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Host Genetics in Malaria Susceptibility

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ABSTRACT

Malaria remains one of the most significant parasitic diseases globally, exerting a disproportionate burden in sub-Saharan Africa, Asia, and Latin America. Host genetic factors play a critical role in determining susceptibility to malaria infection and severity, with evolutionary evidence showing that Plasmodium parasites have shaped human genetic diversity over centuries. Protective adaptations such as hemoglobinopathies, G6PD deficiency, and variations in erythrocyte surface antigens demonstrate the selective pressure malaria has exerted on human populations. Advances in genomics and molecular biology have expanded understanding of single-nucleotide polymorphisms (SNPs), copy number variations (CNVs), and immune-related polymorphisms that modulate host-parasite interactions. This paper reviews major genetic determinants of malaria susceptibility, explores their implications for pathophysiology, and highlights the role of modern genomic tools in uncovering novel protective and risk alleles. By integrating genetic insights with public health strategies, research in this field offers significant opportunities for vaccine development, targeted therapies, and precision medicine approaches in the global fight against malaria.

Keywords: Malaria susceptibility, Host genetics, Hemoglobinopathies, Single nucleotide polymorphisms (SNPs) and Copy number variations (CNVs).

INTRODUCTION

Malaria is a communicable disease caused by unicellular microorganisms transmitted by female anopheline mosquitoes. It remains a significant global health problem, warranting effective control measures. Understanding the role of host genetics in disease susceptibility and the advent of genomic technologies offer promising avenues for new research and intervention strategies [1]. Human genetics has been studied in relation to a variety of different diseases and traits, and the related observations have led many to view humans as a collection of genetically influenced diseases [2]. Numerous candidate genes have emerged, a subset of which are associated with malaria, that link different biological systems and pathways to the disease [2]. In the context of malaria, the use of an evolutionary approach, combined with genomic tools, holds great promise for understanding the genetic basis of susceptibility and identifying key genes involved in protective pathways [3]. Knowledge of the variation and distribution of these genes within and between different populations promises to cast new light on the molecular evolution of malaria and the spread of particular protective alleles [2, 3].

The Role of Genetics in Disease Susceptibility

Host genetic factors play a significant role in influencing susceptibility to infectious diseases [1]. While the degree to which genetic variation modifies susceptibility to malaria remains incompletely understood, the existence of individuals who appear to be innately refractory to disease underscores the strong genetic component mediating clinical susceptibility [3]. Genetic variation constitutes one of several highly variable factors influencing susceptibility to infectious disease and to malaria in particular [3]. Multiple examples are well documented, of common genetic polymorphisms that exert strong influences on the response to a given infection. Malaria itself constitutes an archetypal selective force that has shaped the genetic makeup of affected populations [4]. Present-day allele frequencies therefore reflect the outcome of a long history of malaria-mediated selection, to a greater or

lesser degree. Even modern-day patterns of susceptibility to infectious diseases such as malaria exhibit strong evidence of direct or indirect genetic influences [4].

Malaria Pathophysiology

The pathophysiology of malaria comprises interactions between parasites, host immunity, and genetic factors 5. Malaria is caused by protozoan parasites of the genus Plasmodium [2]. Five species cause disease in humans: Plasmodium falciparum, P. vivax, P. ovale, P. malariae, and P. knowlesi. The female Anopheles mosquito transmits infective sporozoites to the human host during a blood meal. Sporozoites enter hepatocytes, initiate exo-erythrocytic schizogony to produce merozoites, which enter erythrocytes and initiate the erythrocytic stage responsible for the cyclical fever. P. vivax and P. ovale produce hypnozoites that persist and cause relapses [1]. The erythrocytic cycle is the target of host defense mechanisms and drugs. Merozoites invade erythrocytes, develop as trophozoites, either develop into schizonts, producing merozoites that reinvade other erythrocytes, or differentiate into gametocytes, the sexual forms taken up by mosquitoes [2, 3]. Transmission occurs when gametocytes undergo fertilization in the mosquito gut, resulting in sporozoites that invade the mosquito salivary glands. Pathophysiology relates to the infection of erythrocytes, destruction of infected cells and uninfected cells, and vessel obstruction by infected cells [5].

