Human Genetic Background in Susceptibility to Tuberculosis

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Abstract

Tuberculosis (TB), especially in developing countries, is a major threat to human health. The pathogenesis of TB remains poorly understood, and <5%–10% of individuals infected with Mycobacterium tuberculosis (MTB) will develop clinical disease. The human genetic factors contributing to susceptibility or resistance to TB pathogenesis have been investigated by high-throughput and low-throughput association studies. Genetic polymorphisms of several genes including TLR, IGRM, VDR, ASAPI, AGMO, FOXP1, and UBLCP1 effect on the disease phenotype and also the outcome of TB treatment. Recently, microRNAs (miRNAs), which negatively regulated gene expression at the posttranscriptionally level, have gained increasing attention due to their altered expression in various human diseases, including some infections. They are crucial posttranscriptional regulators of immune response in both innate and adaptive immunity. It has been established in recent studies that the host immune response against MTB is regulated by many miRNAs, most of which are induced by MTB infection. Moreover, differential expression of miRNAs in TB patients may help distinguish between TB patients and healthy individuals or latent TB. In this review, we summarize and discuss the literature and highlight the role of selected single nucleotide polymorphisms and miRNAs that have been associated with TB infection.

Keywords: Association study, genetics, microRNA, Mycobacterium tuberculosis, polymorphism

Introduction

Tuberculosis (TB) is the first cause of human death among the infectious diseases, which has a significant global public health burden. Mycobacterium tuberculosis (MTB) is the causative agent of TB.[1] Molecular studies indicated that susceptibility to TB can result from genetic predisposition with the identification of children with Mendelian predisposition to disseminated TB.[2] The question is why the susceptibility and/or resistance of individuals to TB are different. Early twin studies, candidate gene studies, and genome-wide association (GWA) studies have shown that susceptibility to TB has a host genetic component.[3] Twin studies are a special type of epidemiological studies, which allow researchers to measure the contribution of genetic factors in the development of a trait or disorder.[4] Candidate gene studies are based on the previous knowledge of the function of the gene(s) in some way related to the phenotypes or disease states. It should be noted that positive association in candidate gene study for a specific trait should be confirmed in other populations.[5] Rather than focusing on biological candidate genes, GWA study is hypothesis-free method for identifying the associations between genetic loci, genes, and variants and traits.[6] In recent decades, microRNAs (miRNAs) have gained increasing attention due to their role as gene silencers and due to their altered expression in diverse human diseases, including some infections. Recent research regarding miRNAs and TB has revealed that the expression profile for particular miRNAs clearly changes upon TB infection and varies in the different stages of this disease.[7]

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**MicroRNAs Dysregulation in Tuberculosis Infection**

miRNAs are a class of small noncoding RNAs, which function in the posttranscriptional regulation of gene expression. They are powerful regulators of various cellular activities including cell growth, differentiation, development, and apoptosis. They have been linked to many diseases, and currently, mRNA-mediated clinical trial has shown promising results for the treatment of cancer and viral infection.\[9\]

Significant evidence implicated the central role of miRNAs in the modulation of pathogenesis in TB infection.\[9\] It has been shown that gene expression profiles in macrophages and human natural killer (NK) cells from active and latent TB and from TB and healthy controls are different. Several miRNAs have been found to regulate T-cell differentiation and function, and they also play an important role in regulating the innate function of macrophages, human dendritic cells (DCs), and NK cells.\[9\] Innate immune response against TB is regulated by miRNAs. Moreover, differential expression of miRNA in MTB infection can reflect the disease progression and may help distinguish between active and latent TB infection.\[10\] The effects of MTB infection on the expression pattern of host miRNAs have been investigated in several studies. miRNA dysregulations in TB are listed in Table 1.

In a pioneering study, overexpression of let-7e, miR-29a, and miR-886-5p in the human monocyte-derived macrophages was detected in response to mycobacterial infection. Caspases 3 and 7 were introduced as the potential targets of let-7e and miR-29a, respectively.\[11\] In addition, high-throughput miRNA study showed that increased level of circulating miR-29a in the serum of patients with active pulmonary TB compared to the control group could serve as diagnostic biomarkers with a reasonable sensitivity and specificity.\[12\] Mice animal study showed that overexpression of miR-29 in TB infection resulted in the downregulation of IFN-γ. It seems that MTB avoids macrophage digestion through inhibition of IFN-γ and increasing apoptosis of cells involved anti-TB responses.\[13\]

