Review

Discovery Medicine 2026; 38(214): 3419–3429
https://doi.org/10.24976/Discov.Med.202638214.263

DNA Polymorphisms of Immune Genes in Susceptibility to Tuberculosis

Minju Jung[1,2], Sohyeong Kim[1,2], Soyun Kim[1,2], Jieun Lim[1,2], Choseung Kim[2,3], Heechul Park[4,*], Sunghyun Kim[1,2,3,*]

[1]Department of Clinical Laboratory Science, College of Health Sciences, Catholic University of Pusan, 46252 Busan, Republic of Korea
[2]Next-Generation Industrial Field-Based Specialist Program for Molecular Diagnostics, Brain Busan 21 Plus Project, Graduate School, Catholic University of Pusan, 46252 Busan, Republic of Korea
[3]Department of Forensic Science, Graduate School, Catholic University of Pusan, 46252 Busan, Republic of Korea
[4]Department of Clinical Laboratory Science, College of Health Sciences, Hyejeon University, 32244 Hongseong, Chungcheongnam-do, Republic of Korea
*Correspondence: phc2626@hj.ac.kr (Heechul Park); shkim0423@cup.ac.kr (Sunghyun Kim)
Submitted: 11 June 2026 Revised: 10 August 2026 Accepted: 21 August 2026 Published: 25 November 2026

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (MTB), is a major health issue worldwide, contributing to significant morbidity and mortality. Despite widespread exposure to pathogens, only a few infected individuals suffer from active TB (ATB), indicating that the genetic factors of the host play an important role in determining susceptibility to TB. Recent studies suggest that genetic polymorphisms in immune-associated receptors and signaling molecules can influence the immune response of the host. Variations in genes involved in pathogen recognition and immune activation, such as toll-like receptors (TLRs), interferon signaling pathways, interleukins (ILs) and human leukocyte antigen (HLA) molecules, are associated with variations in susceptibility to MTB infection and disease. Several genetic association studies have also identified single nucleotide polymorphisms (SNPs) that can contribute to the variability in the risk of TB among diverse population groups. Therefore, to investigate the association between SNPs in immune-associated genes and susceptibility to TB, we reviewed and synthesized previous findings. In this review, we summarize recent findings on genetic polymorphisms associated with TB susceptibility and discuss their potential role in host immune responses. Understanding how these genetic variations influence the immune response to TB onset may elucidate the mechanisms of TB onset. This knowledge might also be valuable in the development of more optimized diagnostic markers and effective strategies for TB prevention and treatment.

Keywords: tuberculosis; *Mycobacterium tuberculosis*; genetic polymorphism; single nucleotide polymorphism

Introduction

Tuberculosis (TB), one of the leading causes of infectious disease-related morbidity and mortality worldwide, is primarily caused by *Mycobacterium tuberculosis* (MTB) and remains a major global health issue [1,2]. Although a large proportion of the global population is exposed to MTB, only a small number of those infected suffer from active TB (ATB); most remain latent. In addition to environmental and microbial determinants, host-related factors significantly influence susceptibility to TB [2].

Recent epidemiological data have suggested that host gene mutations are responsible for the large differences in immune responses to MTB [3]. In particular, genetic polymorphisms in immune-associated genes are associated with alterations in susceptibility to TB. Variants in cytokine signaling pathways, such as interleukin-6 (*IL-6*), modulate the inflammatory response and influence disease risk [4,5,6]. In addition, polymorphisms in genes involved in innate and adaptive immunity, such as toll-like receptors (*TLRs*) and human leukocyte antigen (*HLA*) genes, play key roles in pathogen recognition and antigen presentation, and their polymorphisms have been extensively studied in relation to TB susceptibility [7,8].

With respect to the methodology of these genetic findings, recent advances in genomic technologies, especially genome-wide association studies (GWAS), have facilitated the identification of novel susceptible loci in diverse populations. Several studies have linked loci such as 18q11.2 with specific genetic variants, including ArfGAP with SH3 domain, ankyrin repeat and PH domain 1 (*ASAP1*) and CD53 molecule (*CD53*), with the risk of TB [9,10,11]. These findings accurately demonstrate the susceptibility of a complex and multidisciplinary host to TB.