Genetic Variations and Malaria

Two major types of genetic variation occur in the human genome: single-nucleotide polymorphisms (SNPs) and copy number variations (CNVs). SNPs represent variation in single nucleotides of the DNA sequence and amount to over 10 million loci in the human genome [3]. CNVs refer to segments of DNA ranging from 50 base pairs to several megabases present in variable copy numbers in the genome [6]. Analyses of genomic datasets suggest the presence of about a thousand CNVs per individual [1]. These CNVs are often located in complex regions of the genome, spanning from genes to regulatory sequences or a combination thereof. This type of structural variant has been linked to susceptibility to infectious and various other diseases [1].

Single Nucleotide Polymorphisms (SNPs)

Malaria remains an impactful disease worldwide. Recent progress in genomics, along with decreasing costs of high-throughput technologies, coupled with large-scale international collaborative efforts, now encourage the investigation of complex genetic traits that modify an individual's susceptibility to malaria [2]. The diverse disease outcomes among infected individuals suggest a role of the host's genetic background. Single nucleotide polymorphisms (SNPs) in candidate genes, selected based on their involvement in different stages of the malaria parasite life-cycle, have been extensively studied in various population groups for their association with malaria infection and susceptibility. However, results from these studies remain inconclusive [1]. This is partly because a large number of SNPs in the human genome, which may influence complex pathways involved in regulating susceptibility to malaria, have yet to be examined[3]. Copy number variations (CNVs) represent another source of genetic variation that could influence the human immune response and contribute to disease susceptibility. With a broader spectrum than SNPs, CNVs could induce changes in general regulation or expression patterns of immune-related genes. Despite the increasing number of such structural variations being discovered in the genome, no screening has been undertaken to establish their role in malaria susceptibility [4]. Genomic approaches, such as next-generation sequencing and genome-wide association studies, now provide an opportunity to identify important genomic loci involved in pathogen response in an unbiased manner, thereby opening new avenues for a comprehensive understanding of the interplay between host genetics and malaria susceptibility [1, 5].

Copy Number Variations (CNVs)

Copy number variations (CNVs) represent structural changes involving amplifications or deletions of genomic loci and account for a significant level of human genomic variation. CNVs have been linked to numerous genetically complex disorders [4]. Although early research focused primarily on single-nucleotide polymorphisms (SNPs), CNVs have recently been found to influence immune response, with several studies suggesting their involvement in genetic susceptibility to infectious diseases, including HIV, HIV-TB coinfection, and malaria[1]. The growing availability of CNV-related genetic variation data presents an opportunity to delve deeper into the connections between CNVs and susceptibility to malaria infection. Several genome-wide association studies (GWASs) have confirmed the importance of CNVs in susceptibility to malaria. The most extensively studied region is the glycophorin gene cluster, situated on chromosome [4]. Glycophorins are glycosylated proteins on the human red blood cell surface and are abundant in sialylated glycans, which serve as receptors for the invasion of Plasmodium merozoite. Another crucial region is the CHRFAM7A gene, considered a dominant negative of the α7 nicotinic acetylcholine receptor. α7 nicotinic receptors are of considerable interest as they are implicated in the cholinergic anti-inflammatory pathway, an anti-inflammatory mechanism in humans. Higher copy numbers of CHRFAM7A

have been reported to correlate with an increased risk of malaria seizures, and deletions of this gene appear protective against cerebral malaria [4].

Immune Response to Malaria

Malaria infection is controlled by the interplay of innate and acquired immune mechanisms [5]. Although immuno-epidemiological studies generally report a protective role of innate immune responses, the limited evidence that P. falciparum induces long-lasting innate immune memory raised questions about its importance [3]. However, in areas of seasonal transmission, monocyte immune components regulated by IFN-γ have been shown to maintain robust protection up to six months after the end of the transmission season. Innate-adaptive cross-talk is key to regulating macrophage activity, which is also regulated by natural killer (NK), TH1, and TH2 cells. Early-stage parasitaemia is thought to be controlled by chemokines released by NK cells and subsequently by CD8-KLRG1+ T cells that kill infected antigen-presenting cells to control parasite biomass [3]. The control of parasite biomass is thought to be the key determinant of transmission season length and disease severity. Immunity to malaria develops after multiple infections and wanes without exposure [2]. Resistance to clinical malaria and tolerance to high parasite density coexist and are thought to rely on separate immune mechanisms. Other important immune mechanisms that facilitate parasite control include macrophage activation, phagocytosis, antibody-dependent cellular inhibition (ADCI), production of reactive oxidative species (ROS) and nitric oxide (NO), and antibody responses to asexual blood stages and subsequent merozoite invasion of erythrocytes [7].