For the first time, differential expression of three miRNAs including miR-3179, miR-147, and miR-19b-2* in the sputum was found in active pulmonary TB. Interestingly, this study found no significant changes in the sputum levels of tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) between active TB group and controls.\[14\] These results indicated that cytokine dysregulation is mainly occurring in the bloodstream.\[9\] It has been suggested that different cell types may respond differently upon infection with MTB. For example, upregulation of miR-155 in mouse bone marrow-derived macrophages infected with MTB\[15\] and downregulation of the peripheral blood mononuclear cell (PBMC)-derived macrophages with MTB have been reported.\[16\] A signature of miRNAs expression including miR-155 and miR-146a, miR-145, miR-222*, miR-27a, and miR-27b was identified in infected primary human monocyte-derived with MTB H37Rv strain. They were predicted to target important immune-related genes.\[17\] A recent study showed that miR-579 was upregulated in the primary human macrophages infected with MTB, which suppressed the expression of two target mRNAs, sirtuin 1 (SIRT1) and pyruvate dehydrogenase kinase 1 (PDK1). In addition, this study showed that forced suppression of miR-579 restored expression of its targets and attenuated MTB-induced apoptosis in human macrophages.\[18\] Upregulation of miR-708-5p in macrophages after MTB infection could

<table>
<thead>
<tr>
<th>miRNA</th>
<th>Target</th>
<th>Dysregulation</th>
<th>Type of host cell</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Let-7e</td>
<td>Caspase 3</td>
<td>Up</td>
<td>Macrophage</td>
<td>[11]</td>
</tr>
<tr>
<td>miR-19b-2*</td>
<td></td>
<td>Down</td>
<td>Sputum</td>
<td>[14]</td>
</tr>
<tr>
<td>miR-27a</td>
<td></td>
<td>Down</td>
<td>Macrophage</td>
<td>[17]</td>
</tr>
<tr>
<td>miR-27b</td>
<td></td>
<td>Down</td>
<td>Macrophage</td>
<td>[17]</td>
</tr>
<tr>
<td>miR-29a</td>
<td>Caspase 7</td>
<td>Up</td>
<td>Macrophage</td>
<td>[11]</td>
</tr>
<tr>
<td>miR-29a</td>
<td></td>
<td>Up</td>
<td>Serum</td>
<td>[12]</td>
</tr>
<tr>
<td>miR-145</td>
<td>TIRAP</td>
<td>Down</td>
<td>Macrophage</td>
<td>[17]</td>
</tr>
<tr>
<td>miR-146a</td>
<td>TRAF6</td>
<td>Up</td>
<td>Macrophage</td>
<td>[17]</td>
</tr>
<tr>
<td>miR-147</td>
<td></td>
<td>Up</td>
<td>Sputum</td>
<td>[14]</td>
</tr>
<tr>
<td>miR-147b</td>
<td>C11orf87</td>
<td>Up</td>
<td>H32Rv-THP-1 cells</td>
<td>[23]</td>
</tr>
<tr>
<td>miR-155</td>
<td></td>
<td>Up</td>
<td>Macrophage</td>
<td>[17]</td>
</tr>
<tr>
<td>miR-222*</td>
<td></td>
<td>Down</td>
<td>Macrophage</td>
<td>[17]</td>
</tr>
<tr>
<td>miR-325-3p</td>
<td>Rab10</td>
<td>Up</td>
<td>Macrophage</td>
<td>[21]</td>
</tr>
<tr>
<td>miR-378d</td>
<td>SIRT1</td>
<td>Down</td>
<td>Macrophage</td>
<td>[22]</td>
</tr>
<tr>
<td>miR-579</td>
<td>PDK1</td>
<td>Up</td>
<td>Macrophage</td>
<td>[18]</td>
</tr>
<tr>
<td>miR-708-5p</td>
<td></td>
<td>Up</td>
<td>Macrophage</td>
<td>[19]</td>
</tr>
<tr>
<td>miR-3179</td>
<td></td>
<td>Up</td>
<td>Sputum</td>
<td>[14]</td>
</tr>
</tbody>
</table>