However, a significant challenge highlighted in recent literature is that the association between genetic polymorphisms and TB susceptibility varies among population and ethnic groups. Studies conducted in various geographic regions, including East Asia, Central Asia, and Europe, have shown results for similar genetic mutations [10,11,12].

Copyright: © 2026 The Author(s). Published by Discovery Medicine. This is an open access article under the CC BY 4.0 license.
Note: *Discovery Medicine* stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

For example, polymorphisms in *HLA* genes and *TLR* pathways have shown population-specific effects. This probably seems to reflect differences in genetic background, environmental exposure, and circulating MTB strains. This highlights the importance of population diversity in TB genetic studies.

In this review, we provide a comprehensive overview of host genetic polymorphisms associated with TB susceptibility, with particular emphasis on immune-associated genes and receptor-mediated pathways. By integrating the findings of genetic associations across diverse populations, we can elucidate the role of host genes in the development of TB. Furthermore, we explore the potential implications for disease prevention, risk prediction, and personalized treatment strategies. In particular, this review highlights the significance of population-specific genetic variation in shaping susceptibility to TB. Recent advances in human genomics and multiple genomics techniques have led to a better understanding of existing immune-associated genes for TB susceptibility [13]. Currently, our understanding of the complex biological pathways that support host defense is considerably clearer [14]. The complex interactions between host genetic polymorphisms and immune responses to MTB infection are summarized in Fig. 1.

Literature Search Strategy

Related studies of host genetic polymorphisms associated with TB susceptibility were identified through literature searches of PubMed, Web of Science, and Scopus. Papers published from January 2016 to March 2026 were selected. The search strategy included a combination of the following keywords: "tuberculosis", "*Mycobacterium tuberculosis*", "host genetics", "genetic polymorphism", "single nucleotide polymorphism (SNP)", "genome-wide association study (GWAS)", "cytokine", "toll-like receptor (TLR)", "human leukocyte antigen (HLA)", and "susceptibility".

Studies examining the association between host genetic variation and susceptibility to TB in human populations, including the original research papers, GWAS, meta-analyses, and systematic reviews of the literature, were included. Studies focusing solely on anti-TB drug response or drug toxicity, *in vitro* studies, conference abstracts, case reports, and studies lacking sufficient genetic association data were excluded. The representative studies were selected based on their relevance to the review topic, clarity of methodology, sample size, and reproducibility of the research findings. Information on the investigated genes, SNPs, study populations, odds ratios (OR), and major outcomes were extracted and compiled. Because this manuscript is a descriptive review rather than a systematic literature review or meta-analysis, no formal quality assessment of individual studies was conducted. Instead, peer-reviewed studies with rigorous methodologies and results that had been reported repeatedly or consistently across diverse population groups were prioritized.

Genetic Susceptibility to Tuberculosis

Cytokine and Immune Signaling Genes

By regulating the balance between protective immunity and pathological inflammation, cytokines play a central role in the host immune response to MTB infection. To comprehensively understand these dynamics, the potential contribution of genetic polymorphisms of cytokine-associated genes in TB susceptibility has been extensively studied.

Focusing on specific molecular targets, *IL-6* has been used as a major mediator of inflammation during MTB infection. A recent Mendelian randomization study suggests that *IL-6* signaling changes may be associated with the risk of TB, which might play a role in disease susceptibility [4]. In addition to *IL-6*, mutations in other cytokine-associated genes seem to modulate the immune responses and influence infection outcomes.

In addition to cytokine-producing genes, genetic variation in cytokine receptor genes may alter downstream immune signals, thus affecting TB susceptibility. The interferon gamma (*IFN-γ*)/interferon gamma receptor 1 (*IFNGR1*) pathway is essential for macrophage activation and endocytosis of MTB, and functional variation of IFNGR1 is associated with decreased anti-mycobacterial immunity and increased susceptibility to TB in several populations [3]. Similarly, interleukin 6 receptor (*IL6R*) variation affects *IL-6*-mediated inflammatory signaling and might affect the balance between protective immune activation and excessive inflammation during MTB infection [4,5]. In addition, the polymorphism of interleukin 10 receptor subunit alpha (*IL10RA*) mediating the immunomodulatory effect of *IL-10* may contribute to differences in inflammatory regulation and host response to TB.