Innate Immunity

The first line of defence against infections relies on innate immune mechanisms. Innate immunity controls P. falciparum infection pre-erythrocytically and results from the action of NK cells, phagocytes, dendritic cells and cytokines. A number of lines of development indicate that sensing of the parasite and killing of infected cells contribute [5]. Innate immune responses during blood-stage malaria rely on the ability of phagocytes to recognize diverse parasitic molecules including haemozoin, GPI anchors and DNA. Recognition of such molecules induces production of cytokines, pro-inflammatory substances and opsonins that contribute to the sequestration of parasite and infected erythrocytes [3]. The extent of phagocytosis of schizonts determines the level of antigen-presenting cell (APC) activation. Owing to their phagocytosis activity and ability to harbour plasmodial antigens, dendritic cells are major players in the generation of potent and efficient adaptive immune responses during a malaria infection [2]. Although yet to be established during a natural infection, TLRs appear to be the prime sensors implicated both in the control of parasitaemia and initiation of immunity through pathogen-sensing and activation of the innate immune response. Cytokines are influential in shaping an effective protective immune response against a malaria infection [1].

Adaptive Immunity

Adaptive immunity against Plasmodium spp. takes several days to develop after the initial or a repeat malaria infection [3]. The humoral immune response plays a fundamental role in eliminating various life-cycle stages in the vertebrate host, including pre-erythrocytic and asexual blood stages, and infected red blood cells (RBCs) sequestered in the microvasculature [6]. Cytophilic immunoglobulin G1 (IgG1) and IgG3 antibodies are responsible for controlling parasitaemia, whereas non-cytophilic IgG2 and IgG4 are associated with susceptibility to malaria. Immunoglobulin M (IgM) naturally occurs in plasma before infection and may also mediate immune protection in semi-immune individuals. Various genetic variations influence antibody responses to parasite antigens. Polymorphisms in the Fc gamma receptor IIB (FCGR2B), a negative regulator of B-cell activation, lead to increase in vitro production of immunoglobulin E (IgE). Elevated plasma IgE levels correlate with severe malaria, indicating that individuals with FCGR2B polymorphisms favoring B-cell oxidation are more susceptible to malaria infection [5]. Polymorphisms in the interferon-γ–inducible protein 16 (IFI16), a DNA sensor and regulator of type I interferons, enhance anti-Plasmodium falciparum IgG antibody responses, which may protect African adults from severe malaria. Other regulatory genetic variations affect pro-inflammatory cytokines mediating the immune response against Plasmodium spp., influencing susceptibility to malaria [3].

Hemoglobinopathies

Malaria remains a major cause of parasitic disease worldwide, with an estimated 340 million clinical cases and one million deaths each year, primarily in sub-Saharan Africa, along with a substantial number of cases throughout Asia and Latin America. Although control programs have reduced the burden in many countries, malaria remains a serious global health threat [1]. The complex nature of the disease is compounded by multiple geographic, cultural, and genetic factors [2]. Numerous population studies have investigated the role of host genetics in malaria susceptibility, determining susceptibility chiefly by examining innate or acquired immunity [2]. Human genetic variation can alter susceptibility and response to a wide range of infectious diseases, and the strongest genetic factor associated with malaria susceptibility is the inheritance of variants related to hemoglobin structure

and function [3]. Mutations in the β-globin gene, such as sickle cell anemia and thalassemias, cause inappropriate hemoglobin chain production, resulting in abnormal erythrocyte morphology and shortened erythrocyte lifespan. These conditions modify the intraerythrocytic environment, thereby impairing parasite development [4]. Multiple lines of evidence have confirmed that individuals heterozygous for the haemoglobin S gene (HbAS or sickle cell trait) are at reduced risk for infection compared to their normal counterparts (HbAA). In addition, the α- and β-thalassemias occur at high frequencies in many malaria-endemic regions, where they have also been shown to modulate malaria susceptibility [12, 9].