miRNAs: MicroRNAs

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**Table 1:** Differential expression of microRNAs in tuberculosis infection and their target MicroRNAs
regulate mycobacterial vitality and inflammatory response to the infection by targeting Toll-like receptor 4 (TLR4).\[19]\n
Behura et al. found that recombinant early secreted antigenic target 6 enhances intracellular survival of mycobacteria by modulating the expression of miR-30a-3p and miR-30a-5p which are the two arms of precursor-miR-30a.\[20]\n
In a recent study, miR-325-3p was upregulated after MTB infection and Mir325-deficient mice showed resistance to MTB. miR-325-3p directly targets ligand of numb-protein X1, an E3 ubiquitin ligase of NIMA-related kinase 6 (NEK6), and that this hampers the proteasomal degradation of NEK6 in macrophages. Accumulation of NEK6 consequently leads to the activation of signal transducer and activator of transcription 3 (STAT3) signaling, thus inhibiting the process of apoptosis and promoting the intracellular survival of MTB.\[21]\n
During TB infection of macrophages, miR-378d was downregulated and decreased TB intracellular survival by targeting Rab10. This process was regulated by the activation of the nuclear factor kappa B subunit and the induction of proinflammatory cytokines, IL-1B, TNF, and IL-6.\[22]\n
According to the results of in vitro study, miR-147b might regulate proliferation and migration of macrophage through targeting chromone 11 open reading frame 87 (C11orf87) via Pi3K/AKT pathway in TB.\[23]\n
### Candidate Gene Studies in Tuberculosis Infection

By direct sequencing, three polymorphisms in the IRGM promoter (IRGM rs4958842, IRGM rs4958843, and IRGM rs4958846) were identified in a case–control study in Chinese Han population. Among them, the IRGM rs4958846 was associated with pulmonary TB. The haplotype ACC (IRGM rs4958842A/rs4958843C/rs4958846C) contributed to the protection against pulmonary TB, while haplotype ACT contributed to increased TB susceptibility. The IRGM promoter haplotypes were shown to regulate expression of IRGM, and the IRGM expression was decreased in patients with pulmonary TB.\[24]\n
Association studies between single nucleotide polymorphisms and TB infection by the candidate gene study are listed in Table 2.

