

Review Article



Genetic resistance to human malaria

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ABSTRACT

Human beings are sometime expose to the same to predisposing factors of a given infectious disease, but the outcome in terms of disease manifestation differs greatly. This variation is mainly attributed to the genetic makeup of such individuals; this is because human genetic has long been associated with the variation in susceptibility to various infectious diseases, which is termed as genetic resistance. Therefore the aim of this paper was to review the state of knowledge on genetic resistance associated with malaria infection. Genetic resistance to malaria can be describe as an inherited alteration or changes in the genetic material of humans specifically DNA molecule and other vital biomolecules which increases the chances of resistance to malaria and thus, result in an increased survival of individuals with those genetic alterations. In addition such changes also affect the general wellbeing and survival of the parasite to the extent that the parasite cannot even multiply or replicate itself while in such infected erythrocyte. This is because such alteration in the DNA molecule interferes with some of the vital chemical and biochemical processes of the parasite (*Plasmodim spp*). Therefore, several genetic disorders and or trait which include: Sickle cell disease, Glucose-6-Phosphatedehydrogenase deficiency, Pyruvate Kinase deficiency, Duffy antigen, Ovalocytocytosis, Thalassemia and ABO blood group are known to offer special protection against malaria disease in individuals who possessed at least one of such disorders or trait.

1. Introduction

Despite the high morbidity and mortality rates in malaria-endemic areas, certain people are less susceptible to malaria infection than others who have recurrent malaria attacks. Specific infectious disease resistance can be conferred by certain genetic circumstances. These genotypes are thought to be preserved preferentially in populations that are regularly exposed to certain infectious agents, particularly those with high virulence[1].

It was For long time that human genetics have linked with differences in susceptibility to numerous infectious diseases. Of all the infectious diseases that affect human population, malaria has generated highest measurable level of selective pressure on

human genome[2]. Nevertheless, most human genetic factors have been shown to provide pertinent protection from the disease, and genome-wide inter population variation has been linked with resistance or susceptibility to malaria. Approximately one-quarter of the total variability in malaria incidence is accounted for by genetic factors[3]. In addition, the outcome of human malaria infection is thought to depend on both parasite and host genetic factors. Therefore genetic resistance to malaria can be describe as an inherited alteration and or changes in the genetic material of humans specifically DNA which increases chances of resistance to malaria and thus, result in an increased survival of individuals with those genetic alterations [4].

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Several genetic disorders, such as Sickle cell Disease, Thalassemia, Glucose-6 phosphatedehydrogenase deficiency (G6PD) and Pyruvate kinase deficiency are known to have caused and confer resistance to *Plasmodium* malaria infection [5]. The presence of such genotypes is largely and likely due to evolutionary pressure exerted by the parasites of the genus *Plasmodium* which cause malaria. This is because, the parasite infects red blood cells (RBCs), these genetic changes are most commonly alterations to molecules essential for red blood cell function and therefore parasite survival, such as haemoglobin or other cellular proteins and or enzymes of RBCs. These alterations generally protect RBCs from invasion by *Plasmodium* parasites and or replication of the parasites within the red blood cell, hence prevent the development of the parasite and thus, establishment of the disease [6, 7].

In anthropology and human genetics, genetic adaptation to malaria is a long-standing research area. Several malaria-endemic regions have reported red blood cell (RBC) abnormalities, including those with change in Red Blood Cell (RBC) shape, for example sickle cell disease that are thought to confer resistance to malaria. The defect distribution supports the theory that subsets of RBC faults became prominent due to natural selection by malaria [8].