Duffy Antigen System

Duffy Antigen System An individual person's blood group system can likewise affect susceptibility to malaria [1]. As an example, the Duffy antigen system is a classification of human blood group antigens based on expression of the Fy glycoprotein on the red blood cell surface. Fy serves as the receptor for chemokines and cytokines and has been shown to play an important role in signal transduction during red blood cell production. Most GWASs have confirmed that the P [2]. vivax parasite needs the Glycophorin A protein on the surface of RBCs for cell entry. However, interference of the Duffy protein by P [4]. vivax during the invasion of RBCs has not been clearly elucidated. The Duffy-null allele Fy(a-b-) causes resistance to infection by P. vivax by creating a deficiency of Duffy antigen expression on red blood cells. Several studies have made efforts to determine the risk of malaria due to different expression levels of Duffy antigen [3].

G6PD Deficiency

Glucose-6-phosphate dehydrogenase (G6PD) deficiency has a long association with malaria, having spread to high frequencies in early human history; the most common variant traced to an origin ~30,000 years ago [8]. However, it is necessary to consider the opposing effects of G6PD deficiency on severe malaria presentations, protection against cerebral malaria matched by increased risk of severe malarial anaemia [9].

Ethnic Variations in Malaria Susceptibility

Genetic background varies with ethnicity, which modifies disease susceptibility in a population and can be investigated in the context of malaria [3]. For example, the Fulani of West Africa have lower susceptibility to Plasmodium infection than Hutu and Tutsi of East Africa, Mossi and Rimaibé of West Africa, and other local ethnic groups [1]. Sickle-cell anaemia is prevalent in sub-Saharan Africa, Middle East, and India. The rate of sickle-cell heterozygote gene carriers in sub-Saharan Africa ranges from 10% to 40% in populations exposed to substantial malarial infection [6].

Population Genetics and Malaria

The distribution of genetic variants among studied populations emerges from complex and dynamic interactions involving evolutionary mechanisms, demography, epidemiology, and ecology [2]. While genetic drift contributes to genetic differentiation, the greater prevalence of protective variants in endemic regions suggests that natural selection plays the dominant role [4]. Most genes affecting malaria susceptibility do not completely prevent clinical episodes, indicating reduced selective pressure, where genetic drift becomes a more significant factor. Genes with homogeneous distributions across malaria-free regions are likely subjected to genetic drift. Genetic variants conferring complete or near-complete protection have a reduced influence of drift [3]. The selection signatures between different protective alleles vary: diseases like sickle cell anemia maintained at low equilibrium frequencies by heterozygous advantage show localized selection peaks, whereas variants without hypothesized associated fitness costs, such as thalassemia, β-globin gene cluster transpositions, and Dantu det-positive, exhibit more extensive haplotype homozygosity spreading beyond candidate regions. Even in the absence of malaria, some variants maintain selective advantages unrelated to the disease [3].

Genetic Drift

Genetic drift can influence the susceptibility or resistance of an individual to malaria. It refers to random changes in the frequency of alleles in the gene pool of a population [7]. These changes may be due to a natural disaster, disease epidemic, or any other event that wipes out a large segment of the population. If the eradication event is not related to the gambler's genes, it is known as genetic drift. However, if a particular genotype is more likely to be wiped out by the disease, it is an example of natural selection [8]. Genetic drift causes a more rapid rate of alteration in small populations. For example, a population of false-click beetles in New Zealand has three genetically different populations that are kept apart primarily by distance. Population structure refers to the distribution of pattern of genetic variation arising from the nonrandom mating of individuals [11].

Natural Selection

Human populations living in malaria-endemic areas harbor multiple genetic variants that modify the risk of malaria infection and disease [1, 6]. These genetic associations test our understanding of the mechanisms that determine susceptibility to malaria [5]. Malaria has imposed intense selective pressure on humans, shaping

genome variation and contributing to the unusual distribution of genetic variants worldwide. Some polymorphisms not only protect against malaria but also affect other infectious diseases. Despite a strong heritable component to malaria susceptibility, only a fraction has been explained. Genetic studies of malaria have also highlighted the role of genetic architecture and genome-wide approaches [2].