Circulating inflammatory cytokines are associated with TB risk, thus supporting the notion that genetic mutations affecting cytokine production or signaling pathways may contribute to individual differences in disease susceptibility [5]. The data suggest that cytokine-mediated immune responses are genetically regulated and play an important role in determining host defense against MTB infection.

Crucially, although extended evidence indicates that polymorphisms in cytokines and immune signaling genes are important determinants of TB susceptibility, the reported associations do not always coincide throughout the study. These differences may be attributed to variations in study populations, environmental factors, and methodological approaches. Therefore, more large-scale and multi-ethnic studies are needed to clarify the functional significance of these genetic variants and their contribution to the development of TB.

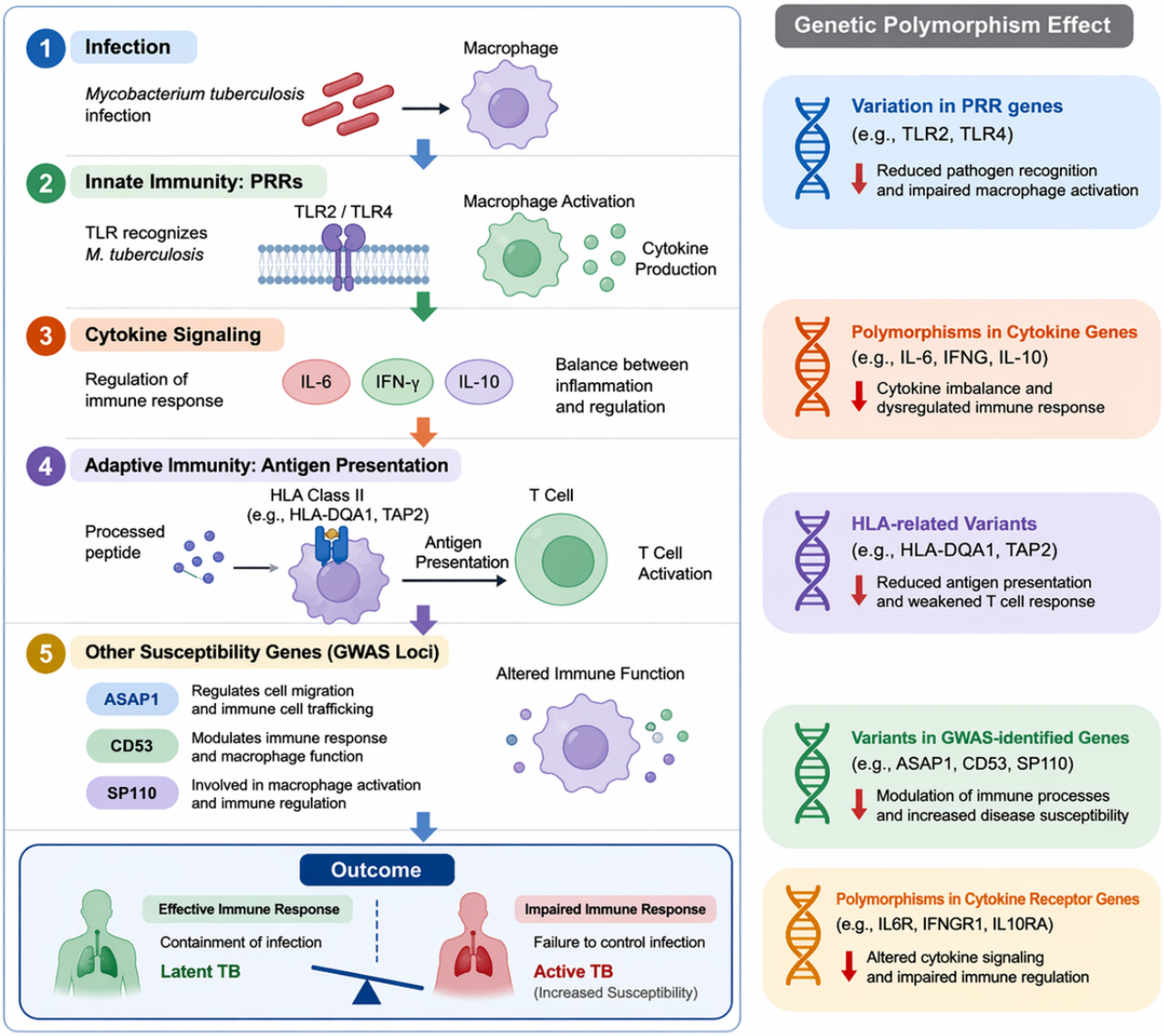


Fig. 1. Mechanism of host genetic susceptibility to tuberculosis. Polymorphisms in immune-related genes induced by genetic mutations can directly affect multiple stages of the immune response to *Mycobacterium tuberculosis*. These changes interfere with key pathways, such as pathogen recognition, cytokine signaling, antigen presentation, and immune cell function, ultimately altering latent infection and progression to active tuberculosis (Microsoft PowerPoint, Microsoft 365, Microsoft Corporation, Redmond, WA, USA; BioRender.com, Toronto, Canada).

Interestingly, the effects of *IL-6*-related variants have not been completely consistent throughout the study. This variability may differ in the balance between protective inflammation and immunopathology, as excessive cytokine responses can cause tissue damage, even if they promote antibacterial immunity.

Pattern Recognition Receptors and Innate Immunity

Pattern recognition receptors (PRRs) are key to the innate immune system and significantly contribute to the early detection of MTB infection. These receptors initiate downstream signaling pathways that capture pathogen-associated molecular patterns and induce inflammatory and antimicrobial defenses. Among the various PRRs, TLRs have been extensively studied in terms of TB susceptibility.

Genetic polymorphisms of *TLR* genes at the molecular level might alter how efficiently the host perceives pathogens and immune activation. Changes in *TLR2* and associated signaling pathways are associated with an increased risk of pulmonary TB in diverse populations [7]. This polymorphism may alter cytokine output, macrophage activation, and the overall ability of the host to mount an effective immune response to MTB infection.

