REVIEW

Genetic factors that confer resistance and susceptibility to malaria

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ABSTRACT

Malaria is one of the major causes of morbidity and mortality in tropical and sub-tropical countries. The genetic basis of malaria resistance is complex, multi-genic and regulated at several levels. Its severity varies from asymptomatic to severe life-threatening forms, which depends on complex interplay of the parasite virulence, parasite transmission dynamics, and the host immune responses as well as to the host genetic make-up. Studies have confirmed that besides environmental factors and population diversity, human too has developed numerous defense mechanisms to protect themselves from severe forms of malaria. There are growing evidences of ethnic differences in susceptibility to malaria and of the diverse genetic adaptations to malaria that have arisen in different populations. Therefore, the purpose of this review was to summaries the genetic variations related to the resistance and susceptibility to malaria. A comprehensive search was conducted in Medline, Embase and Google scholar to obtain the relevant literature related to the malaria resistance and susceptibility. From the literature, it is evident that resistance and susceptibility to malaria is modulated by an array of genetic variants that determine RBC variants, pathogen receptors, cyto-adherence, inflammation, and immunity. Critical insights of these information will help future research for vaccine development and biomarker selection for the detection of malaria.

KEYWORDS: Malaria, polymorphism, genetic variations, Cytokines, resistance, susceptibility

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INTRODUCTION

Malaria is one of the major causes of morbidity and mortality in tropical and sub-tropical countries and is also one of the strongest known forces for evolutionary selection in the recent history of humans (Eid et al., 2010), (Tishkoff et al., 2001). The pathogenesis of malaria is not only complex but is essentially the species and stage specific. Its impact varies extremely depending on the age groups and population architecture as well as to the geographic regions. The severity of the disease varies from asymptomatic to severe life-threatening forms and depends on the complex interplay of host genetic make-up, the parasite virulence, parasite transmission dynamics and the host immune responses (Baird, 1995, Das et al., 2012, Guinovart et al., 2012). Several host genes have been found to be involved along with environmental and parasite genetic factors (Miller et al., 1986). Further, studies have confirmed that besides environmental factors and population diversity, human too has developed numerous defense mechanisms to protect themselves from severe forms of malaria. Genetic polymorphisms in innate immunity genes, such as Toll-like receptors (*TLR2*, *TLR4*, *TLR9*), chemokines, adhesion molecules, cytokines and their receptors, have been shown to play important roles and modulate malaria pathogenesis (Fell et al., 1994, Driss et al., 2011, Srivastava et al., 2008, Morrell et al., 2011, Jha et al., 2013a, Jha et al., 2012). In addition, a plethora of studies have documented that genetic heterogeneity in many immune genes are associated with malaria susceptibility (Driss et al., 2011, Jha et al., 2012, Jha et al., 2013a, Jha et al., 2013b, Jha et al., 2014, Verma et al., 2016).

Detection and elimination of invading microorganisms are essential for the survival of all living creatures. *Plasmodium* evades and disables the human immune system, making it difficult for the immune system to fight the disease. Failure of the immune system to recognize invading pathogens at an early stage favors the unrestricted growth of microbes, which leads to potentially life threatening complications for the host. Inflammatory mediators of the immune system have been shown to modulate the severity of the disease; giving rise to the widely held belief that severe malaria outcome is an immune-mediated disease (Fell et al., 1994, Driss et al., 2011, Srivastava et al., 2008, Morrell et al., 2011, Jha et al., 2013a, Jha et al., 2012, Crosnier et al., 2011, Eid et al., 2010, Kwiatkowski, 2005, Verra et al., 2004, Stevenson et al., 2004). The fundamental attribute of the innate immune system is to recognize the pathogen and react swiftly to control the early infection while signaling to specific adaptive immune response. Malarial infection is characterized by pro-inflammatory responses during early stages of infection followed by anti-inflammatory responses during disease progression (Gowda et al., 2012). Among various effector molecules of the immune system, cytokines play a crucial role as they speed up the host inflammatory responses and coordinates the cell-mediated and humoral immune responses for the elimination and containment of invading microbes (Renner et al., 2005). Cytokine genes play a central role in balancing the pro- and anti-inflammatory immune responses and ultimately affect the course and outcome of the disease (McDevitt et al., 2006, Stevenson et al., 2004). Increasing epidemiological and experimental evidences suggest that the host genetic variations play an essential role to thwart actively or passively the parasite invasion and disease progression (Stevenson et al., 2004, Hill, 1999) and these genetic differences among individuals are responsible for their variable susceptibility to disease, resistance to infection, and response to drug treatment (Dhandapany et al., 2009, Jha et al., 2012, Jha et al., 2013a, Khattri et al., 2009a, Khattri et al., 2009b). Studies have revealed the evolution of population-, geographic- and environment-specific natural genetic defense mechanisms against *Plasmodium* infection (Tishkoff et al., 2001). Probably, these genetic variations, such as polymorphisms responsible for the sickle cell trait, glucose-6-phosphate dehydrogenase (G6PD) deficiency, Duffy