Although the CCLI rs2072069 of the gene has been associated with TB meningitis in a Vietnamese population,\[25]\n
this association was not confirmed in pulmonary TB and TB meningitis in a Chinese population.\[26]\n
In a case–control association study of chemokine genes (CCL2, CXCL9, CXCL10, and CXCL11) in a Thai population, only CCL2 rs1024611 polymorphism was significantly associated with TB susceptibility.\[27]\n
Another chemokine CCL5 rs2107538 polymorphism was associated with an increased risk of pulmonary TB in an Iranian population.\[28]\n
In the Southern Chinese Han population, the MC3R rs6127698 polymorphism, which accompanying an increased expression of MC3R protein, was associated with susceptibility to multifocal TB. Presence of the rs6127698G allele increased the risk of developing multifocal TB.\[29]\n
In a recent study by Zhang et al., a total of Chinese patients with TB and healthy people serving as controls were genotyped for 12 selected polymorphisms rs2071277, rs2071285, rs206016, rs438475, rs2256594, rs429853, rs422951, rs415929, rs915895, rs443198, rs3830041, and rs375244 in the notch receptor 4 (NOTCH4) gene. Their results implied that the NOTCH4 rs2071277G and NOTCH4 rs422951G alleles influence the susceptibility to TB in a Chinese population, suggesting that Notch signaling is involved in the pathogenesis of TB.\[30]\n
Jiao et al. in a recent case–control study investigated the association of four polymorphisms within the neutrophil cytosolic factor 2 (NCF2) gene. They found for the first time that the NCF2 rs10911362G allele provided a protective role against TB risk in the Western Chinese Han population.\[31]\n
A case–control study analyzed four polymorphisms IL17A rs2275913, IL17A rs3748067, IL17F rs763780, and IL17F rs9382084 in TB patients from a Chinese population and found that only IL17A rs763780 was associated with an increased risk of TB.\[32]\n
In contrast, the IL17A rs763780 was not associated with TB in a Croatian population.\[33]\n
In a recent study, IL17A rs8193036 polymorphism in the promoter region of the gene was associated with susceptibility to TB in Chinese Han population. The frequency of minor IL17A rs8193036T allele was significantly lower in the patients with active TB compared to the healthy controls (odds ratio [OR] = 0.81; 95% confidence interval [CI], 0.71–0.93). PBMCs from individuals carrying IL17A rs8193036C genotypes produced significantly lower amount of IL17A upon CD3/28 stimulation as compared to the individuals carrying IL17A rs8193036T genotypes. Functional assay demonstrated that IL17A rs8193036C allele exhibited significantly lower promoter transcription activities.\[34]\n
A meta-analysis of six studies showed that IL17A rs2275913 polymorphism was not associated with TB susceptibility in Asians or Caucasians. The IL17A rs3748067 and IL17F rs763780 polymorphisms were associated with TB susceptibility in Asians, but not in Caucasians.\[35]\n
Li et al. studied the association of seven polymorphisms of IL27 and STAT3 using multiplex ligation detection reaction method in 900 patients with TB and 1534 healthy controls. Their results revealed that IL27 rs17855750 polymorphism plays a protective role on the susceptibility to TB.\[36]\n
Lee et al. investigated four polymorphisms Apal (rs7975232), TaqI (rs731236), BsmI (rs1544410), and FokI (rs2228570) in Vitamin D receptor (VDR) genes and three polymorphisms rs4588, rs7041, and rs4725 in the Vitamin D receptor binding protein (VDBP) in TB patients and healthy controls from a Han Taiwanese population. The VDR rs731236, VDR rs1544410, and VDBP rs7041 polymorphisms were significantly associated with susceptibility to TB.\[37]\n
The VDR rs731236 was associated with TB meningitis in an Indian population, and Vitamin D deficiency was more common among patients with TB meningitis as compared to controls and patients with pulmonary TB.\[38]\n
Meyer and Thye screened the exons of TLR1, TLR2, and TLR4 genes and the adaptor molecule TIRAP in a large sample cohort
of TB cases and controls from Ghana. *TLR1* rs3923647 was significantly associated with TB in this study. The association was further confirmed by an independent replication analysis and an analysis of data provided by a recent TB study of 533 African
Another study investigated the effect of $TLR2$ rs3764880 and $IFNG$ rs62559044 on infertility in Indian women with genital TB and healthy female controls. The $IFNG$ rs62559044 was associated both with susceptibility to TB infection and with infertility, while $TLR2$ rs5743708 polymorphism was not associated with female genital TB.\(^{[42]}\) Similarly, the $TLR2$ rs5743708 and $TLR2$ rs5743704 were not associated with TB meningitis in an Indian population.\(^{[39]}\) $TLR2$ rs3804099 was associated with susceptibility to TB meningitis rather than with susceptibility to pulmonary TB in a case–control study of a Chinese cohort.\(^{[26]}\) Another study investigated possible associations of 16 polymorphisms of six $TLR$ genes and $TIRAP$ with TB susceptibility in a Chinese population. $TLR2$ rs3804100 and $TLR9$ rs5743836 were associated with latent TB, while the $TLR2$ rs5743708, $TLR4$ rs7873784, and $TLR8$ rs3764879 polymorphisms were associated with patent pulmonary TB.\(^{[43]}\)

$TLR9$ rs352142 polymorphism was positively associated with meningeal TB, while variant $TWF2$ rs352143 was associated with pulmonary TB in a Vietnamese cohort.\(^{[44]}\) In a small case–control study in an Iranian population, the $TLR4$ rs4986790 and $TLR4$ rs4986791 were associated with pulmonary TB.\(^{[45]}\) In addition, $TLR10$ rs11096957 polymorphism was found to be associated with an increased risk of TB in a Croatian population.\(^{[33]}\) These data show that $TLR$ polymorphisms are significantly associated with TB susceptibility, underlining the crucial role of $TLRs$ in the immune response to MTB infection.