In addition to TLRs, other components of the innate immune system, including macrophage-associated path-

ways, are involved in the development of TB. An integrative genomic study reveals that genetic mutations in the host may influence macrophage responses to intracellular mycobacteria, thereby supporting the significance of innate immunity in determining disease outcomes [15].

In other words, the association between *PRR*-related genetic variants and TB susceptibility does not always coincide between studies. This discrepancy may result from differences in genetic background, environmental exposure, and pathogen diversity. Therefore, further studies incorporating genetic, functional, and population-level approaches are needed to elucidate the role played by innate immune receptors in TB susceptibility.

A meta-analysis of 37 recent case-control studies supports this. Of the many *TLR2* polymorphisms tested, only rs5743708 was consistently associated with a high risk of TB. Most of the other variants showed no significant results. Therefore, the genetic effects of *TLR2* vary widely among populations, indicating the presence of heterogeneity [16].

Inconsistent *TLR* findings may partly reflect regional differences in MTB strains. Changes in mycobacterial surface components may alter receptor–ligand interactions and downstream immune activation.

HLA and Antigen Presentation

HLA molecules play a central role in adaptive immunity by mediating antigen presentation to T cells, thereby initiating and regulating the immune responses to MTB infection. Genetic polymorphisms of *HLA* genes reflecting important functions in immune recognition have been extensively investigated for their association with susceptibility to TB.

A study has reported a significant association between specific *HLA* alleles and the risk of TB. Notably, variations in class II *HLA* genes, such as *HLA-DQA1*, are associated with differences in disease susceptibility and developmental age in some populations [17]. These patterns suggest that genetic variation in antigen presentation pathways might influence T cell activation and the efficiency of subsequent immune responses to MTB.

In addition to classical *HLA* genes, the polymorphism of genes involved in antigenic processing and presentation, such as transporter 2, ATP-binding cassette subfamily B member (*TAP2*), is associated with TB susceptibility [18]. These genes are essential for the correct loading of antigenic peptides into *HLA* molecules. Therefore, the repertoire of antigenic peptides presented to T cells may be altered if the antigens are diverse, thus causing changes in host defense.

