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## REVIEW

# Host genome polymorphisms and tuberculosis infection: What we have to say?

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**Abstract** Several epidemiology studies suggest that host genetic factors play important roles in susceptibility, protection and progression of tuberculosis infection. Here we have reviewed the implications of some genetic polymorphisms in pathways related to tuberculosis susceptibility, severity and development. Large case-control studies examining single-nucleotide polymorphisms (SNPs) in genes have been performed in tuberculosis patients in some countries. Polymorphisms in natural resistance-associated macrophage protein 1 (NRAMP1), toll-like receptor 2 (TLR2), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF- $\alpha$ ), interleukin-1 receptor antagonist (IL-1RA), IL-10, vitamin D receptor (VDR), dendritic cell-specific ICAM-3-grabbing non-integrin (DC-SIGN), monocyte chemoattractant protein-1 (MCP-1), nucleotide oligomerization binding domain 2 (NOD2), interferon-gamma (IFN- $\gamma$ ), inducible nitric oxide synthase (iNOS), mannose-binding lectin (MBL) and surfactant proteins A (SP-A) have been reviewed. These genes have been

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variably associated with tuberculosis infection and there is strong evidence indicating that host genetic factors play critical roles in tuberculosis susceptibility, severity and development.

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## Introduction

Tuberculosis remains a major global health problem by causing ill-health among millions of people each year and ranking as the second leading cause of death from an infectious disease worldwide [1]. The latest estimates were almost 9 million new tuberculosis cases and 1.4 million tuberculosis-related deaths in 2011 [1]. It has been well established that both innate and adaptive immune responses are required for host control of tuberculosis infection [2,3]. In tuberculosis pathogenesis, the host cellular immune response determines whether an infection is arrested as latent or persistent infection or progresses to the next stages, active tuberculosis infection. Efficient cell-mediated immunity hinders tuberculosis infection by permanently arresting the infection at latent or persistent stage, but if the initial infection in the lung is not controlled or if the immune system becomes weakened, *Mycobacterium tuberculosis* can cause active pulmonary or extra pulmonary tuberculosis [4]. Therefore, it is expected that the genetic variants of molecules involved in innate host-defense mechanisms are associated with host susceptibility to tuberculosis [5].

Approximately 90% of tuberculosis-infected individuals will remain asymptomatic with latent infection and only 10% will develop active disease, again, suggesting that host genetic factors play an important role to regulate the progression of tuberculosis infection [5]. Differential rates of tuberculosis infection and clinical outcomes among races, ethnicities, and families suggest a plausible genetic contribution toward tuberculosis susceptibility [6]. Complex interactions of *M. tuberculosis* with environmental and host genetic factors play a critical

role in tuberculosis infection [6]. Several genomic studies demonstrate that host genetics strongly influence tuberculosis susceptibility [7–10]. Unraveling the mechanisms underlying the genetic variations that influence the susceptibility or resistance to tuberculosis may lead to better understanding tuberculosis pathogenesis and the development of novel strategies for prevention and treatment of tuberculosis [5].

Assessing the contributions and functional consequences of human genetic polymorphisms to tuberculosis susceptibility or disease progression remains a major challenge. In previous publications, our group has discussed the role of human genetic polymorphisms in sepsis and dengue virus infection [11–13]. Here, we will review the implications of specific human genetic polymorphisms related to susceptibility and severity of tuberculosis infection.

## Discussion

### *Natural resistance-associated macrophage protein 1 (NRAMP1)*

NRAMP1 is located on the endocytic compartment of resting macrophages and is recruited to the membrane of the phagosome depending on the pH gradient [14]. NRAMP1 acts as a divalent cation transporter or antiporter across phagosomal membranes that is expressed only in reticuloendothelial cells [6,15]. These facts suggest that NRAMP1 may inhibit the replication of intracellular pathogens by altering the phagolysosomal environment. NRAMP1 is a critical mediator in the innate immune response to tuberculosis infection which leads

to decreased DNA replication and respiratory chain function in *M. tuberculosis* [16], but the precise function of this protein remains unclear [6]. Several polymorphisms have been described in the NRAMP1 gene and these polymorphisms alter the gene's function [17]. Four NRAMP1 polymorphisms; 3'-UTR, D543N, 5'(GT)n, and INT4 have been associations with *M. tuberculosis* infection in humans [6]. In terms of the 5'(GT)n polymorphism, a study found that there was a significant association of this NRAMP1 polymorphism type with tuberculosis when considering an interaction with Toll-like receptor 2 (TLR2) [17]. Most of the variants' associations were established in a meta-analysis of China populations [18]. Another study found that NRAMP1 polymorphisms at the D543N and INT4 loci contribute to severe pulmonary tuberculosis [19]. However, NRAMP1 polymorphisms at the D543N and INT4 were not associated with tuberculosis in an Indonesian population [14].