### Table 3: Meta-analysis of previous studies on association of polymorphisms and tuberculosis infection

<table>
<thead>
<tr>
<th>Polymorphisms</th>
<th>Genes</th>
<th>Alleles</th>
<th>MAF</th>
<th>Functional Consequence</th>
<th>Number of Study</th>
<th>Association</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2228570</td>
<td>VDR</td>
<td>A&gt;C,G,T</td>
<td>A=0.328</td>
<td>Initiator Codon</td>
<td>16</td>
<td>Associated TB risk in an East Asian population with an OR of 1.5</td>
<td>[66]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>32</td>
<td>Associated with TB with an estimated OR of 1.34</td>
<td>[65]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>34</td>
<td>Associated with an increased TB risk, especially in East and Southeast Asian populations</td>
<td>[67]</td>
</tr>
<tr>
<td>rs3331426</td>
<td>18q11.2</td>
<td>G&gt;A</td>
<td>G=0.170</td>
<td>-</td>
<td>5</td>
<td>Not associated with TB</td>
<td>[61]</td>
</tr>
<tr>
<td>rs3748067</td>
<td>IL17A</td>
<td>C&gt;T</td>
<td>T=0.077</td>
<td>3’-UTR</td>
<td>6</td>
<td>Associated with TB susceptibility in Asians, but not in Caucasians</td>
<td>[35]</td>
</tr>
<tr>
<td>rs763780</td>
<td>IL17F</td>
<td>T&gt;C</td>
<td>C=0.093</td>
<td>Missense</td>
<td>6</td>
<td>Associated with TB susceptibility in Asians, but not in Caucasians</td>
<td>[35]</td>
</tr>
<tr>
<td>rs1800629</td>
<td>TNF</td>
<td>G&gt;A</td>
<td>A=0.090</td>
<td>2 KB Upstream</td>
<td>18</td>
<td>Associated with pulmonary TB in all study participants</td>
<td>[62]</td>
</tr>
<tr>
<td>rs361525</td>
<td></td>
<td>G&gt;A</td>
<td>A=0.061</td>
<td>2 KB Upstream</td>
<td>18</td>
<td>Associated with pulmonary TB in all study participants</td>
<td>[62]</td>
</tr>
<tr>
<td>rs735239</td>
<td>CD209</td>
<td>A&gt;G</td>
<td>G=0.217</td>
<td>2 KB Upstream</td>
<td>12</td>
<td>Associated with decreased susceptibility to pulmonary TB in all subjects</td>
<td>[63]</td>
</tr>
<tr>
<td>rs4804803</td>
<td></td>
<td>A&gt;G</td>
<td>G=0.233</td>
<td>2 KB Upstream</td>
<td>12</td>
<td>Associated with increased susceptibility to pulmonary TB in Asians</td>
<td>[63]</td>
</tr>
<tr>
<td>rs9061</td>
<td>SP110</td>
<td>C&gt;T</td>
<td>T=0.131</td>
<td>Missense</td>
<td>13</td>
<td>Associated with the risk of TB</td>
<td>[64]</td>
</tr>
<tr>
<td>rs1155687</td>
<td></td>
<td>G&gt;A</td>
<td>A=0.097</td>
<td>Missense</td>
<td>13</td>
<td>Associated with TB risk in Asian populations</td>
<td>[64]</td>
</tr>
</tbody>
</table>

**TB:** Tuberculosis, **VDR:** Vitamin D receptor, **MAF:** Minor allele frequency, **OR:** Odds ratio

Ghanavi, et al.: Human genetic background and tuberculosis

International Journal of Mycobacteriology ¦ Volume 9 ¦ Issue 3 ¦ July-September 2020
Meta-Analysis of Association Studies of Polymorphisms with Tuberculosis Infection

Results of a recent meta-analysis showed that IL8 rs4073 polymorphism increased TB risk. Subgroup analyses based on race revealed that the IL8-251A/T polymorphism might be associated with the risk of TB in African but not Asian individuals.[59] In a recent meta-analysis of six case–control studies, significant association between TLR2 Arg677Trp polymorphism and TB risk was found neither under allele contrast nor under recessive genetic model.[60] Another meta-analysis of five studies in Chinese populations for rs4331426 polymorphism at 18q11.2 showed no association with TB.[61]

A meta-analysis was performed to evaluate the potential associations of the four TNF polymorphisms, rs1800629, rs1800630, rs1799724, and rs361525, with susceptibility to pulmonary TB, including 18 studies. TNF rs1800629 and TNF rs361525 polymorphisms were associated with pulmonary TB in all-study participants. When stratified by ethnicity, the TNF rs1800629 was associated with pulmonary TB in Asians, while TNF rs361525 was associated with pulmonary TB in African individuals.[62]

Another meta-analysis of 12 case–control studies assessed the associations of three common polymorphisms in the CD209 with pulmonary TB. The CD209 rs735239 polymorphism was associated with decreased susceptibility to pulmonary TB in all subjects. The CD209 rs4804803 polymorphism was associated with increased susceptibility to pulmonary TB in Asians, while the CD209 rs2287886 polymorphism did not show any association with pulmonary TB.[63] A meta-analysis of 13 studies indicated that SP110 rs9061 polymorphism was associated with the increased risk of TB. In addition, the study also revealed that polymorphism SP110 rs11556887 was associated with TB risk in Asian populations.[64]