phenotype and Beta-thalassemia are maintained in malaria endemic populations by balancing selection (Boldt et al., 2006, Kwiatkowski, 2005, Bhaskar et al., 2015, Jha et al., 2018). The present review focuses on genetic variations that confer resistance or susceptibility to malaria.

Human genetic variations and malaria resistance

The genetic basis of malaria resistance is complex, multi-genic and regulated at several levels. Numerous genes have been shown to be involved and that they interact with epigenetic variables as well as with parasite genetic factors (Eid et al., 2010, Driss et al., 2011, Jha et al., 2012, Jha et al., 2013a, Stevenson et al., 2004). There are growing evidences of ethnic differences in susceptibility to malaria and of the diverse genetic adaptations to malaria that have arisen in different populations (Tishkoff et al., 2001, Jha et al., 2013b, Jha et al., 2014, Jha et al., 2012, Jha et al., 2013a). The most striking example of differential disease susceptibility is of Duffy negative genotype, which is almost in fixation in most of the sub-Saharan populations of Africa, provides complete resistance against *Plasmodium vivax* infection. Whereas, all other human populations are susceptible to *vivax* malaria (Grimberg et al., 2007, Beeson et al., 2007). Similarly, the sickle cell trait developed as the balanced polymorphism and protect against *Plasmodium*. *falciparum* malaria. Individuals with the sickle cell trait do not suffer from malaria, as *Plasmodium falciparum* cannot develop properly in their erythrocyte (Aidoo *et al.*, 2002; Allison, 1954). The haplotype based analysis has shown that the malaria-protective genes are under recent positive selection (Tishkoff et al., 2001, Boldt et al., 2006). In the era of post human genome project, several loci have been reported that appear to affect malaria susceptibility directly or indirectly by modulation of the immune response, or by interfering with host-parasite interactions.

RBC variants and malaria resistance

A series of RBC variants viz. *HbS*, *HbC*, *HbE*, thalassemia, *SLC4A1*, *DARC*, *GPYB*, *PKLR*, *G6PD* raised as a result of evolutionary selection in human against malaria and is maintained in different endemic populations (Timmann et al., 2012, Allison, 1954, Aidoo et al., 2002, Tarazona-Santos et al., 2011, Machado et al., 2010, Tishkoff et al., 2001). The heterozygous allele *HBS* protects against severe malaria and is widespread in malaria endemic regions (Aidoo et al., 2002; Allison, 1954). *HbC* allele protects from malaria by reducing cytoadherence of infected erythrocytes (Agarwal et al., 2000, Modiano et al., 2001) while *HbE* inhibits erythrocyte invasion by merozoites and enhanced phagocytosis of infected RBC (Hutagalung et al., 1999, Chotivanich et al., 2002). *PKLR* deficiency variant has been shown to protect by enhanced macrophage clearance of ring-stage infected erythrocyte (Durand et al., 2008). Similarly, studies have shown that low activity alleles of *G6PD* reduce the risk of malaria infection. Further, these variants are maintained in high frequency in malaria endemic regions including Africa, despite the fact that these variation cause hemopathologies (Tishkoff et al., 2001). In contrast, increased susceptibility to infection by *Plasmodium falciparum* has been shown to be associated with *GPBS*+ variants in Brazilian Amazons population (Tarazona-Santos et al., 2011). However, the relationship between these genetic disorder and malaria susceptibility is not so simple. The epistatic interactions between genetic disorders have been reported, which modulates the outcome differently. For example, a study on Kenyan population has shown that the malaria protective effect of *HbS* allele (Sickle cell trait) is nullified by the co-inheritance of alpha-thalassemia (Williams et al., 2005).