#### *Toll-like receptor 2 (TLR2)*

TLRs are transmembrane molecules that serve as sentries for pathogen detection, by a kind of evolutionary recognition of molecular patterns associated with past infections [20]. TLR expression found in many cell types, including host immune cells, serves as critical mediators of the immune response to a variety of pathogens, including *M. tuberculosis* [21]. Several types of TLRs have strong links with tuberculosis, including TLR1, TLR2, TLR4, TLR6 and TLR9. The genetic variant most often associated with tuberculosis is found in TLR2 [6]. A TLR2 heterodimer, in combination with the TLR1, binds 19-kD mycobacterial lipoprotein, suggesting TLR2 is an adhesion molecule for *M. tuberculosis* [22]. A previous study suggests that Toll interleukin 1 receptor domain containing adaptor protein (TIRAP), an adaptor that mediates signals from TLRs activated by mycobacterial molecules, induced a strong proinflammatory response to tuberculosis [6]. Studies in animal and human revealed that TLRs play pivotal roles in innate immune response to tuberculosis via many pathways (a) TLR activation triggers a complex of cascade that leads to induction of a large range of proinflammatory genes [23]; (b) TLRs activate nuclear factor  $\kappa$  beta (NF $\kappa$ B) which is the first line of defense against many pathogens [24]; (c) TLRs play integral roles in the activation of inflammatory cytokine signaling pathways and adaptive immune responses [25].

A number of reports found SNPs in TLR2 gene that affect tuberculosis susceptibility, including R753Q (exon), R677W (exon), -597T/C and P631H [26–28]. TLR2 -R753Q influenced tuberculosis progression in children [27] and TLR2 -597T/C strongly associated with miliary tuberculosis [28]. Another study found that TLR2 -975C/T was associated with protection against tuberculosis, resultant from attenuation of TLR2 signal transduction [29]. Moreover, a microsatellite region within intron 2 of TLR2, TLR -975C/T, has significant frequency variation across populations and may also influence gene function [28]. In a Korean population, a study found an association between this SNP and pulmonary tuberculosis [30]. The possible reason is the C allele has a high level of linkage with the allele of the GT microsatellite that affects TLR2 gene regulation. Another TLR2 SNP, TLR2 P631H, was significantly over-represented in tuberculosis patients compared to controls in a Croatian Caucasian population [31]. These

evidences suggested that TLR2 gene SNPs likely play important roles in tuberculosis infection.

#### *Interleukin-6 (IL-6)*

IL-6, a mayor mediator of fever and acute-phase reactions, is expressed in hepatocytes, monocytes, B cells lymphocytes, macrophages, and neutrophils in humans [11]. It is also found on a subset of T-cell lymphocytes [32]. As a key proinflammatory cytokine, IL-6 is associated with the pathogenesis of many chronic inflammatory diseases, including tuberculosis [33]. Briefly, IL-6 is likely to be associated with several tuberculosis-related roles: (a) IL-6 blocks interferon (IFN)- $\gamma$  mediated signaling; (b) IL-6 downregulates IL-6 receptor (IL-6R) expression in CD4 T-cells and is associated with T-helper cell depletion; (c) IL-6 induces IL-4 production; and (d) IL-6 is involved in macrophage and cytotoxic T-cell differentiation [6,34,35].

Genetic variants in IL-6 have been linked to susceptibility and severity of a wide range of diseases, including chronic hepatitis C virus infection and respiratory tract infection [36,37]. In an animal model study, IL-6 is required for rapid expression of an initial protective IFN- $\gamma$  response during *M. tuberculosis* infection [35]. In humans, a higher level of IL-6 may be detrimental to resistance against *M. tuberculosis* infection [38]. A genome-wide scan of Ugandans with tuberculosis revealed a linkage to a locus on chromosome 7 which contains the IL-6 gene [39]. Zhang et al. [38] reported that the nonsynonymous SNP in the IL-6 gene promoter -572C > G is associated with higher resistance to tuberculosis. They also found that -572GG genotype contributed to protection against tuberculosis in the Han Chinese population through downregulation of IL-6 production. Another SNP, the G allele or GG genotype in the IL-6 gene promoter region (-174), was associated with high IL-6 production [34,40] in tuberculosis patients which may have promoted tuberculosis by inhibiting other cytokines production such as tumor necrosis factor (TNF) and IL-1 $\beta$  [6].