Genetic Epidemiology of Malaria

Population-level studies of host response to malaria have a long history and remain an important research aim. A variety of research methods used in population genetics and epidemiology can be applied to host genetics [1]. As an example, genetic epidemiology at the population level supports conclusions drawn from individual-level studies. Observations of ethnic groups highlight variation in malaria susceptibility depending on the genetic background of the population [3]. Evidence for the involvement of genetic drift or natural selection can also be observed in the genes, and an examination of their distribution among populations can provide additional understanding of disease susceptibility [2]. Recent developments in genomics open up another major avenue of investigation into the relationship between host genetics and malaria. Next-generation sequencing is becoming increasingly used in population studies, and genome-wide association studies offer an opportunity to investigate the full genome in the search for malaria susceptibility genes [1, 10].

The Role of Genomics in Malaria Research

Genomic technologies and resources have resulted in a better definition of gene activities modulating pathology or resistance to malaria infection [7]. A more objective, population-based approach featured by genome-wide association studies has become much more feasible following the recent advances in SNP genotyping technologies and the publication of the HapMap database [8]. The malaria-host framework represents one situation in which the disease-associated SNPs show very great natural population differentiation and thus some of the traditional criteria for filtering false positives may not be directly applicable. The understanding of the contribution of host genetics to malaria susceptibility therefore, promises further rapid progress in the coming years. The application of Next-Generation Sequencing is revealing many new candidate genes influencing the malaria infection outcome, and Animal Models can aid in identifying their biological roles [3]. The availability of the complete human genome sequence and the rapid development of high-throughput analysis tools have also facilitated genome-scale research into malaria and complicated malaria.

Next-Generation Sequencing

Since the completion of the first Human Genome Project (HGP) in 2003, South-East Asia and Africa, where the greatest burden of infectious diseases exists, have benefited from the exploitation of massively parallel sequencing technologies, termed next-generation sequencing (NGS) [3]. These developments have transformed the ways in which populations are studied, assessed, and analysed in every genetic research undertaking. Technological advances and increased accessibility have enabled the deployment of NGS more broadly, including in individuals from malaria-endemic countries [6]. New projects have emerged to make vast genomic data publicly accessible, making population genetics investigations more in-depth than ever. In malaria research, these global population and NGS data sets have played a pivotal role in identifying the genetic components underlying malaria susceptibility, offering distinct perspectives and more intensive efforts than previously possible. The application of these technologies has been indispensable in determining the genes and loci involved in the susceptibility or resistance against malaria, deeply enriching the understanding of the disease, the parasite, and the complicated interactions with the human host [3, 7].

Association Studies (GWAS)

Genome-wide association studies (GWAS) allow researchers to identify loci throughout the genome involved in malaria resistance, for which the effects of individual loci are unknown or difficult to predict [3]. The main limitation of GWAS remains sample size, but the steady decrease in sequencing costs allows increasingly powerful experiments. While GWAS have been performed for over a dozen years, malaria-specific ones were possible only with a sufficiently powered study in a well-defined, geographically and phenotypically diverse cohort. The first GWAS was published in 2010, but it was unable to identify any novel resistance loci; however, it did confirm the HBB and ABO associations [4]. What makes GWAS in the context of malaria particularly challenging is the pronounced differences in case definitions, age groups and other non-genetic factors; the very high genetic diversity endemic populations compared to the populations of European descent for which commercial SNP-arrays have been designed; as well as the relative low linkage disequilibrium in African populations that makes imputation more challenging. A number of strategies suggest how to maximize the utility of GWAS for malaria resistance [3].

Animal Models in Malaria Research

Animal models provide unique insights into the interactions between malaria and host genetics that cannot be obtained by studying humans alone [5, 7]. Genetic variation in laboratory strains of both the mouse and the non-human primate has been exploited to begin to identify loci influencing susceptibility to blood-stage malaria [5]. Inbred mice provide a tool for investigating the genetics that influence severity of malaria phenotypes that may be difficult to study in humans and, so far, around 30 malaria-resistance loci have been mapped using classical genetic approaches. Several of these loci have been characterized in greater detail, providing convincing evidence for widespread epistasis and for a correlation between parasite load and mortality [5, 8].