Variations in pathogen receptors and cytoadherence genes

Further, several studies have shown the association of malaria resistance and susceptibility with genes involved in cell adhesion (*CD36*, *CR1*, *ICAM1*, *PECAM1*, *MARVELD3*, *Basigin*) and those function as pathogen receptors (FAS, *MBL2*, *TLR2*, *TLR4*,

TLR9) (Zakeri et al., 2011, Timmann et al., 2012, Schuldt et al., 2011, Driss et al., 2011, Crosnier et al., 2011, Kwiatkowski, 2005, Jha et al., 2014). The association of *ICAM1* variant with cerebral malaria is well known. Down-regulation of *ICAM1* in brain lowers the sequestration of parasitized RBC within the microvasculature of the brain and protects from the development of cerebral malaria (van der Heyde et al., 2006, Vigario et al., 2007). A recent study in Ghanaian children showed an association between *FAS* gene promoter variant *-436C>A* and severe childhood malaria (Schuldt et al., 2011). Another recent study showed an association between *TIRAP: S180L* variant, an important gene of *TLR* signaling pathway, and malaria severity in Iranian population, however, the association were not observed in African populations (Zakeri et al., 2011). A genome-wide study in the Ghanaian population has shown a strong association with *ATP2B4* gene, which encodes the erythrocyte calcium pump (Timmann et al., 2012). This study has also shown the association of an inter-genic SNP *rs2334880T>C*, linked to a neighboring gene encoding tight-junction protein MARVELD3 on 16q22.2, with malaria severity.

MBL2 is a C-type soluble pattern recognizing receptor secreted by the liver as part of the acute-phase response and plays an important role in recognition, initiation, regulation, and amplification of innate immune defense (Boldt et al., 2006). It binds to an array of glycoconjugates on the surface of bacteria, yeast, viruses and parasitic protozoa including *P. falciparum* (Klabunde et al., 2002) and activates the complement system. MBL interacts with MBL associated serine proteases (MASP-1, -2, -3 and Map19) and activates the membrane attack complex or complement mediated phagocytosis (Boldt et al., 2006, Larsen et al., 2004, Klabunde et al., 2002) and also regulates the release of pro-inflammatory cytokines (Jack et al., 2003). Our analysis of *MBL2* genetic variants in Indian populations has demonstrated that functional variants *MBL2*B* and *MBL2*C* increase the risk towards severe malaria and high expression MBL-haplotype *MBL2*LYPA* confers protection (Jha et al., 2014).

Genes involved in inflammation and immunity

Several studies have shown that the genetic variations in genes involved with host immunity, including human leukocyte antigen system (HLA), cytokine genes as well as complement regulatory genes (*FCGR2A*, *HLA-B*, *HLA-DR*, *IFNAR1*, *IFNG*, *IL1A*, *IL1B*, *IL4*, *IL10*, *MBL2*, *TNF*, *TIRAP*, *TRAF* etc.) regulate the host response and disease progression (Fell et al., 1994, Driss et al., 2011, Srivastava et al., 2008, Morrell et al., 2011, Jha et al., 2013a, Jha et al., 2012, Crosnier et al., 2011, Eid et al., 2010, Kwiatkowski, 2005, Verra et al., 2004, Jha et al., 2013b, Jha et al., 2014). Although these polymorphisms do not cause host genetic pathology themselves, they are associated with malaria severity. The human *IL4* is an anti-inflammatory cytokine produced by CD4+ Th2 cells, basophils and mast cells. IL4 regulates variety of cell types (Gyan et al., 2004) and play an essential role in differentiation of Th2 effector cells, suppression of Th1 signaling, promoting humoral immunity and Ig class switching and a dominant role in immunopathology (Murphy et al., 2002, Guo et al., 2002, Banchereau et al., 1994). Studies have established that IL4 as a key regulator in malaria and three regulatory *IL4* polymorphisms (-590C/T, -34C/T and in intron-3 VNTR) have been shown to regulate serum IL4 levels, IgG, IgE, disease progression and survival in various populations around the world (Luoni et al., 2001, Verra et al., 2004, Hunt et al., 2000, Marsh et al., 1995, Nakashima et al., 2002, Farouk et al., 2005, Perlmann et al., 1994, Perlmann et al., 1997, Perlmann et al., 2000, Jha et al., 2012).