Malaria has been a major driver of evolutionary selection on the human genome for almost half a century, and some hematological abnormalities have increased in frequency in malaria-endemic areas because they lessen the chance of mortality from malaria. For example, lack of Sickle hemoglobin (HbS) and glucose-6-phosphate dehydrogenase (G6PD) are frequently cited instances of natural selection due to malaria, and many other genetic connections with malaria resistance or susceptibility have been found [9]. Furthermore, malaria resistance has been linked to a number of other disorders, including hemoglobinopathies, enzymopathies, and the lack of an erythrocyte surface protein. Other genetic disorders can cause malaria resistance, but these three in particular offer unique insights into anti-malarial techniques. These situations have

provided the incentive for researchers to better understand the genetic underpinnings of resistance, which could be used to design new medicines or improve existing ones [10]. As a result, malaria resistance genes are the best illustration of human population natural selection. Furthermore, a number of other host genetic variations influence illness risk and/or appearance [11].

Understanding the genetic basis of malaria resistance and susceptibility is critical for developing effective medicines, vaccines, diagnostics, and risk prediction tools, as well as understanding the molecular mechanisms of host-parasite interactions. According to population genetics studies, genetic variables may account for a considerable amount of the variation in malaria incidence among persons living in malaria-endemic areas. Furthermore, both parasite and host genetic variables are known to influence the fate of human malaria infection [12-15]. This suggests that, in addition to the well-known genetic variants in red cell components, there are a number of other genetic changes that affect malaria susceptibility, but with a less evident phenotype. It's not surprising, then, that all components of RBC, including hemoglobin (S, C, E, and thalassemia), membrane antigens (Duffy antigen, ovalocytosis, and blood group O), and enzymes (G6PD), play a role in malaria prevention [16].

2. Sickle cell disease

Haemoglobinopathies are thought to protect against severe life-threatening malaria manifestations. The most important of these is the sickle cell disease (SCD) mutation, which reduces the risk of severe *Plasmodium falciparum* malaria in children in Sub-Saharan Africa by 90%. Sickle cell disease is a hereditary chronic haematological illness caused by a single mutation in the globin gene that causes Glutamic acid to be replaced by Valine at position 6 of the peptide [17]. In tropical Africa, SCD is a severe health issue that the World Health Organization has designated as a public health priority. The resistance it confers to *Plasmodium falciparum* malaria in its heterozygous state, known as sickle cell trait (SCT), has been credited to its persistence in human populations [18]. The sickle allele (HbS) is

found all over the world, and while the sickle cell disease (HbSS) has grave effects for the carrier, the heterozygote condition (HbAS) is often phenotypically normal and is linked to lower malaria susceptibility [19].

The presence of Haemoglobin S (HbS), an aberrant form of the oxygen-carrying protein in the red blood cell, causes sickle-cell disease. The disease is caused by inheriting the sickle cell gene from both parents, whereas inheriting the gene from only one parent causes the sickle cell trait, which is normally asymptomatic (Figure 1). Sickle cell disease is marked by chronic haemolytic anemia interspersed with abrupt exacerbations of sickness known as crises [20]. Because polymers cause biochemical and rheological changes in RBCs, forming aggregates, blood flow is impaired, resulting in haemolytic anemia, bone pain crises, increased susceptibility to infections, particularly with encapsulated organisms like *Streptococcus pneumoniae*, and finally organ dysfunction [21]. In locations where mosquitoes and *falciparum* malaria are endemic, the sickle cell gene is most common [22], this is because of a survival benefit in carriers against death due to *Plasmodium falciparum* malaria, haemoglobin S (HbS) has been selected to high frequencies in many tropical communities [23].

In the case of Sickle Cell Disease, it was suggested that, while sickle-cell homozygous individuals usually die before adulthood, the gene responsible for Sickle Cell Disease could reach high frequencies due to malaria resistance conferred by the heterozygous carrier state, resulting in a balanced polymorphism; it has been observed that *P. falciparum* development in HbS-containing red cells is difficult, and it is also rare to find an HbS carrier struck by cerebral malaria, a common cause of death in this disease [24, 25]. There is also substantial evidence that patients with sickle cell anaemia (SCA) are protected from malaria infection, both in terms of the incidence of infection and the density of parasites [26, 27].