#### *Tumor necrosis factor alpha (TNF- $\alpha$ )*

TNF- $\alpha$  is an important proinflammatory cytokine, which is produced primarily by monocytes, macrophages, and dendritic cells when stimulated by mycobacterial metabolites; therefore, TNF- $\alpha$  is likely involved in host protective responses against *M. tuberculosis* infection [6]. TNF- $\alpha$  also has immunoregulatory properties and synergistic effects to IFN- $\gamma$  in macrophage activation [41]. However, systemic excess of TNF- $\alpha$  may account for unwanted inflammatory effects like fever and malaise [41]. Briefly, there are many effects of TNF- $\alpha$  on the host immunological response to *M. tuberculosis* infection. Neutralization of TNF- $\alpha$  causes persistent tuberculosis reactivation, characterized by an increase of tissue bacillary burden and severe pulmonic histopathological deterioration that was associated with changes indicative of squamous metaplasia and fluid accumulation in the alveolar space. In addition, analysis of pulmonic gene and protein expression in mice revealed that nitric oxide synthases were attenuated after TNF- $\alpha$  neutralization [42].

The TNFA gene, which encodes cytokine TNF- $\alpha$ , is located within the major histocompatibility complex (MHC) between

human leukocyte antigen-B (HLA-B) and the HLA class III genes region at the short arm of chromosome 6. The production of TNF- $\alpha$  is both transcriptionally and post-transcriptionally regulated [43]. Some SNPs in the TNFA gene substantially regulate TNF- $\alpha$  production by regulating its transcription, including eleven SNPs in promoter region -1031 (T/C), -863 (C/A), -857 (C/T), -308 (G/A), -238 (G/A), -1196 (C/T), -1125 (G/C), -572 (A/C), -316 (G/A), -163 (G/A), and -70 (G/A) [44,45]. In clinical studies, the most common SNP in the TNFA promoter region is TNFA -238G/A; however, the associations between this SNP and tuberculosis remain unclear. Amirzargar et al. found a negative association between the -238G/A genotype and tuberculosis; however, G/G genotype had a positive association [40]. Previously, a study identified a significant association between TNFA -238G/A and tuberculosis susceptibility [46]. However, another study found that the TNFA -238G/A SNP allele did not associate with tuberculosis [47]. Additionally, a study in Iran documented that the SNP TNFA -857C/T increased the host susceptibility to tuberculosis infection [48]. These contradictory results underscore the need to establish the associations of TNFA genotypes with tuberculosis clinical outcomes in different human populations.

#### *Interleukin-1 receptor antagonist (IL-1RA)*

The IL-1 family consists of IL-1 alpha (IL-1 $\alpha$ ), IL-1 beta (IL-1 $\beta$ ), and IL-1RA. IL-1 $\alpha$  and IL-1 $\beta$  bind to the IL-1 receptor (IL-1R) and initiate an inflammation cascade to induce vascular dilation and fever [11]. IL-1RA is a competitive inhibitor of IL-1 to induce proinflammatory activity. The IL-1RA gene is polymorphic, resulting in quantitative differences in IL-1RA and IL-1 $\beta$  production [48]. The polymorphic region within intron 2 of the IL-1RN\* gene contains a 86-bp variable numbers of tandem repeats (VNTR) locus. Five alleles of the IL-1RN\* VNTR have been reported (\*1-5), corresponding to 2, 3, 4, 5 and 6 copies of the 86-bp sequence, respectively [11]. A previous study investigated the effect of polymorphisms in the IL-1RA genes on *M. tuberculosis* - stimulated cytokine production *in vitro* and their relevance in patients with tuberculosis [49]. It was reported that induction of both IL-1RA mRNA and a secreted protein by *M. tuberculosis* in IL-1RA allele A2<sup>+</sup>-positive (IL-1RA A2<sup>+</sup>) of healthy subjects was higher than in IL-1RA A2<sup>-</sup> subjects. In addition, the IL-1RA A2<sup>+</sup> haplotype was associated with a reduced Mantoux response. This study confirmed that the IL-1RA polymorphism was a determinant of delayed-type hypersensitivity and disease expression in the human immune response.

The IL-1RA A2<sup>+</sup> variant is associated with higher serum levels of IL-1RA [48]. Therefore, being IL-1RA A2<sup>+</sup> homozygous has a more prolonged and more severe proinflammatory immune response. The IL-1RA A2<sup>+</sup> genotype was also associated with a reduction in the delayed type hypersensitivity response to purified protein derivative and was inversely related to the development of pleural tuberculosis [48].

