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-loci 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, 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). HbS 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 nullifed 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, SLC4A1, DARC, GPYB, PKLR, G6PD).
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 rs34383331T>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
population with a low prevalence of hemoglobin S. Blood 96: 2358-63.


POLYMORPHISM


