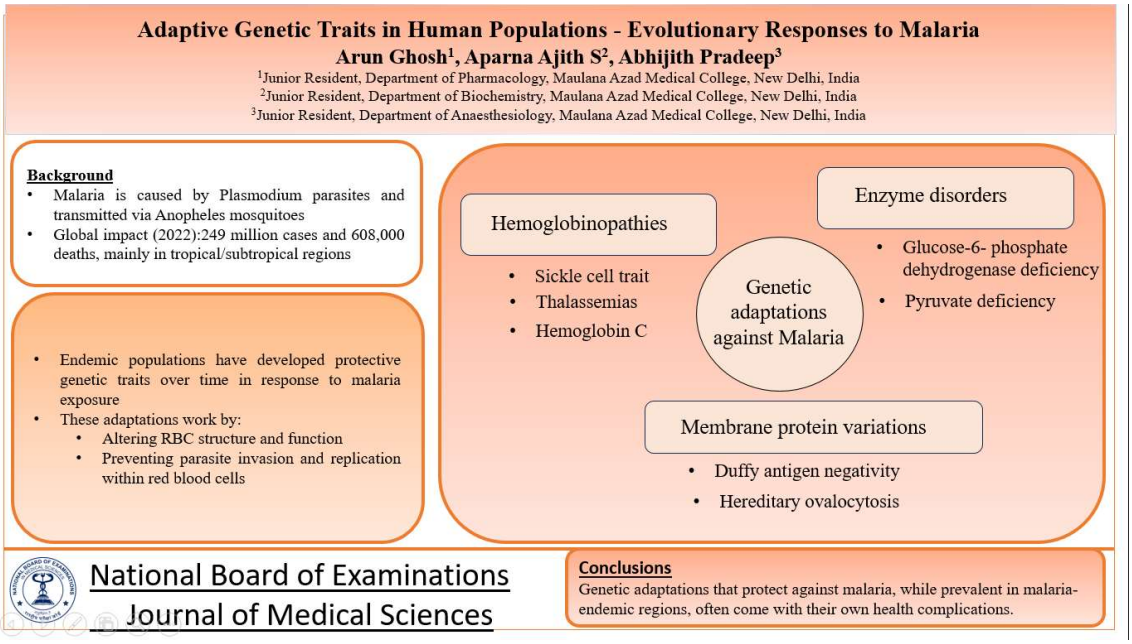
Graphical Abstract



Introduction

Malaria, a parasitic disease caused by *Plasmodium* and transmitted by *Anopheles* mosquitoes, has posed a persistent public health problem. The disease still impacts millions of people globally, especially in tropical and subtropical regions including Africa and Southeast Asia. Globally in 2022, there were an estimated 249 million malaria cases and 608 000 malaria deaths in 85 countries [1].

The malarial parasites first invade the liver cells before targeting red blood cells (RBCs), which causes symptoms like fever, chills, and anemia. In severe cases, it can be potentially fatal. A targeted Plasmodium infection begins when Anopheles mosquitoes inoculate sporozoites during blood feeding, followed by hepatic invasion and subsequent erythrocytic cycles of merozoite proliferation and host cell lysis. The parasitic cycle reaches completion through gametocyte formation in human blood, followed by sexual reproduction and sporozoite development within the mosquito vector [2].

Over time, populations where malaria is endemic have developed various genetic traits as protective adaptations. These adaptations primarily affect the structure and function of RBCs, and hinder the invasion by the parasites or their replication within RBCs [3].

This review article examines the adaptations humans have developed, including their underlying mechanisms and the geographical distribution. It also discusses how these adaptations provide protection while potentially impacting health in other ways.

Genetic adaptations against malaria

These genetic traits can be classified into (1) hemoglobinopathies, (2) enzyme disorders, and (3) membrane protein variations.

I. Hemoglobinopathies

Certain blood disorders, including sickle cell trait and thalassemias, provide

protection against malaria by making red blood cells less suitable for the survival and reproduction of the Plasmodium parasite. These genetic variations typically lead to altered red blood cell structure or reduced hemoglobin production, which can impair the parasite's ability to invade, grow, or reproduce effectively, thereby conferring a degree of protection against severe malaria.

1. *Sickle cell trait*

Sickle cell anemia is an autosomal recessive disorder characterized by the production of abnormal hemoglobin S (HbS), with the genotype SS. Sickle cell trait results when an individual inherits a gene for normal hemoglobin (A) and a gene for sickle hemoglobin Hb (S) that results in the genotype AS [4].