#### *Interleukin-10 (IL-10)*

IL-10, a major anti-inflammatory cytokine associated with several diseases, is an important immunoregulatory mediator produced by activated monocytes/macrophages, dendritic cells, T

and B lymphocytes [50]. IL-10 production in human monocyte cells is induced by *M. tuberculosis* phagocytosis, but IL-10 also suppresses the proinflammatory response by downregulating cytokine production; therefore, IL-10 is considered a macrophage-deactivating cytokine [51]. However, IL-10 potentially helps *M. tuberculosis* persistence in humans by inhibiting phagosome maturation in macrophages [52]. In mice, IL-10 produced by macrophages was higher in mice that had been stimulated with purified protein derivative of *M. tuberculosis* than in wild type resistant mice. Moreover, *M. tuberculosis* activated TNF- $\alpha$  and IL-10 - dependent signals that induce apoptosis in mice [53]. Many IL-10 gene SNPs have been described in previous studies, including -1082G/A (promoter) and -592A/C (promoter) [6,54-56]. A review by Azad et al. found that IL-10 promoter SNPs play a significant role in *M. tuberculosis* infection [6]. IL-10 -1082G/A and -592A/C have been associated with higher IL-10 protein expression [55]. Despite many studies establishing associations between these SNPs and tuberculosis, other studies reported that these SNPs had no association with tuberculosis [54,56-60]. In a candidate gene linkage study using microsatellite markers, the IL-10 gene was implicated in clinical tuberculosis [61]. This study found a strong association between IL-10 microsatellite polymorphisms, TNF levels and tuberculosis. A study in Gambia investigated that NRAMP1 influenced tuberculosis susceptibility by regulation of IL-10 [53]. They also found that IL-10 plasma levels measured higher among tuberculosis patients compared with the control group. Higher IL-10 levels could lead to tuberculosis development via two different mechanisms: (a) IL-10 controls *M. tuberculosis* infection through macrophage up-regulation and production of microbicidal compounds, including reactive oxygen and nitrogen intermediates, and TNF- $\alpha$ . (b) IL-10 regulates secondary immune response development in tuberculosis. Based on the reported results, manipulation of the IL-10 pathway may be a novel immunotherapy for tuberculosis treatment in the future.

#### *Vitamin D receptor (VDR)*

The VDR gene encodes a transcription factor, when activated by vitamin D, modulates diverse biologic processes, including calcium homeostasis and immune function. VDR mediates the immunoregulatory effects of 1,25-dihydroxyvitamin D<sub>3</sub> (1,25D<sub>3</sub>), which activates monocytes, stimulating cellular immune responses and suppressing immunoglobulin production and lymphocyte proliferation [11]. Genetic variation in VDR shows striking differences in allele frequency between populations and has been associated with disease susceptibility, including autoimmunity disorders and tuberculosis [62]. Several VDR polymorphisms have been identified, namely TaqI (TT, Tt and tt), ApaI (AA, Aa and aa) and BsmI (BB, Bb and bb) [63]. Recent studies suggested a protection association between VDR polymorphisms and infectious diseases including tuberculosis, *Leishmania major*, Human Immunodeficiency Virus (HIV), dengue hemorrhagic fever and *Staphylococcus aureus* infection [63-67]. These associations led to the suggestion that the tt genotype may be associated with a relatively stronger TH1-type cellular immune response than the TT genotype; interestingly, 1,25D<sub>3</sub> has been found to alter IL-12 expression and dendritic cells maturation [68]. A previous study found that the tt genotype was less frequent in patients with pulmonary tuberculosis in Gambia [69].



However, research in West African populations failed to find the association between VDR haplotypes and tuberculosis infection [70].

Vitamin D has been linked to tuberculosis pathogenesis through VDR action [71,72]. It suppressed *M. tuberculosis* growth in macrophages through induction of antimicrobial peptide cathelicidin and likely via the TLR signaling [71–73]. Several VDR polymorphisms with nomenclature derived from their restriction enzyme cleavage sites, such as FokI, TaqI, BsmI, and ApaI, and their combination as a haplotype, have been tested in population studies for tuberculosis associations [74]. A study investigated the role of FokI, BsmI, ApaI, and TaqI VDR gene polymorphisms on child tuberculosis in Indonesian populations [75]. This study documented that FokI variant was more frequently found in the tuberculosis group than the control group, while BsmI, ApaI, and TaqI variants did not differ significantly between the tuberculosis and control group. This study suggested that the FokI variation is a risk factor for child tuberculosis. However, a study in Turkey found that there was no correlation between FokI and TaqI frequencies with tuberculosis infection but the BsmI variation might play an important role in tuberculosis susceptibility [76]. Another study in West African populations reported that ApaI had a significant association with tuberculosis, suggesting ApaI variation as a potential risk factor for tuberculosis [77]. A meta-analysis by Gao et al. found inconsistent results [74]. They found that among the Asian population, the FokI ff genotype showed an association with tuberculosis, a significant inverse association with tuberculosis was observed for the BsmI bb genotype. However, in African and South American populations, none of the VDR gene polymorphisms were significantly related to tuberculosis. Andraos et al. reported a complex association between VDR gene methylation and the TaqI genotype, which highlighted the need to consider how both genetic and epigenetic variation associates with tuberculosis [62]. The variation in VDR gene methylation, and its impact on VDR expression and tuberculosis susceptibility remain to be determined.