Similarly, *IFNB1*, a type I interferon and an anti-inflammatory cytokine, has shown to posses a number of anti-proliferative and immune modulatory roles (Belardelli et al., 1996). The anti-inflammatory effect of *IFNB1* on erythropoiesis and subsequent severe malarial pathogenesis has been demonstrated in humans and mouse model of

experimental cerebral malaria (ECM) (Chang et al., 2004, McGuire et al., 1999, Othoro et al., 1999) as well as in case-control study (Jha et al., 2013a).

Another important cytokine *MIF*, expressed constitutively with various other cytokines, promotes pro-inflammatory functions in both innate and acquired immunity (Renner et al., 2005, Calandra et al., 2003). Our study observed that ncRNA gene *LOC284889A* variant rs34383331*T>A* in *MIF region* was significantly associated with increased risk to malaria (Jha et al., 2013b). Studies on Zambian children with malaria demonstrated that higher *CATT* repeats (*-794CATT*6/7/8*) were correlated with increased parasitemia, whereas *-794CATT*5* was correlated with a decrease in parasitemia (Zhong et al., 2005). In line to this finding, a study on Kenyan children demonstrated that higher STR repeats *-794(CATT)7-8* and *-173G* were associated with increased risk of severe malarial anaemia (Awandare et al., 2009).

Conclusion and future directions

Malaria is a global disease and to achieve the goal of malaria control, eradication strategies must be flexible enough to cater with the predominance of parasite species, variations in vector biology and ecology along with different epidemiologic and geographic settings. Over the last century, efforts have been made to control, eliminate and eradicate malaria, using tools such as antimalarial drugs and insecticides. However, inadequate maintenance of control programs, as well as logistic and behavioral factors, limited the effective use of interventions. In addition, the parasites and mosquitoes rapidly developed resistance to common drugs and insecticides. To achieve the ultimate goal of elimination and eradication of malaria, we critically require new tools, vaccines, improved diagnostics, new drugs, and vector management approaches. Further, to support the timely development of those tools and to generate a broad knowledge base, we need to accelerate the pace of malaria research.

Several studies highlight the underlying complexity of malaria and the need of newer methods and tools as well as of genomic studies. The large-scale genomic study can identify genetic factors which, can answer the basic questions such as how infected individuals clear parasites from the bloodstream or why malaria cause cerebral complications in some people but not in others. It will also pave the way for the discovery of novel molecular pathways of protective immunity, which can provide critical insights for the development of a vaccine as well as biomarkers for early diagnosis (Andrade et al., 2011). Further, understanding how nature copes with this devastating infectious disease, how the strong selective pressure against malaria during the course of evolution has shaped the innate mechanism of protection, we may find the better way to protect people from malaria. For example discovery of Duffy negative genotype and resistance to *Plasmodium vivax* malaria provided a way for vaccine development, which is already in clinical trial (Kwiatkowski, 2005). Further, the effective vaccine development is difficult due to the large genome of *Plasmodium*, which adapts quickly in response to selection pressure. In addition, varied disease response due to population architecture, age groups and geographical location complicate the malaria management, both in terms of research as well as interventions.

Conflict of interest statement

The author has declared to have no competing or conflict of interest.