Despite the fact that sickling of infected RBCs, increased splenic phagocytosis, premature haemolysis, and parasite death

have all been identified as major human malaria resistance factors, individuals with homozygous form of the gene (HbSS) are at greater risk, the exact mechanism of resistance is unknown, and various mechanisms to explain AS malaria resistance have been proposed, including sickling of infected red [28].



Fig. 1. Normal and Sickle Erythrocyte [29]

Therefore, to this effect there are various explanations as to why people with sickle cell trait are malaria resistant or have milder episodes, this is due to the fact that they are hosts to weaker and fewer parasites. Other possible explanations are: an acid is produced by the parasite inside the red cell, therefore HbS has a tendency to polymerize in the presence of the acid, causing the cell to sickle [30]. Because sickle cells are killed as blood passes through the spleen, parasites are also destroyed. Secondly, malaria parasites do not survive in low-oxygen environments. Because the spleen has low oxygen levels and diseased red cells tend to become trapped there, they may be killed there [31]. Another thing that happens when the temperature is low is that potassium seeps out of HbS-containing cells, and to develop, the parasites require a high potassium level. Therefore this could explain why the parasite doesn't grow in HbS-containing red blood [32, 33].

3. G6PD

The major enzyme in the oxidative pentose phosphate pathway, G6PD, transforms Nicotinamide Adenine Dinucleotide Phosphate (NADP) to its reduced form, NADPH. In erythrocytes, NADPH is required

for defense against oxidative stress. G6PD deficiency makes erythrocytes more vulnerable to hydrogen Peroxide (H_2O_2) and other reactive oxygen species, which can induce hemolytic anemia, favism persistent non-spherocytic hemolysis, and spontaneous miscarriages [34]. The most frequent enzymopathological disease in humans is G6PD deficiency. A widespread, heritable X-chromosome related defect is described as this disease.

In malaria-endemic regions such as Asia, Africa, Central and South America, highly polymorphic frequencies, which are markers of G6PD deficit, are detected, whereas in non-endemic regions, these rates decrease, implying a link between G6PD deficiency and malaria [35]. Two key results emerge from this relationship, one of them is that G6PD deficiency protects against malaria infection, particularly *falciparum* infections. G6PD deficiency, on the other hand, has lately been shown to create major issues in the fight against malaria. Erythrocytes that lack G6PD are more vulnerable to injury [34]. Malaria parasite penetration worsens the situation, rendering the cells more vulnerable to phagocytosis. Infected G6PD-deficient erythrocytes have a distinct morphology than non-infected ones, making them more vulnerable to phagocytosis [10]

This protection's specific mechanism is currently unknown. However, two theories have been proposed. According to the first theory, parasites that cause malaria can only thrive in low-oxygen environments. This indicates how vulnerable these parasites are to oxidative stress. *Plasmodium* parasites oxidize NADPH and diminish the level of reduced glutathione (GSH) in erythrocytes, according to the second theory [36]. This impact becomes more severe in the presence of G6PD deficiency, causing oxidative damage to erythrocytes. Furthermore, *Plasmodium* parasites degrade hemoglobin and produce toxic components such as iron, which cause hemolysis, as a result, *Plasmodium* parasite development rates are reduced. Additionally, the immune system uses phagocytosis to destroy RBCs that have been damaged by oxidative stress. Because it happens at the early ring-stage of parasite maturation, its

removal significantly reduces parasite growth [37]. As a result, all of these findings suggest that G6PD deficiency can protect against malaria infections.

4. Deficiency in Pyruvate Kinase (PK)

Pyruvate kinase is an enzyme that catalyzes the conversion of Phosphoenolpyruvate (PEP) to pyruvate, resulting in the production of ATP from Adenosine Diphosphate (ADP). Because erythrocytes lack mitochondria, a Pyruvate Kinase shortage leads in decreased intra-erythrocytic ATP, which cannot be compensated for by oxidative phosphorylation. This causes spleen membrane injury, haemolysis, and premature destruction [38]. The PK-LR gene, found on chromosome 1, regulates the production of PK. Over 150 distinct mutations in the PK-LR gene have been linked to PK deficiency so far [39]. Loss-of-function mutations in the PKLR gene cause PK deficiency, which is the most prevalent inherited glycolysis condition in humans, it is inherited as an autosomal recessive characteristic [40].