#### *Dendritic cell-specific ICAM-3-grabbing non-integrin (DC-SIGN)*

DC-SIGN, a C-type lectin encoded by the CD209 gene, plays an important role in the early interaction of pathogens with dendritic cells and has a key role in dendritic cell T-cell interaction, dendritic cell migration, and pathogen uptake [11]. DC-SIGN is a type II transmembrane protein predominantly expressed in dendritic cells that are induced in alveolar macrophages from *M. tuberculosis*-infected patients [6]. It directly mediates phagocytosis of *M. tuberculosis* by dendritic cells and interferes with dendritic cells maturation [78,79].

Some polymorphisms in the DC-SIGN gene have been reported, two of these polymorphisms, DC-SIGN –336A/G and –871A/G, occur within DC-SIGN promoter [11]. These variants affect DC-SIGN promoter activity with multiple transcription factor binding sites [80]. Some studies documented that these variants have been associated with bacterial and viral infection [79,81]. Previous study suggests that DC-SIGN –336A/G and –871A/G had significant associations with tuberculosis infection [82]. Recently, a study investigating the associations between DC-SIGN 336A/G and –871A/G and

tuberculosis susceptibility in an Eastern Chinese population did not associate the DC-SIGN variation with tuberculosis susceptibility [83]. However, DC-SIGN –336A/G and –871A/G genotypes were shown to have protective associations against tuberculosis in a South African population [84]. Additionally, in a Chinese population, the G allele at –336 had a significant association with tuberculosis protection [83]. The DC-SIGN –336G allele affects an Sp1 binding site and decreases DC-SIGN expression resulting in less efficient cytokine and chemokine secretion [85]. Polymorphisms within the 5'- and 3'-UTRs of both DC-SIGN and DC-SIGN receptor (DC-SIGNR), presumably affecting transcription and translation, have possible associations with tuberculosis susceptibility in both Caucasian Canadian and indigenous African populations [6].

#### *Monocyte chemoattractant protein-1 (MCP-1)*

The human MCP-1 gene is located on chromosome 17, consists of 76 amino acids and is 13 kDa in size [86,87]. MCP-1, a member of the C-C chemokine family, has a role as potent chemotactic factor for monocytes, which play critical roles in recruitment of macrophages and T lymphocytes for controlling *M. tuberculosis* dissemination [88,89]. Numerous studies investigated the association of MCP-1 genetic variants and tuberculosis susceptibility [86,89–91].

The MCP-1 –2518A/G functional SNP, locates on the promoter region and plays a key role in various pathologies [6]. MCP-1 –2518A/G affects the transcriptional activity of the distal regulatory region, and modulates monocyte MCP-1 production [90]. Compared with the MCP-1 –2518A allele, the MCP-1 –2518G allele was associated with higher MCP-1 protein production in monocytes. Additionally, higher levels of MCP-1 increase the protective effects against tuberculosis infection [92]. Moreover, an *in vivo* study further suggests that low levels of MCP-1 in mice impaired granuloma formation and conferred lower tuberculosis susceptibility [92].

Population-based studies have reported an association between MCP-1 –2518A/G with risk of tuberculosis, but the results were inconclusive. Some studies reported that MCP-1 –2518A/G was associated with increased risk of tuberculosis in Mexicans, Koreans, Chinese and Peruvians, while other studies fail to establish an association between this SNP and tuberculosis infection such as in South African Coloreds, Indians, and Ghanaians [85,90,93–95]. Interestingly, Ben-Selma et al. found an association between MCP-1 –2518A/G with resistance/susceptibility of active pulmonary tuberculosis development in Tunisian populations [88]. This group also observed that the MCP-1 –2518G allele and GG genotype (high MCP-1 producer) frequencies were significantly higher in the active pulmonary tuberculosis group than the control group. However, wild type allele MCP-1 –2518A and AA genotype were over represented in the control group and seem to be protective factors against tuberculosis. Recent study also indicated that GG homozygote carriers had a higher risk of tuberculosis compared to individuals with an A allele [87]. In the subgroup analysis by ethnicity for this locus, a highly significant risk was found in Asians and Latinos with the GG genotype, but not in Africans. Other studies also confirmed that MCP-1 –2518GG genotype associated with tuberculosis outcome and resistance [86,91].