Authors' contributions

ANJ conceived, designed and drafted the manuscript all through.

REFERENCES

Agarwal A, Guindo A, Cissoko Y, Taylor JG, Coulibaly D, Kone A, et al. (2000). Hemoglobin C associated with protection from severe malaria in the Dogon of Mali, a West African

population with a low prevalence of hemoglobin S. *Blood* 96: 2358-63.

Aidoo M, Terlouw DJ, Kolczak MS, McElroy PD, ter Kuile FO, Kariuki S, et al. (2002). Protective effects of the sickle cell gene against malaria morbidity and mortality. *Lancet* 359: 1311-2.

Allison AC (1954). Protection afforded by sickle-cell trait against subtertian malareal infection. *Br Med J* 1: 290-4.

Andrade BB and Barral-Netto M (2011). Biomarkers for susceptibility to infection and disease severity in human malaria. *Mem Inst Oswaldo Cruz* 106 Suppl 1: 70-8.

Awandare GA, Martinson JJ, Were T, Ouma C, Davenport GC, Ong'echa JM, et al. (2009). MIF (macrophage migration inhibitory factor) promoter polymorphisms and susceptibility to severe malarial anemia. *J Infect Dis* 200: 629-37.

Baird JK (1995). Host age as a determinant of naturally acquired immunity to Plasmodium falciparum. *Parasitology Today* 11: 105-11.

Banchereau J, Briere F, Galizzi JP, Miossec P and Rousset F (1994). Human interleukin 4. *J Lipid Mediat Cell Signal* 9: 43-53.

Beeson JG and Crabb BS (2007). Towards a vaccine against Plasmodium vivax malaria. *PLoS Med* 4: e350.

Belardelli F and Gresser I (1996). The neglected role of type I interferon in the T-cell response: implications for its clinical use. *Immunol Today* 17: 369-72.

Bhaskar LVKS and Patra PK (2015). Sickle Cell Disease is autochthonous and unique in Indian populations. *Ind. J. Phys. Anthrop. & Hum. Genet* 34: 201-210.

Boldt AB, Luty A, Grobusch MP, Dietz K, Dzeing A, Kombila M, et al. (2006). Association of a new mannose-binding lectin variant with severe malaria in Gabonese children. *Genes Immun* 7: 393-400.

Calandra T and Roger T (2003). Macrophage migration inhibitory factor: a regulator of innate immunity. *Nat Rev Immunol* 3: 791-800.

Chang KH and Stevenson MM (2004). Malarial anaemia: mechanisms and implications of insufficient erythropoiesis during blood-stage malaria. *Int J Parasitol* 34: 1501-16.

Chotivanich K, Udomsangpetch R, Pattanapanyasat K, Chierakul W, Simpson J, Looareesuwan S, et al. (2002). Hemoglobin E: a balanced polymorphism protective against high parasitemias and thus severe P falciparum malaria. *Blood* 100: 1172-6.

Crosnier C, Bustamante LY, Bartholdson SJ, Bei AK, Theron M, Uchikawa M, et al. (2011). Basigin is a receptor essential for erythrocyte invasion by Plasmodium falciparum. *Nature* 480: 534-7.

Das A, Anvikar AR, Cator LJ, Dhiman RC, Eapen A, Mishra N, et al. (2012). Malaria in India: the center for the study of complex malaria in India. *Acta Trop* 121: 267-73.

Dhandapany PS, Sadayappan S, Xue Y, Powell GT, Rani DS, Nallari P, et al. (2009). A common MYBPC3 (cardiac myosin binding protein C) variant associated with cardiomyopathies in South Asia. *Nat Genet* 41: 187-91.

Driss A, Hibbert JM, Wilson NO, Iqbal SA, Adamkiewicz TV and Stiles JK (2011). Genetic polymorphisms linked to susceptibility to malaria. *Malar J* 10: 271.

Durand PM and Coetzer TL (2008). Pyruvate kinase deficiency protects against malaria in humans. *Haematologica* 93: 939-40.