When malarial parasites enter the red blood cells of individuals with sickle cell trait, the infected cells tend to undergo sickling, likely due to deoxygenation and the reduction in pH caused by the parasite. This selective sickling of parasitized red blood cells in individuals with AS genotype facilitates their recognition and removal by phagocytosis, thereby disrupting the parasite's life cycle and mitigating the severity of the infection [5].

Sickle cell trait is more prevalent among individuals of African descent. In the United States, the prevalence of sickle cell trait is approximately 9% among African Americans and 0.2% among Caucasians. Globally, an estimated 300 million people carry the sickle cell trait, with one-third of this population residing in sub-Saharan Africa, a region where malaria is highly endemic [6].

2. *Thalassemias*

Thalassemias are inherited blood disorders that result from mutations in either α-globin or β-globin genes. The protective effect of thalassemia against malaria is attributed to several mechanisms.

These include reduced parasite growth in altered red blood cells, enhanced phagocytosis of infected cells, increased oxidative stress unfavorable to the parasite, and the presence of malaria-resistant fetal hemoglobin in some thalassemia variants [7].

This evolutionary advantage explains the high prevalence of thalassemia in malaria-endemic regions, such as in the Mediterranean region, as it confers a survival benefit against severe malaria, particularly *Plasmodium falciparum* infections [8].

3. *Hemoglobin C*

Hemoglobin C is a variant of normal adult hemoglobin resulting from a mutation in the beta-globin gene, where glutamic acid is replaced by lysine at position 6.

This variant confers protection against malaria, particularly *Plasmodium falciparum* infections, through several mechanisms. These include altering red blood cell structure to inhibit parasite growth, enhancing immune recognition of infected cells, reducing cytoadherence of infected cells to blood vessel walls, and potentially damaging the parasite through crystal-like structures formed under low oxygen condition [9].

Several studies have observed a protective effect in both heterozygotes (HbAC) and homozygotes (HbCC) against malaria infection [9,10]. It has also been observed that the hemoglobin variant occurs at a high frequency in Western Africa, a region known for being endemic to malaria [11].

II. Enzyme disorders

Glucose-6-phosphate dehydrogenase deficiency and pyruvate kinase deficiency are two genetic disorders affecting red blood cell metabolism that, despite their potential health drawbacks, protect against severe malaria caused by *Plasmodium falciparum*.

Glucose-6-phosphate dehydrogenase deficiency

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common enzymatic disorder of red blood cells, affecting over 400 million people worldwide. This X-linked genetic condition results in reduced activity of G6PD, a crucial enzyme in the pentose phosphate pathway that protects cells from oxidative stress [12].

Paradoxically, this deficiency confers protection against severe malaria, particularly caused by *Plasmodium falciparum*. The protective mechanism is multifaceted: G6PD-deficient erythrocytes are more susceptible to oxidative damage, leading to their premature hemolysis when infected by malaria parasites. This accelerated destruction of infected cells limits parasite proliferation and disease severity [13].

The prevalence of G6PD deficiency closely mirrors the historical distribution of *Plasmodium falciparum* malaria. In areas with high malaria transmission, G6PD deficiency can reach frequencies of 5-25%, as in Sub-Saharan Africa and Southeast Asia, compared to a global prevalence of 4.9% [12].

1. *Pyruvate Kinase deficiency*

Pyruvate kinase deficiency is an inherited disorder of red blood cell metabolism caused by mutations in the PKLR gene. This enzyme deficiency leads to impaired glycolysis in erythrocytes, resulting in decreased ATP production, shortened red blood cell lifespan, and chronic hemolytic anemia of varying severity, with symptoms ranging from mild to severe depending on the specific genetic mutations involved [14].

Pyruvate kinase deficiency confers protection against *Plasmodium falciparum* malaria through a dual mechanism. First, in homozygous individuals, there is an invasion defect where erythrocytes are more resistant to parasite entry. Second, both homozygotes and heterozygotes exhibit enhanced macrophage clearance of ring-stage infected erythrocytes. These combined effects result in a reduced overall parasite burden and limit the progression of infected cells to more mature stages [15].

III. Membrane protein variations

1. *Duffy antigen negativity*

The Duffy antigen, also known as the Duffy Antigen Receptor for Chemokines (DARC), serves as the primary receptor for P. vivax merozoites to invade human RBCs.

Without the Duffy antigen receptor on RBCs, P. vivax merozoites cannot attach to and invade the cells, effectively blocking the parasite's ability to establish infection and reproduce within the host.