In particular, the clinical association between *HLA* gene polymorphisms and TB susceptibility appears to be highly population dependent. Studies conducted in diverse ethnic groups have reported diverse results, with certain *HLA* alleles providing risk or protection in certain population groups but not in others [8]. This variability may be due to genetic background, environmental factors, and the diversity of MTB strains circulating in different regions.

Overall, existing literature highlights the importance of *HLA*-mediated antigen presentation in host immune response to TB. However, further studies are needed to elucidate the functional implications of *HLA* polymorphisms and their interaction with other genetic and environmental factors in determining disease susceptibility.

HLA-associated variants may have a more direct effect on adaptive immunity than other susceptibility genes. They determine which mycobacterial antigens are presented to T cells, which might explain why *HLA* associations continue to appear in genetically different populations even when certain alleles differ.

GWAS-Identified Susceptibility Loci

GWAS has significantly elucidated the genetic structures underlying susceptibility to TB by enabling the identification of novel risk loci in an unbiased manner. In contrast with conventional candidate gene studies, this genomic approach provides a comprehensive strategy for detecting genetic mutations associated with disease susceptibility across the entire genome.

Epidemiologically, several large-scale screening analyses have identified distinct susceptibility loci in different populations. One of the best-known loci is located on chromosome 18q11.2, and a SNP rs4331426 is associated with increased susceptibility to TB in certain populations [19]. Moreover, mutations in the *ASAP1* gene are consistently associated with TB susceptibility, suggesting that it can potentially contribute to host immune cell migration and function [20,21]. Recently, pathogen lineage-based GWAS has revealed additional loci, including *CD53*, which could affect host–pathogen interactions and disease progression [11]. Integrative host–pathogen analysis across genomes revealed specific genetic interaction points between humans and MTB genome. TB susceptibility is shaped by variation in host and pathogen genomes [22]. These findings highlight the significance of incorporating host and pathogen genetic factors to elucidate TB outbreaks.

Genomic mapping analysis performed in diverse ethnic groups, including Han Chinese, Tibetan, and multiethnic groups, revealed both shared and population-specific genetic associations [9,10,23]. These population data highlight the complex and multigenic nature of TB susceptibility and suggest that several genetic variants with moderate effects collectively contribute to disease risk.

Despite these notable developments, GWAS results for TB have not always been reproduced cleanly throughout the study. These observed discrepancies can be attributed to differences in sample size, population structure, environmental exposure, and genetic heterogeneity. Therefore, further large-scale studies combining GWAS with functional genomics are needed to validate the identified loci and fully elucidate their biological significance.

To synthesize this development, GWAS provides valuable insights into the genetic basis of TB susceptibility by identifying novel locations and pathways involved in host defense. These findings contribute to a more comprehensive understanding of the molecular mechanisms underlying TB and might ultimately aid in the development of improved diagnostic and treatment strategies.

Interestingly, loci identified by multiple GWASs are not directly linked to classical immune pathways. This finding suggests that TB susceptibility may involve cell migration, intracellular trafficking, and tissue-specific immune regulation, a mechanism that has historically received less attention than cytokine-mediated responses.

Other Host Genetic Factors

Various host genetic factors are associated with susceptibility to TB, as are cytokine-associated pathways, pattern recognition receptors, and *HLA*-associated pathways. These distinct genes are involved in various biological processes, including immune regulation, intracellular pathogen control, and host–pathogen interactions.

Focusing on these alternative loci, SP110 nuclear body protein (*SP110*) has been identified as a potential susceptible gene for TB. Polymorphisms in *SP110*, which are deeply involved in macrophage function and immune regulation, are associated with changes in the risk of TB in certain populations [21]. Variants in genes such as *ASAP1* have been identified primarily through GWAS but are thought to influence cell migration and immune response, thus further supporting the role of non-traditional immune pathways in TB susceptibility [20].

In addition to individual gene associations, integrative genomic approaches have provided additional insight into the complex mechanisms by which hosts are susceptible to TB. A study combining gene expression profiling and genomic data has demonstrated that genetic variation can influence transcriptional responses to MTB infection, particularly in immune cells such as macrophages [24]. Therefore, the genetic factors of the host may be influenced by structural gene variation and gene expression regulation.