Ethical Considerations in Genetic Research

The study of host genetics has changed our understanding of infectious diseases, with malaria susceptibility and infection once considered the consequence of biology, geography and exposure [5]. Certain individuals were considered more predisposed to infection, by proximity to stagnant water or zones of greater poverty. The concept that a disease is entirely caused by environmental factors is fundamentally flawed; organisms have a genetic make-up, which is continuously exposed to epigenetic and environmental stimuli, capable of triggering diverse individuals in different ways. In truth, disease is rarely caused by genes alone [9]. Evidence suggests that infectious diseases are indeed influenced not only by the host, but also by the pathogen and environmental-related factors. Genetic variation in pathogens is recognised for a wide range of medically important microbes, with each strain of a disease-causing microorganism carrying a set of genetic variation, which could possibly influence disease susceptibility [1, 3]. The environment can also influence susceptibility, if an exposed individual is perhaps malnourished or has limited access to potable water. The host of the organism influences human susceptibility to disease, and in all mankind some will prove more susceptible to clinical disease than others [1, 2].

Future Directions in Malaria Genetics Research

Recent technological and logistical progress in genetic research allows expansion of malaria investigations beyond well-recognized candidate genes toward an unbiased genome-wide perspective, crucial in light of the limited knowledge regarding genetic control of host-parasite interactions [8]. Genome-wide association studies (GWAS) of severe malaria, leveraging multi-center data and the Malaria Genomic Epidemiology Network (MalariaGEN) platform, have pinpointed additional loci beyond the established HbS observation. Sequencing within the MHC region reveals extensive variation, highlighting the challenge of defining authentic protective alleles at this highly polymorphic locus [8]. Emerging research priorities encompass the host genome's structural diversity and its functional consequences at disease-associated difference sites, such as within the ATP2B4 gene encoding the Plasmodium falciparum calcium pump, potentially pivotal during apical merozoite invasion [12]. Given the heterogeneity of malaria epidemiology and genetic architecture reflected by discrepancies in association outcomes across endemic regions longitudinal cohort studies from under-studied settings hold promise for a more comprehensive disease susceptibility assessment [7]. Future research should also incorporate the parasite genome due to the strong evolutionary interplay shaping human and parasite genetic variation. Until a viable vaccine emerges, understanding the complex human genetic landscape of malaria susceptibility remains a prerequisite. MalariaGEN exemplifies growth through collaborative science, disseminating and hosting integrated malaria-genetics datasets to accelerate malaria-elimination efforts [7].

Case Studies of Genetic Resistance to Malaria

Malaria can be defined as a parasitic disease characterized by febrile episodes or paroxysms, followed by symptoms such as chills, rigor, backache, general malaise, nausea and vomiting, pleuritic chest pain, and diaphoresis [1]. These symptoms occur periodically and frequently. Malaria is one of the leading causes of morbidity and mortality in tropical and subtropical countries. It is mainly spread by a bite from an infected female mosquito of the genus Anopheles [5]. The disease has high extensions, with more than 2.5 billion individuals at risk of infection, mostly in Africa, Asia, Central and South America, the Caribbean, the Middle East, and Oceania. In 2010, 216 million clinical cases of malaria and approximately 655,000 deaths were reported, mainly in children less than five years of age [10]. The principal features of a host's genetic constitution are inherited from its parents and can explain, at least in part, the biological variability among individuals in a population [8]. Different species and individuals within a species have heterogeneous expressions, and there are also differences in susceptibility to infectious diseases, including malaria. Sickle hemoglobin, thalassemias, glucose-6-phosphate dehydrogenase (G6PD) deficiency, human leukocyte antigen (HLA), and the Duffy antigen are well-established genetic traits associated with protection from severe malaria. There are four forms of genetic variation: (i) nucleotide substitution or single nucleotide polymorphisms (SNPs), (ii) repeats of a different number, (iii) rearrangement of a chromosome segment, and (iv) deletion or acquisition of a chromosome segment. SNPs are the most common, comprising 90% of all human genetic polymorphisms. Malaria has also driven natural selection through the effects of random drift over

many generations. Although in vivo and in vitro immune responses have been extensively described, very little is known about the role of host genetic variation in this response [6].