Pyruvate kinase deficiency causes erythrocyte membrane stiffness to change, thereby inhibiting *Plasmodium* infection. Furthermore, pyruvate kinase deficit decreases the intracellular concentration of glucose, a critical source of energy for *Plasmodium's* intracellular life cycle [10], making Pyruvate Kinase an important target for medicines and vaccines against *Plasmodium falciparum* infection.

5. Duffy Antigen

After the genes for sickle cell anaemia, thalassemia, and G6PD, the Duffy antigen gene is the fourth gene linked to malaria resistance. The Duffy antigen, which is found on both the red and white blood cell surfaces, was identified in 1950 [41] and is named for the patient who discovered it [42].

The impact of Duffy antigen on malaria infection genetic resistance is mostly linked to *Plasmodium vivax* and *Plasmodium knowlesi*. *Plasmodium vivax* causes a milder sickness, but it can be severe, and recurring episodes are linked with significant morbidity. Because the human population in Africa is primarily

Duffy antigen negative, *vivax* malaria is substantially less common [43]. The Duffy antigen forms an irreversible junction important for merozoite invasion of reticulocytes on erythrocytes, acting as a receptor for invasion by the human malaria parasites *P. vivax* and *P. knowlesi* [44]. The Duffy blood group antigen, also known as the Duffy antigen/receptor for chemokines (DARC) or the FY gene, has been found as a scavenger on the surface of RBCs that removes excesses of circulating harmful chemokines. This is the key molecule that allows *Plasmodium vivax* and *Plasmodium knowlesi* parasites to invade red cells via the *P. vivax* Duffy binding protein (PvDBP) [45]. Because polymorphisms modify the binding to the parasite's DBP and the density of the antigen on the erythrocyte surface, different susceptibilities to *P. vivax* have been linked to the Duffy blood group antigens [46].

A single-nucleotide polymorphism (SNP) in a GATA-1 transcription factor binding region of the gene promoter (33T C) that controls erythroid production explains Erythrocyte Duffy negativity [47], glycosylated membrane protein is the protein encoded by this gene. The Duffy antigen receptor gene is found on chromosome 1's long arm. It is a broad receptor with some chemokine specificity. This genetic anomaly is the only malaria genetic defense mechanism that hasn't been linked to any harmful effects on human health. Duffy antigen protein expression is affected by polymorphisms in the DARC gene, which determines the Duffy blood group system [48]. In the case of malaria, Duffy blood group negative is common among Africans and makes erythrocytes resistant to *Plasmodium vivax* and *Plasmodium knowlesi* infection [42].

Before its function was revealed in the 1970s, epidemiological studies had suggested Duffy negativity as a susceptibility factor. Merozoite invasion is thought to be resistant in Duffy negative individuals whose erythrocytes do not express the receptor [49]. Erythrocytes responsible for Duffy negativity are only found in West Africa and their New World descendants, including the vast majority of Afro-Americans, carry Duffy negativity in the form of heterozygotes, and the only area on the planet where

homozygotes for Duffy negativity exist is in the United States. In other ethnic groups, this genetic anomaly is extremely unusual. Duffy negativity is so powerful at protecting against *vivax* malaria that some US researchers failed to infect volunteers with *P. vivax* on purpose [50]. Therefore the link between the Duffy blood group (FY) and human malaria caused by *P. vivax* has been well documented, with Duffy-negative individuals naturally resistant to infection [51].