A meta-analysis of the results of 32 studies showed that the VDR rs228570 polymorphism was associated with TB with an estimated OR of 1.4 [Table 3]. Stratification by ethnicity revealed that the this polymorphism was associated with TB exclusively in an Asian, but not in Caucasian and African populations.[65] Another meta-analysis of 16 studies assessed the associations of the VDR rs228570, rs731236, rs1544410, and rs7975232 polymorphisms with susceptibility to pulmonary TB. The VDR rs228570 polymorphism was not associated with pulmonary TB in all subjects. However, when stratified by ethnicity, the VDR rs228570 polymorphism was associated with pulmonary TB risk in an East Asian population with an OR of 1.5. In contrast, the VDR rs731236, VDR rs1544410, and rs7975232 polymorphisms were not associated with TB in all study participants or in distinct ethnicities.[66] This positive association for VDR rs228570 in East and Southeast Asian populations was confirmed by another meta-analysis of 34 studies.[67] VDR gene polymorphisms (Cdx-2 and 3′UTR rs731236 variants) might modulate the levels of chemokines, which are regulated by Vitamin D, again suggesting that VDR gene polymorphisms may influence the inflammatory response during active infection.[68] Cathelicidin (LL-37), a host defense peptide, can alter the response of macrophages by regulating expression of proinflammatory and anti-inflammatory cytokines during mycobacterial infection.[69] Variants of VDR and VDBP are associated with LL-37 levels, indicating that VDR and VDBP polymorphisms may be involved in the immune response during mycobacterial infection by regulating LL-37 levels.[70]

Genome-Wide Association Studies in Tuberculosis Infection

Drug-induced liver injury is a well-recognized adverse event of anti-TB drugs possibly associated with genetics. In GWA studies and independent replication study, RIPOR2 rs10946737 was associated with anti-TB drug-induced liver toxicity in Ethiopian patients.[71] In a GWA study by Curtis et al., association between two intronic polymorphisms of ASAP1 gene, rs4733781 (P = 2.6 × 10⁻¹⁷) and rs10956514 (P = 1.0 × 10⁻⁶⁸), with pulmonary TB were found in Russian population. ASAP1 expression was reduced in DCs after MTB infection, and rs10956514 was associated with the level of reduction of ASAP1 expression. The ASAP1-depleted DCs showed impaired matrix degradation and migration. Therefore, genetically determined excessive reduction of ASAP1 expression in MTB-infected DCs may lead to their impaired migration, suggesting a potential mechanism of predisposition to TB.[72] However, a replication study in Western Chinese and Tibetan populations did not confirmed the association of ASAP1 rs10956514 polymorphism with susceptibility to TB. These results highlight the importance of validation of association studies in different ethnicities.[73]

In another GWA study and independent replication study in Moroccan population, two intragenic polymorphism (rs358793 and rs17590261) and two intragene polymorphisms, FOXP1 rs6786408 and AGMO rs916943, were associated with pulmonary TB. Both FOXPI and AGMO are involved in the function of macrophages, which are the site of latency and reactivation of MTB.[74] It is hypothesized that HIV-positive individuals who do not develop TB, despite living in areas where it is hyperendemic, provide a model of natural resistance. In a GWA study of TB resistance using HIV-positive Ugandan and Tanzanian population, an intronic common polymorphism UBLCP1 rs4921437 was significantly associated with TB. This variant lies within a genomic region that includes IL-12B and is embedded in an H3K27Ac histone mark.[75]

In a GWA study of early TB progression of active TB cases and their household contacts in Peru, the study revealed that TB progression has a strong genetic basis. This study identified a novel association between early TB progression and rs73226617 polymorphism located in a putative enhancer region on chromosome 3q23.[76] To identify genetic variants associated with susceptibility or resistance to MTB infection, Bhattacharyya et al. performed an exome-wide association study among TB patients and their clinically asymptomatic
household contacts. The strongest association was identified for a synonymous polymorphism SIGLEC15 rs61104666. They also found association of noncoding variants in the 3'UTR region of HLA-DRA gene. Two polymorphisms rs13209234 and rs3177928 were associated with the protection from TB.[77]

**CONCLUSION**

Host genetic factors may play a crucial role in the modulation of immune responses to MTB infection and in clinical progression of TB. We explained that genetic polymorphisms of the several genes including TLR, IGRM, VDR, ASAP1, AGMO, FOXP1, and UBLCP1 have some effects on the TB phenotype and the outcome of disease treatment. The associations of most of identified host genetic factors should be confirmed in other populations. Therefore, functional studies of the impact of genetic actors are required to verify the relevance and functional implications of human genetic variation in TB.

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**Conflicts of interest**

There are no conflicts of interest.

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