Eid NA, Hussein AA, Elzein AM, Mohamed HS, Rockett KA, Kwiatkowski DP, et al. (2010). Candidate malaria susceptibility/protective SNPs in hospital and population-based studies: the effect of sub-structuring. *Malar J* 9: 119.

Farouk SE, Dolo A, Bereczky S, Kouriba B, Maiga B, Farnert A, et al. (2005). Different antibody- and cytokine-mediated responses to Plasmodium falciparum parasite in two sympatric ethnic tribes living in Mali. *Microbes Infect* 7: 110-7.

Fell AH, Currier J and Good MF (1994). Inhibition of Plasmodium falciparum growth in vitro by CD4+ and CD8+ T cells from non-exposed donors. *Parasite Immunol* 16: 579-86.

Gowda NM, Wu X and Gowda DC (2012). TLR9 and MyD88 are crucial for the development of protective immunity to malaria. *J Immunol* 188: 5073-85.

Grimberg BT, Udomsangpetch R, Xainli J, McHenry A, Panichakul T, Sattabongkot J, et al. (2007). Plasmodium vivax invasion of human erythrocytes inhibited by antibodies directed against the Duffy binding protein. *PLoS Med* 4: e337.

Guinovart C, Dobano C, Bassat Q, Nhabomba A, Quinto L, Manaca MN, et al. (2012). The role of age and exposure to Plasmodium falciparum in the rate of acquisition of naturally acquired immunity: a randomized controlled trial. *PLoS One* 7: e32362.

Guo L, Hu-Li J, Zhu J, Watson CJ, Difilippantonio MJ, Pannetier C, et al. (2002). In TH2 cells the Il4 gene has a series of accessibility states associated with distinctive probabilities of IL-4 production. *Proc Natl Acad Sci U S A* 99: 10623-8.

Gyan BA, Goka B, Cvetkovic JT, Kurtzhals JL, Adabayeri V, Perlmann H, et al. (2004). Allelic polymorphisms in the repeat and promoter regions of the interleukin-4 gene and malaria severity in Ghanaian children. *Clin Exp Immunol* 138: 145-50.

Hill AV (1999). The immunogenetics of resistance to malaria. *Proc Assoc Am Physicians* 111: 272-7.

Hunt PJ, Marshall SE, Weetman AP, Bell JI, Wass JA and Welsh KI (2000). Cytokine gene polymorphisms in autoimmune thyroid disease. *J Clin Endocrinol Metab* 85: 1984-8.

Hutagalung R, Wilairatana P, Looareesuwan S, Brittenham GM, Aikawa M and Gordeuk VR (1999). Influence of hemoglobin E trait on the severity of Falciparum malaria. *J Infect Dis* 179: 283-6.

Jack DL and Turner MW (2003). Anti-microbial activities of mannose-binding lectin. *Biochem Soc Trans* 31: 753-7.

Jha AN, Mishra H, Verma HK, Pandey I and Lakkakula B (2018). Compound Heterozygosity of beta-Thalassemia and the Sickle Cell Hemoglobin in Various Populations of Chhattisgarh State, India. *Hemoglobin* 42: 84-90.

Jha AN, Singh VK, Kumari N, Singh A, Antony J, van Tong H, et al. (2012). IL-4 haplotype -590T, -34T and intron-3 VNTR R2 is associated with reduced malaria risk among ancestral indian tribal populations. *PLoS One* 7: e48136.

Jha AN, Singh VK, Singh R, Pati SS, Patra PK, Singh L, et al. (2013a). A rare non-synonymous c.102C>G SNP in the IFNB1 gene might be a risk factor for cerebral malaria in Indian populations. *Infect Genet Evol* 14: 369-74.

Jha AN, Sundaravadivel P, Pati SS, Patra PK and Thangaraj K (2013b). Variations in ncRNA gene LOC284889 and MIF-794CATT repeats are associated with malaria susceptibility in Indian populations. *Malaria journal* 12: 345.

Jha AN, Sundaravadivel P, Singh VK, Pati SS, Patra PK, Kremsner PG, et al. (2014). MBL2 Variations and Malaria Susceptibility in Indian Populations. *Infection and immunity* 82: 52-61.