6. Ovalocytosis

Ovalocytosis is one of the many changes that can occur in the membrane protein of a red blood cell. Is a syndrome that can be caused by a variety of genetic mutations and is thought to be a powerful malaria-protective candidate [52]. Ovalocytosis is caused by a 9-amino-acid deletion in the erythrocyte membrane band 3 gene on chromosome 17, resulting in a functional deficiency of the band 3 proteins on the erythrocyte membrane [8]. The cytoplasmic domain preserves cell shape by linking the cell membrane to the cell cytoskeleton, and the trans-membrane domain boosts the blood's capacity to carry carbon dioxide by exchanging intracellular bicarbonate for chloride [53]. Ovalocytosis is a clinically asymptomatic condition marked by the oval shape of RBCs. In Southeast Asia and Melanesia, this type of heredity has been extensively seen, with prevalence rates as high as 50% in some groups [8]. Despite the fact that it is most typically asymptomatic, the illness has been linked to moderate haemolysis symptoms such as intermittent jaundice and gallstones.

Many erythrocyte antigens are expressed less strongly in ovalocytic erythrocytes. Ovalocytes are notable for their in vitro resistance to several strains of malaria, including *Plasmodium falciparum* and *Plasmodium knowlesi*. Furthermore, in areas where malaria is endemic, ovalocytic subjects have lower numbers of intracellular parasites in vivo [54].

7. Thalassemia

Thalassemias are a group of diseases caused by one of the many genetic abnormalities linked to a reduction in the synthesis of one or more globin chains [55].

Human thalassemias are the most frequent Mendelian disorders and represent a serious worldwide health concern. They are a set of clinical illnesses caused by deletions or other disturbances that result in faulty production of α - or β -globin chains on chromosome 11 and 16 [56]. The wide range of clinical phenotypes reflects the wide range of genetic variants that exist, and the fact that α^+ -globin is produced by two identical genes, HBA1 and HBA2, adds to the complexity. In general, homozygous thalassemia causes serious sickness or death, but heterozygotes are healthy with the exception of moderate anaemia. When one of the HBA1 or HBA2 genes, but not both, is disrupted, some α -globin can be produced. This is classified as " α^+ thalassemia," and homozygotes with this disease are only moderately anemic. Thalassemia is thought to be the world's most common single-gene illness [19]. In numerous malaria-endemic locations, such as the Mediterranean, Southeast Asia, Africa, and the Indian subcontinent, the prevalence of α -thalassemia is relatively high [57].

Population genetic studies and the extreme diversity of the molecular basis of these conditions provided the initial evidence that both forms of thalassaemia protect against malaria [58]. The presence of thalassemia and malaria has been shown to protect infected hosts from malaria caused by *Plasmodium falciparum* [59]. The α -thalassaemias are among the most well-known malaria-protective polymorphisms, with rates as high as 80% in some groups. They are now considered the most frequent monogenic illnesses in humans. Nonetheless, both the mechanisms of protection and their malaria specificity are unknown [60]. However, different hemoglobinopathies (sickle-cell trait, beta thalassemia trait, homozygous HbH, HbAS) have different mechanisms conferring protection against severe and complicated malaria [61]. Reduced parasite erythrocyte invasion, decreased intra-erythrocytic parasite growth, enhanced phagocytosis of parasite-infected erythrocytes, and increased immune response against parasite-infected erythrocytes are among the most important mechanisms [62].

8. ABO-Blood group vii

The clinical outcome of *falciparum* malaria in endemic areas is linked to erythrocyte polymorphisms, including the ABO blood groups, among other things. The ABO blood group is a collection of carbohydrate antigens found on human erythrocytes and other cells [63]. The ABO blood group system is undoubtedly the most well-known, yet functionally perplexing, human genetic variation. ABO is the most important system for blood group compatibility in clinical practice [64].

The development of a protective immune response by the host is required for Malaria resistance. The ABO blood type is thought to play a key role in malaria protection, particularly severe malaria. There are three alleles in the ABO blood group gene: A, B, and O it determines an individual's blood group by coding for different forms of agglutinogens bound to the surface of RBCs [65]. Individuals with blood group "A" have been reported to be particularly vulnerable to *falciparum* malaria, whilst those with blood group "O" are said to be protected from more complex instances. Individuals with blood group "O" have been found to have low parasitaemia and uncomplicated *P. falciparum* malaria [63]. Several possible pathogenic mechanisms attributed to the cause of severe infection include cyto-adherence and rosetting. A link has been shown between the 'O' blood group and decreased rosetting capability [66].