### Nucleotide oligomerization binding domain 2 (NOD2)

NOD2 is a member of the conserved nod-like receptor (NLR) protein family that acts as an intracellular pattern recognition receptor (PRR) [96]. NLR family proteins share typical tripartite domain structure: a C-terminal ligand recognition domain (LRR), a central NOD domain with ATPase activity involved in self-oligomerization and a N-terminus comprised of protein-protein interaction domains, such as caspase recruitment domains (CARDs) or pyrin domains [96,97]. Expression of NOD2 is regulated by proinflammatory cytokines, for instance TNF- $\alpha$  positively regulates its expression and is augmented by IFN- $\gamma$  [98]. In tuberculosis pathogenesis, C-terminal protein domain of NOD2 and C-terminal LRR domain have a crucial role in membrane targeting, which could detect the component of *M. tuberculosis* cell wall, such as derived-peptides of peptidoglycan (PGN) degradation and recognizes muramyl dipeptide (MDP), a component of PGN [99].

Polymorphisms of NOD2 gene have been associated with increased risk of pulmonary sarcoidosis and leprosy [100,101]. Recently, a review by Azad et al. showed three common non-synonymous SNPs of the NOD2 gene play important roles in tuberculosis, including Pro268Ser, Arg702Trp, and Ala725Gly [6]. A population-based study sequenced exon 4 coding regions of NOD2 gene in African-Americans with tuberculosis and ethnically matched controlled subjects [102]. This study found that Pro268Ser and Arg702Trp variations were protective against tuberculosis and Ala725Gly had a positive association with tuberculosis susceptibility. However, there was no association found between these polymorphisms and tuberculosis infection in a South African population study [103]. Recently, one case control study investigated the role of NOD2 gene SNPs in the tuberculosis susceptibility of Han Chinese, Uygur and Kazak populations [105]. This study found that the Arg587Arg SNP in NOD2 associated with susceptibility to tuberculosis and may be a risk factor for the development of tuberculosis in the Han Chinese populations. However, further work will be required both to confirm this association and to explore possible mechanisms.

Another experiment showed that polymorphisms of NOD2 associated with tuberculosis [104]. Macrophages from NOD2 knockout mice produced a significantly lower level of cytokines than control cells did. This group also found that macrophages isolated from human subjects homozygous for the 3020insC mutation of NOD2 produced 65–80% fewer cytokines after stimulation with *M. tuberculosis* than individuals' heterozygous or homozygous for the wild-type genotype. The NOD2 ligand MDP had a strong synergistic effect on TNF production induced by TLR2 ligand, the 19-kDa lipoprotein of *M. tuberculosis*. This synergism was lost in individuals' homozygous for NOD2 3020insC mutation or macrophages harvested from NOD2 knockout mice.

### Interferon-gamma (IFN- $\gamma$ )

IFN- $\gamma$  is a member of the INF family which plays a crucial role in the reaction of the immune system in resistance to pathogens such as *M. tuberculosis* [106]. IFN- $\gamma$  is produced by natural killer (NK) cells, characterizes the T helper 1 (Th1) pattern, and has a wide range of effects including monocyte and macrophage activation [107]. The Th1 cell response, which

is required to contain *M. tuberculosis* infection, is largely characterized by IFN- $\gamma$  production [106]. Furthermore, IFN- $\gamma$  and other cytokines can activate macrophages in vascular endothelium and promote plasma extravasations [11]. Convincing evidence for the importance of IFN- $\gamma$  to control *M. tuberculosis* infection has been found in both experimental and clinical studies. Mice with a disrupted IFN- $\gamma$  gene (IFNG) show increased susceptibility to tuberculosis and replacement of this gene into the lung confers resistance [108,109]. In most tuberculosis patients the production of *M. tuberculosis*-induced IFN- $\gamma$  by peripheral blood mononuclear cells is reduced at the time of diagnosis. During and after successful treatment, these levels increase significantly [106]. Although IFN- $\gamma$  is required for an initial protective Th1 cell response to *M. tuberculosis*, the increased production of this cytokine post-infection is indicative of the risk of developing active tuberculosis. A recent study showed that macaque monkeys with high IFN- $\gamma$  levels two months post infection with *M. tuberculosis* were more likely to develop active tuberculosis and similar observations have been made in humans [110,111]. Humans with mutations in genes of the IL-12/IL-23/IFN- $\gamma$  axis have an increased susceptibility to even nonpathogenic tuberculosis and are extremely susceptible to *M. tuberculosis* and *Salmonella*, but not to other bacteria [112].