The genetic basis of Duffy antigen negativity is a point mutation (-33T>C) in the GATA box of the FY gene promoter, which disrupts the binding site for the GATA-1 transcription factor, specifically abolishing Duffy antigen expression in erythroid cells. This erythroid-specific mutation is found in African Americans (70%) and West Africans (approaching 100%) [16].

Plasmodium vivax is considered to be absent from Western Africa, where the

prevalence of Duffy-negative red blood cell phenotype proves to be very high [17].

2. *Hereditary Ovalocytosis*

Ovalocytosis, particularly Southeast Asian Ovalocytosis (SAO), protects against malaria by altering the structure and function of red blood cells. The red blood cells in individuals with ovalocytosis are more rigid and less deformable due to a mutation in the SLC4A1 gene, which affects the membrane protein Band 3. This rigidity makes it difficult for malaria parasites, especially *Plasmodium falciparum*, to invade and thrive within the ovalocytic cells. The parasite relies on flexible red blood cells to enter, replicate, and spread. With the stiffened ovalocytes, invasion and intracellular growth are hindered, providing a degree of natural protection against malaria [18].

Several studies have observed reduced severity and incidence of malaria in regions where ovalocytosis is more prevalent, such as Southeast Asia and the Pacific Islands, including Papua New Guinea and Malaysia [19].

A summary of adaptive genetic traits that offer protection against malaria is given in Table 1.

Table 1. Adaptive genetic traits that offer protection against malaria

Genetic Trait/Disease	**Mechanism of Protection**	**Active Against**	**Regions with Most Prevalence**
Sickle Cell Trait (HbAS)	Infected red blood cells undergo sickling, leading to their early removal by the immune system, disrupting parasite growth.	*Plasmodium falciparum*	Sub-Saharan Africa, parts of the Americas
Thalassemias (α and β)	Reduced parasite growth in altered RBCs, enhanced phagocytosis of infected cells, increased oxidative stress.	*Plasmodium falciparum*	Mediterranean, Southeast Asia, Middle East
Hemoglobin C (HbAC, HbCC)	Alters RBC structure to inhibit parasite growth, enhances immune recognition, reduces cytoadherence, damages parasite in low oxygen conditions.	*Plasmodium falciparum*	Western Africa
G6PD Deficiency	Infected RBCs are more prone to oxidative damage and hemolysis, limiting parasite proliferation and reducing disease severity.	*Plasmodium falciparum*	Sub-Saharan Africa, Southeast Asia, Mediterranean
Pyruvate Kinase Deficiency	Erythrocytes are more resistant to invasion, enhanced macrophage clearance of infected cells, leading to reduced parasite burden.	*Plasmodium falciparum*	Scattered worldwide, rare, with cases in the Middle East and Europe
Duffy Antigen Negativity	Prevents *Plasmodium vivax* merozoites from invading RBCs, as they rely on the Duffy antigen for entry.	*Plasmodium vivax*	West Africa, African Americans
Hereditary Ovalocytosis	Rigid RBCs make it difficult for parasites to invade and thrive, reducing replication and spread of malaria.	*Plasmodium falciparum*	Southeast Asia, Pacific Islands (e.g., Papua New Guinea, Malaysia)

Health consequences of protective mechanisms

The protective mechanisms against malaria, such as hemoglobinopathies, enzyme disorders, and membrane protein variations, come with significant health consequences also. For example, individuals with the sickle cell trait are protected from *Plasmodium falciparum*, but homozygotes (HbSS) suffer from sickle cell disease, a debilitating condition characterized by chronic pain, anemia, and organ damage. Thalassemias also offer defense against malaria but come with their own health challenges, mainly the ongoing anemia due to red blood cell destruction. In severe cases, patients need regular blood transfusions throughout their lives.

Balancing selection maintains these traits in populations where the survival advantage against malaria outweighs the health burdens. This evolutionary pressure is particularly strong in areas where malaria is common. In these areas, individuals with heterozygous genes experience a survival benefit, which contributes to the persistence of these genetic traits within the population.

Conclusion

Various genetic adaptations, including hemoglobinopathies, enzyme deficiencies, and membrane protein variations, have been observed to be protective against malaria, especially Plasmodium falciparum malaria. These variations are also found to be prevalent in regions that are highly endemic for malaria. Despite their protective role against malaria, these genetic variations also introduce certain health challenges that demand careful management.

Statements and Declarations

Conflicts of interest

The authors declare that they do not have conflict of interest.

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