Integrative Approaches to Malaria Control

Integrative approaches harness genetic insights to inform strategies for malaria control. Genetic studies at various levels of organization reveal the complexity of host-parasite interactions and highlight genetic variation among human hosts as a key factor shaping malaria susceptibility and clinical outcomes [10]. The success of integrating genomics, epidemiology, and population genetics to understand host-pathogen evolution underscores the value of such comprehensive analyses in characterizing malaria susceptibility [5].

Public Health Implications of Genetic Research

Genetic variation in the human genome can influence susceptibility to disease in one of two ways: variation in an increased risk of acquiring a disease, or variation in the disease course after host invasion by pathogens [7]. Host genetics influences the susceptibility to many infectious diseases, including HIV, tuberculosis, leprosy and malaria. Malaria is a parasitic infectious disease caused by parasites that belong to the Plasmodium group [8]. The association of genetic traits either with protection or risks to malaria infection has long been an important area of investigation. Investigations that focused on particular genes with an assumed role in malaria pathogenesis provided insights into malaria susceptibility and protection, but they gave only a limited picture [12]. The two approaches that later shaped genetic studies of complex diseases more generally have been applied in the context of malaria studies [8]. Candidate-gene association studies have explored in depth a limited number of relevant polymorphisms and deep population-genetic analyses explored the effects of malaria-induced genetic selection on human populations more broadly [9]. The majority of these studies were conducted using simple genetic markers, such as single-nucleotide polymorphisms and, to a lesser extent, copy-number variations. Both susceptibility and protection are mediated through many variations and gene variants, in many different ways [10]. Any insights into the different reactions to malaria play a crucial role in anti-malaria drug design and development.

Challenges in Malaria Genetics Research

Despite important efforts, progress in identifying malaria susceptibility variants and developing novel genome-wide approaches remains challenging [1, 3]. The genetic origin of malaria susceptibility is highly complex, as related polymorphisms can drive highly divergent biological consequences, and malaria remains predominant in low-income countries, where research support, epidemiological data, and the availability of technology required for genetic analysis are often limited [1]. The complexity of such traits can potentially be explained by a combination of polygenic inheritance, epistatic and epigenetic effects, and gene–environment interactions [3]. Analyses of malaria susceptibility in fragile endemic regions therefore require the development of powerful statistical techniques in conjunction with interdisciplinary approaches strengthened through global malaria initiatives. Understanding how host genetics affects malaria susceptibility is essential to identify vulnerable individuals and provide innovative public health and treatment programmes [1].

Collaboration in Global Health Initiatives

Large collaborative studies on host genetics of malaria across endemic countries have become feasible through the MalariaGEN network [11]. The network employs standardized protocols and online analytical tools that allow malaria-endemic country partners to retain control of their data, with openly accessible summary statistics facilitating genome-wide meta-analyses [12]. This infrastructure forms the basis of a comprehensive case control study of severe malaria conducted across 11 countries and three continents, all managed through the MalariaGEN platform. The ability to assemble large collaborations involving endemic countries is critical for studying and understanding the genetics of malaria susceptibility at a global scale [11, 12].

CONCLUSION

Malaria continues to exert a profound influence on global health, particularly in endemic regions where host genetics significantly shapes patterns of susceptibility and resistance. Evidence from hemoglobinopathies, the Duffy antigen system, G6PD deficiency, and other polymorphisms demonstrates how human populations have adapted to centuries of selective pressure exerted by Plasmodium parasites. Beyond SNPs, structural variations such as CNVs highlight the complexity of the genetic landscape influencing disease outcomes. Advances in genomic technologies, including next-generation sequencing and genome-wide association studies, have accelerated the discovery of protective and risk alleles, enabling a more complete understanding of host parasite interactions. At the same time, challenges remain. The polygenic nature of malaria susceptibility, the interplay of genetic, environmental, and socio-economic factors, and the limited resources in many endemic regions complicate research and application. Nevertheless, the integration of genomic insights into public health strategies holds great promise. By identifying vulnerable individuals, informing vaccine development, guiding novel therapeutic approaches, and supporting global initiatives such as MalariaGEN, genetic research can play a transformative role

in malaria control and eventual elimination. Ultimately, the study of host genetics in malaria susceptibility not only advances scientific knowledge but also provides a roadmap for precision medicine and equitable global health strategies aimed at reducing the burden of one of the world's most persistent infectious diseases.