An SNP in intron 1 of IFNG, IFNG + 874A/T, associates with tuberculosis development in several populations, including Sicilians, South Africans, Hong Kong and Chinese, and Spanish [57,113–115]. However, study in Malawians, Houston, West Africa, and South India failed to demonstrate an association between this SNP and tuberculosis development [116–119]. Recently, a study showed that the IFNG + 874A allele frequency was higher in patients with tuberculosis than in healthy individuals and had a significant association with susceptibility to tuberculosis in an Iranian population [123]. In addition, a meta-analysis reported a protective effect of the +874T allele against the development of tuberculosis [58].

The genotype IFNG –56CC in the promoter region and the cytosine-adenine repeat polymorphism on intron 1 were reported to be associated with tuberculosis development [118,120]. Etokebe et al. conducted a study to confirm the associations between IFNG SNPs (T + 874A and G + 2109A) and tuberculosis infection in Croatia [121]. They found that these SNPs did not associate with tuberculosis infection; however, they suggested that the presence or absence of these SNPs could provide useful information on public health decision such as the duration of patient isolation as well as the clinical course of treated tuberculosis patients. These SNPs may be a diagnostic test in tuberculosis cases [122].

### Inducible nitric oxide synthase (iNOS)

The Nitric oxide synthase (NOS) gene, present on the human chromosome 17q11.2–12, transcribes NOS enzymes that cause the oxidative deamination of amino acid L-arginine to form nitric oxide (NO). There are three isoforms of NOS enzymes: neuronal nitric oxide synthase (nNOS), endothelial nitric oxide synthase (eNOS) and inducible nitric oxide synthase (iNOS) [124]. iNOS (also known as NOS2 and encoded by human NOS2A), was expressed by mycobacterium-infected macrophages and epithelial cells, an effectors' molecule with bactericidal activity against *M. tuberculosis* [6,125]. In pulmonary

host-defense mechanism, iNOS plays a major role in response to infections with bacteriostatic processes. The alveolar macrophages induced by *M. tuberculosis* are capable of producing TNF- $\alpha$  and IL-1. These cytokines along with IFN- $\gamma$  produced by T-cells can induce NO synthesis via action of iNOS. Thus, NO and radical nitrogen intermediate can inhibit intracellular mycobacterium pathogens [124].

Genetically, the action of iNOS in the immune system is well known, SNP variation in the promoter region has been implicated in several diseases including bacterial meningitis, HIV and hepatitis C virus [126–128]. These associations led to the suggestion that the presence of polymorphisms in promoter regions transcriptionally deregulate the iNOS gene, altering the level of gene product. SNPs in coding regions of exon 16 alter the activity of iNOS gene product. Alteration in the level and activity of iNOS might be responsible for the susceptibility, severity and outcome of genetic as well as infectious disease [124]. Beisiegel et al. investigated combinations such as, challenging inducible nitric oxide synthase – deficient (iNOS $-/-$ ) and wild-type mice with two related *M. tuberculosis* strains that differ markedly in virulence. They found that the combination of host susceptibility and *M. tuberculosis* virulence determines the role of iNOS in the protection and control of inflammation [129].

Several allele/polymorphisms in the iNOS gene have been reported in many populations, including CCTTT and TAAA in Columbia, –1026G allele in Brazil, rs2274894 (intron) and rs7215373 (3'-UTR) in African-American and –954G/C in Mexican populations [130–132]. However, not all of these polymorphisms have associations with tuberculosis infection. In Northwestern Colombian populations, the genotype frequencies for iNOS CCTTT differ significantly between tuberculosis patients and controls, but no individual association with iNOS TAAA was detected [130]. In Mexicans, the iNOS –954G/C SNP was not associated with tuberculosis infection [133]. Interestingly, this SNP has a significant association with tuberculosis susceptibility in a Brazilian population [131]. These incongruent associations further suggest that more research is needed to better understand genetic variation underlying iNOS-related clinical phenotypes in admixed populations.

#### *Mannose-binding lectin (MBL)*

MBL is an acute phase protein secreted by the liver, which mediates carbohydrate dependent activation of the classical complement pathway [6,11]. Moreover, MBL plays an important role in pattern recognition and innate immune defense [134]. Briefly, host defense mechanisms against *M. tuberculosis* use MBL in many pathways: (a) MBL acts as opsonin; (b) MBL enhances both complement dependent and independent phagocytosis; (c) and MBL promotes inflammation and releases cytokines [135,136].

In a prospective study, the levels of MBL protein were found to be higher in tuberculosis patients than in healthy control [137]. However, a study examining the role of the complement system in protection against respiratory tract infection indicated an important pathway of the complement system controls respiratory tract infection and potential influences tuberculosis severity in humans. Soborg et al. found a positive association between MBL concentration in human serum and

the level of *M. tuberculosis* neutralizing activity, which indicated low levels of MBL protein or its activity as an independent risk factor for tuberculosis infection morbidity and mortality [138].