The frequency of rosetting parasites in blood isolated from group O patients was lower than in blood isolated from patients with blood groups A, B, and AB, according to clinical studies conducted in Thailand and East Africa [67]. *P. falciparum* creates rosettes with group O RBCs with a lower frequency than group A and B RBCs, according to other research. Furthermore, rosettes formed by group O RBCs are smaller and more easily disturbed than rosettes formed by groups A, B, and AB erythrocytes [68]. It has been discovered that the *Plasmodium* parasite has a reduced ability to infiltrate group O erythrocytes. While macrophages that target *P. falciparum*-infected erythrocytes have been demonstrated to clear infected group O erythrocytes more readily than infected A and

B erythrocytes, this could indicate that group O is resistant to the severe form of malaria. This link is supported by the fact that blood group O is more prevalent in malaria-endemic Sub-Saharan Africa than in other regions of the world [65].

The A and B antigens are trisaccharides coupled to separate glycolipids and glycoproteins on the erythrocyte surface: A, GalNAc1-3(Fuca1-2) Gal1b1; and BGal1a1-3(Fuca1-2) Galb1. The enzyme glucotransferase is required for the synthesis of antigens A and B. Blood type 'O,' on the other hand, has a disaccharide H antigen (Fuca1-2Galb1) due to the lack of the enzyme glucotransferase. Variations in the gene encoding functional glucotransferase have been linked to protection against severe *P. falciparum* malaria, and a recent genome wide association study has confirmed this. The 'A' and 'B' blood group tri saccharides are thought to operate as receptors and are a crucial factor in rosetting on uninfected RBCs. They bind to parasite rosetting ligands such PfEMP-1 and trigger sequestering [69]. In comparison to blood groups A, B, and AB, RBCs of blood group 'O' do not express trisaccharide, and rosettes generated by infected 'O' blood group RBCs are smaller and more easily destroyed. Because the A and B trisaccharides are known to have a role in rosette formation, blood group O may be a protective factor against severe malaria due to its rosette-reducing properties [70].

Finally, Malaria cases are less likely to be severe in people with blood group O, but much more severe in those with blood group AB. Individuals with blood group O tend to be less susceptible to the severe illness produced by Pf infection. Because parasite density does not necessarily predict survival, clinical severity, rather than the incidence or prevalence of detectable parasitemia, is a more meaningful outcome to measure ABO group and survival[69].

9. Conclusion

Genetic resistance to malaria definitely demonstrate high level of potentiality in drastically reducing the menace of malaria disease through various mechanisms, as all these disorders prevent successful survival

and or replication of the parasite (*P. falciparum*) in the erythrocyte. Though some of these genetic disorders like sickle cell disease in most cases are deleterious to the survival of the host while others like Duffy antigen are not. Splenic phagocytosis, Premature haemolysis of the infected erythrocyte, oxidative stress/damage, increased stiffness of the infected erythrocytes especially in *P.vivax* and *P.knowlesi*, reduced parasite invasion and increased immune response against parasite infected erythrocyte are some of the main techniques adopted by the host as a result of genetic variability to genetically resist to the adverse consequences of malaria parasite.

Abbreviation

G6PD:glucose-6-phosphate dehydrogenase

RBCs: red blood cells

SCD: sickle cell disease

Conflict of Interests

All authors declare no conflict of interest.

Ethics approval and consent to participate

The author did not use any human or animal samples for this study

Consent for publications

All authors read and approved the final manuscript for publication.

Authors' Contribution

All authors had equal role in study design, work, and manuscript writing.

Informed Consent

The authors declare not used any patients in this research.

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