REFERENCES

1. Sepúlveda N, Manjurano A, Campino SG, Lemnge M, Lusingu J, Olomi R, Rockett KA, Hubbart C, Jeffreys A, Rowlands K, Clark TG. Malaria host candidate genes validated by association with current, recent, and historical measures of transmission intensity. The Journal of infectious diseases. 2017 Jul 1;216(1):45-54.
2. Lwanira CN, Kironde F, Kaddumukasa M, Swedberg G. Prevalence of polymorphisms in glucose-6-phosphate dehydrogenase, sickle haemoglobin and nitric oxide synthase genes and their relationship with incidence of uncomplicated malaria in Iganga, Uganda. Malaria journal. 2017 Aug 9;16(1):322.
3. Kariuki SN, Williams TN. Human genetics and malaria resistance. Human genetics. 2020 Jun;139(6):801-11.
4. Lima-Junior JD, Pratt-Riccio LR. Major histocompatibility complex and malaria: focus on Plasmodium vivax infection. Frontiers in immunology. 2016 Jan 27;7:13.
5. Ndila CM, Uyoga S, Macharia AW, Nyutu G, Peshu N, Ojal J, Shebe M, Awuondo KO, Mturi N, Tsofa B, Sepúlveda N. Human candidate gene polymorphisms and risk of severe malaria in children in Kilifi, Kenya: a case-control association study. The Lancet Haematology. 2018 Aug 1;5(8):e333-45.
6. Band G, Leffler EM, Jallow M, Sisay-Joof F, Ndila CM, Macharia AW, Hubbart C, Jeffreys AE, Rowlands K, Nguyen T, Goncalves S. Malaria protection due to sickle haemoglobin depends on parasite genotype. Nature. 2022 Feb 3;602(7895):106-11.
7. Timmann C, Thye T, Vens M, Evans J, May J, Ehmen C, Sievertsen J, Muntau B, Ruge G, Loag W, Ansong D. Genome-wide association study indicates two novel resistance loci for severe malaria. Nature. 2012 Sep 20;489(7416):443-6.
8. Shah SS, Rockett KA, Jallow M, Sisay-Joof F, Bojang KA, Pinder M, Jeffreys A, Craik R, Hubbart C, Wellems TE, Kwiatkowski DP. Heterogeneous alleles comprising G6PD deficiency trait in West Africa exert contrasting effects on two major clinical presentations of severe malaria. Malaria journal. 2016 Jan 7;15(1):13.
9. Clarke GM, Rockett K, Kivinen K, Hubbart C, Jeffreys AE, Rowlands K, Jallow M, Conway DJ, Bojang KA, Pinder M, Usen S. Characterisation of the opposing effects of G6PD deficiency on cerebral malaria and severe malarial anaemia. elife. 2017 Jan 9;6:e15085.
10. Grant AV, Roussilhon C, Paul R, Sakuntabhai A. The genetic control of immunity to Plasmodium infection. BMC immunology. 2015 Mar 26;16(1):14.
11. Milet J, Nuel G, Watier L, Courtin D, Slaoui Y, Senghor P, Migot-Nabias F, Gaye O, Garcia A. Genome wide linkage study, using a 250K SNP map, of Plasmodium falciparum infection and mild malaria attack in a Senegalese population. PLoS One. 2010 Jul 15;5(7):e11616.
12. Timmann C, Evans JA, König IR, Kleensang A, Rüschendorf F, Lenzen J, Sievertsen J, Becker C, Enuameh Y, Kwakye KO, Opoku E. Genome-wide linkage analysis of malaria infection intensity and mild disease. PLoS genetics. 2007 Mar;3(3):e48.

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