Three structural mutations, affecting codons 52, 54, and 57, in the first exon of MBL2 gene have been found, and the corresponding alleles were designated D, B, and C, respectively (A is the wild-type allele for all three positions) [139]. Mutations at these codons result in low or nearly absent serum MBL levels in hetero- or homozygote individuals. However, the study with MBL alleles, genotypes, or haplotypes, based on these polymorphisms; has yielded conflicting results [140].

Mutation in the MBL promoter region has also been reported [139]. Some studies found significant associations between MBL2 promoter polymorphisms, serum MBL levels and tuberculosis susceptibility, while another study did not find any significant association [140–143]. According to a case control study in a Spanish population, the MBL D variant and HYPD haplotype were significantly more frequent in controls than in tuberculosis cases. This result indicates that these alleles could contribute toward protection against pulmonary tuberculosis development. However, high MBL levels appear to correlate with several diseases [144]. Individuals with different levels of MBL2 due to known polymorphisms in the MBL2 gene demonstrated a positive correlation between human MBL2 levels and neutralization of *M. tuberculosis* [137]. This result linked together subsequent findings related to humans with particular polymorphisms in the MBL2 gene which suggested that the MBL pathway contributes to protection against *M. tuberculosis* infection in humans [145].

#### *Surfactant proteins A (SP-A)*

SP-A is predominantly expressed by lung alveolar type II epithelial cells and non-ciliated cells. SP-A is a hydrophilic protein consisting of a collagen like domain in the N terminus that mediates oligomerization, a coiled-coiled area, and a globular Ca-dependent carbohydrate recognition domain at the C terminus [148]. The human SP-A locus has been mapped in chromosome region 10q22-q23 and consists of two highly similar isoforms encoded by separate genes, SP-A1 and SP-A2 [6,147]. SP-A plays an important role in pattern recognition and the innate immune system with the ability to bind exposed carbohydrate residues on the surface of *M. tuberculosis* and regulates the macrophage expression and the function of TLR2 and -4 [4,146]. Previously, *in vitro* studies showed that SP-A could modulate the anti-tuberculosis response by contributing to bacterial agglutination that can enhance *M. tuberculosis* association with alveolar epithelium [148,149]. This agglutination, however, was not associated with bacterial killing, since SP-A signaling has also been reported to reduce the production of reactive nitrogen and oxygen intermediates [146,150].

Several synonymous and non-synonymous SNPs have been identified in the SP-A1 and SP-A2 genes, including –1416C/T (intron), –1382C/G (intron) –307G/A (exon), –776C/T (exon), –355C/G (exon) and –751A/C (exon) [147–151]. SP-A1/2 alleles have been shown to be associated with infectious pulmonary disease, including respiratory syncytial virus infection and pulmonary tuberculosis [147,152–154]. In an Indian population, seven SNPs (4 exonic and 3 intronic) have been



identified in collagen regions of SP-A1 and SP-A2 genes [151]. Two intronic SNPs, -1416C/T and -1382C/G, showed significant association with pulmonary tuberculosis. This study also found that a redundant of SP-A2 gene SNPs showed significant association with pulmonary tuberculosis. These data replicate previous findings in a Mexican tuberculosis cohort [153]. Several intronic and exonic SP-A1 and SP-A2 SNPs, which affect splicing and/or mRNA maturation, had associations with tuberculosis [147]. This study also suggested that SP-A1 and SP-A2 SNPs influence the production of TNF- $\alpha$  and IL-8 in THP-1 cells. Furthermore, alleles in the SP-A1 and SP-A2 genes also influence the ability of SP-A to self-aggregate and to induce lipopolysaccharide aggregation, which is consistent with an inflammatory role of SP-A [155]. Thus, SP-A1 and SP-A2 may be contributing factors to susceptibility and severity of tuberculosis infection.

### Conclusion

In summary, we presented compelling evidence demonstrating several host genetic factors as important components in tuberculosis infection. Recent studies targeting candidate genes and “case-control” associations have revealed numerous genetic polymorphisms implicated in host susceptibility to tuberculosis. A number of critical genetic factors will converge to yield a comprehensive and dynamic representation of tuberculosis pathogenesis. Further analysis of the genetic basis of tuberculosis infection in different populations will likely contribute to the development of new preventative and therapeutic interventions.

### Authors' contributions

SAK and HH, responsible for work design, data collection and interpretation, drafted the first and final manuscript, and revised the manuscript. WW and II participated in data interpretation and revised the manuscript. MM advised and supervised the work. All authors read and approved the final manuscript.

### Conflict of Interest

There is no conflict of interest in writing of this manuscript.

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