Khattri A, Pandey RK, Gupta NJ, Chakravarty B, Deenadayal M, Singh L, et al. (2009a). APOB gene signal peptide deletion polymorphism is not associated with infertility in Indian men. *J Androl* 30: 734-8.

Khattri A, Pandey RK, Gupta NJ, Chakravarty B, Deendayal M, Singh L, et al. (2009b). CA repeat and RsaI polymorphisms in ERbeta gene are not associated with infertility in Indian men. *Int J Androl* 32: 81-7.

Klabunde J, Uhlemann AC, Tebo AE, Kimmel J, Schwarz RT, Kremsner PG, et al. (2002). Recognition of plasmodium falciparum proteins by mannan-binding lectin, a component of the human innate immune system. *Parasitol Res* 88: 113-7.

Kwiatkowski DP (2005). How malaria has affected the human genome and what human genetics can teach us about malaria. *Am J Hum Genet* 77: 171-92.

Larsen F, Madsen HO, Sim RB, Koch C and Garred P (2004). Disease-associated mutations in human mannose-binding lectin compromise oligomerization and activity of the final protein. *J Biol Chem* 279: 21302-11.

Luoni G, Verra F, Arca B, Sirima BS, Troye-Blomberg M, Coluzzi M, et al. (2001). Antimalarial antibody levels and IL4 polymorphism in the Fulani of West Africa. *Genes Immun* 2: 411-4.

Machado P, Pereira R, Rocha AM, Manco L, Fernandes N, Miranda J, et al. (2010). Malaria: looking for selection signatures in the human PKLR gene region. *Br J Haematol* 149: 775-84.

Marsh DG, Neely JD, Breazeale DR, Ghosh B, Friedhoff LR, Schou C, et al. (1995). Total serum IgE levels and chromosome 5q. *Clin Exp Allergy* 25 Suppl 2: 79-83; discussion 95-6.

McDevitt MA, Xie J, Shanmugasundaram G, Griffith J, Liu A, McDonald C, et al. (2006). A critical role for the host mediator macrophage migration inhibitory factor in the pathogenesis of malarial anemia. *J Exp Med* 203: 1185-96.

McGuire W, Knight JC, Hill AV, Allsopp CE, Greenwood BM and Kwiatkowski D (1999). Severe malarial anemia and cerebral malaria are associated with different tumor necrosis factor promoter alleles. *J Infect Dis* 179: 287-90.

Miller LH, Howard RJ, Carter R, Good MF, Nussenzweig V and Nussenzweig RS (1986). Research toward malaria vaccines. *Science* 234: 1349-56.

Modiano D, Luoni G, Sirima BS, Simpore J, Verra F, Konate A, et al. (2001). Haemoglobin C protects against clinical Plasmodium falciparum malaria. *Nature* 414: 305-8.

Morrell CN, Srivastava K, Swaim A, Lee MT, Chen J, Nagineni C, et al. (2011). Beta interferon suppresses the development of experimental cerebral malaria. *Infect Immun* 79: 1750-8.

Murphy KM and Reiner SL (2002). The lineage decisions of helper T cells. *Nat Rev Immunol* 2: 933-44.

Nakashima H, Miyake K, Inoue Y, Shimizu S, Akahoshi M, Tanaka Y, et al. (2002). Association between IL-4 genotype and IL-4 production in the Japanese population. *Genes Immun* 3: 107-9.

Othoro C, Lal AA, Nahlen B, Koech D, Orago AS and Udhayakumar V (1999). A low interleukin-10 tumor necrosis factor-alpha ratio is associated with malaria anemia in children residing in a holoendemic malaria region in western Kenya. *J Infect Dis* 179: 279-82.

Perlmann H, Helmby H, Hagstedt M, Carlson J, Larsson PH, Troye-Blomberg M, et al. (1994). IgE elevation and IgE anti-malarial antibodies in Plasmodium falciparum malaria: association of high IgE levels with cerebral malaria. *Clin Exp Immunol* 97: 284-92.

Perlmann P, Perlmann H, Flyg BW, Hagstedt M, Elghazali G, Worku S, et al. (1997). Immunoglobulin E, a pathogenic factor in Plasmodium falciparum malaria. *Infect Immun* 65: 116-21.

Perlmann P, Perlmann H, Looareesuwan S, Krudsood S, Kano S, Matsumoto Y, et al. (2000). Contrasting functions of IgG and IgE antimalarial antibodies in uncomplicated and severe Plasmodium falciparum malaria. *Am J Trop Med Hyg* 62: 373-7.

Renner P, Roger T and Calandra T (2005). Macrophage migration inhibitory factor: gene polymorphisms and susceptibility to inflammatory diseases. *Clin Infect Dis* 41 Suppl 7: S513-9.

Schuldt K, Kretz CC, Timmann C, Sievertsen J, Ehmen C, Esser C, et al. (2011). A -436C>A polymorphism in the human FAS gene promoter associated with severe childhood malaria. *PLoS Genet* 7: e1002066.

Srivastava K, Cockburn IA, Swaim A, Thompson LE, Tripathi A, Fletcher CA, et al. (2008). Platelet factor 4 mediates inflammation in experimental cerebral malaria. *Cell Host Microbe* 4: 179-87.

Stevenson MM and Riley EM (2004). Innate immunity to malaria. *Nat Rev Immunol* 4: 169-80.

Tarazona-Santos E, Castilho L, Amaral DR, Costa DC, Furlani NG, Zuccherato LW, et al. (2011). Population genetics of GYPB and association study between GYPB*S/s polymorphism and susceptibility to P. falciparum infection in the Brazilian Amazon. *PLoS One* 6: e16123.

Timmann C, Thye T, Vens M, Evans J, May J, Ehmen C, et al. (2012). Genome-wide association study indicates two novel resistance loci for severe malaria. *Nature* 489: 443-6.

Tishkoff SA, Varkonyi R, Cahinhinan N, Abbes S, Argyropoulos G, Destro-Bisol G, et al. (2001). Haplotype diversity and linkage disequilibrium at human G6PD: recent origin of alleles that confer malarial resistance. *Science* 293: 455-62.

van der Heyde HC, Nolan J, Combes V, Gramaglia I and Grau GE (2006). A unified hypothesis for the genesis of cerebral malaria: sequestration, inflammation and hemostasis leading to microcirculatory dysfunction. *Trends Parasitol* 22: 503-8.

Verma HK, Jha AN, Khodiar PK, Patra PK and Bhaskar LV (2016). Identification of the Rare, Four Repeat Allele of IL-4 Intron-3 VNTR Polymorphism in Indian Populations. *Iran J Immunol* 13: 124-31.

Verra F, Luoni G, Calissano C, Troye-Blomberg M, Perlmann P, Perlmann H, et al. (2004). IL4-589C/T polymorphism and IgE levels in severe malaria. *Acta Trop* 90: 205-9.

Vigario AM, Belnoue E, Gruner AC, Mauduit M, Kayibanda M, Deschemin JC, et al. (2007). Recombinant human IFN-alpha inhibits cerebral malaria and reduces parasite burden in mice. *J Immunol* 178: 6416-25.

Williams TN, Mwangi TW, Wambua S, Peto TE, Weatherall DJ, Gupta S, et al. (2005). Negative epistasis between the malaria-protective effects of alpha+-thalassemia and the sickle cell trait. *Nat Genet* 37: 1253-7.

Zakeri S, Pirahmadi S, Mehrizi AA and Djadid ND (2011). Genetic variation of TLR-4, TLR-9 and TIRAP genes in Iranian malaria patients. *Malar J* 10: 77.

Zhong XB, Leng L, Beitin A, Chen R, McDonald C, Hsiao B, et al. (2005). Simultaneous detection of microsatellite repeats and SNPs in the macrophage migration inhibitory factor (MIF) gene by thin-film biosensor chips and application to rural field studies. *Nucleic Acids Res* 33: e121.