In addition, genetic risk prediction models incorporate multiple variants to better identify those at high risk of developing TB [23]. This approach highlights the multidisciplinary nature of TB susceptibility and the potential clinical utility of genetic information.

Despite developments, the exact contribution of many host genetic factors has not been comprehensively elucidated. Study design differences, limited sample sizes, and population-specific effects continue to pose challenges in identifying consistent genetic determinants. Therefore, further large-scale and integrated studies are needed to clarify the role of these additional genetic factors in TB susceptibility.

In summary, existing literature has shown that TB susceptibility is strongly influenced by various host genetic factors beyond the classical immune pathways, which directly reflects the complex and multi-factor nature of host–pathogen interactions.

This functional classification highlights the different biological pathways by which host genetic polymorphisms successfully influence susceptibility to TB and provides a framework for interpreting subsequent quantitative and population-based analyses (Table 1).

To contextualize these effects, Table 2 (Ref. [7,8,17,18,20,21]) presents a summary of the representative genetic variants and polymorphisms associated with TB susceptibility in various population groups.

Furthermore, the overall effect sizes of these genetic variants are expressed in odds ratios and summarized comprehensively in Table 3 (Ref. [4,7,11,17,18,20,21]).

Most genetic variants showed moderate effects, and odds ratios generally ranged from 0.7 to 1.7 (Table 3). Reflecting these quantitative dynamics, these findings support the polygenic nature of TB susceptibility, where multiple variants contribute moderate effects rather than a single major determinant.

Population-Specific Differences in Genetic Susceptibility to Tuberculosis

Genetic susceptibility to TB varies among populations, largely reflecting differences in genetic background and environmental exposure. Studies conducted in various geographic regions and ethnic groups have reported both consistent and inconsistent associations, suggesting that the host's TB susceptibility is significantly influenced by population-specific factors.

When evaluating genomic screening data, GWAS performed in diverse populations including Han Chinese, Tibetan, and multiethnic groups identified both covalent and intrinsic susceptibility loci [9,10,19]. A study reported genetic variants in *ASAP1* [20]. However, their association strength and reproducibility differ among groups. Likewise, the associations identified in one ethnic group do not always replicate in another, further highlighting the complexity of genetic susceptibility to TB.

Focusing on immunogenetic pathways, variations in immune-related genes, including *HLA* and *TLR* pathways, also exhibit population-dependent effects. Studies in Asian populations have frequently reported significant associations between *HLA* polymorphisms and TB susceptibility. Results of studies in other population groups, such as European cohorts, were more diverse [7,17]. TLR-associated polymorphisms have shown discriminatory effects among population groups. This could potentially reflect differences in innate immune responses.

Several distinct factors can contribute to these population-specific differences. Changes in genetic background and allele frequency can have considerable impact on the detection and intensity of associations. Differences

Table 1. Functional classification of host genetic factors associated with TB susceptibility.

Functional category	Genes	Biological role	Impact of polymorphism
Cytokine signaling	*IL6*, *IFNG*, *IL10*	Regulation of inflammatory response	Dysregulated cytokine production and immune imbalance
Cytokine receptor genes	*IL6R*, *IFNGR1*, *IL10RA*	Cytokine signal transduction	Altered cytokine signaling and impaired immune response
Pattern recognition receptors (PRRs)	*TLR2*, *TLR4*	Pathogen recognition and innate immune activation	Reduced pathogen recognition and macrophage activation
Antigen presentation	*HLA-DQA1*, *TAP2*	Antigen processing and presentation to T cells	Impaired antigen presentation and reduced T cell activation
GWAS-identified loci	*ASAP1*, *CD53*	Immune cell migration and regulation	Altered immune cell function and increased susceptibility
Other host factors	*SP110*	Host immune regulation and cellular defense mechanisms	Modulation of host susceptibility to TB

TB, tuberculosis; IL, interleukin; IFNG, interferon gamma; IFNGR1, interferon gamma receptor 1; TLR, toll-like receptor; HLA, human leukocyte antigen; DQA1, major histocompatibility complex, class II, DQ alpha 1; TAP2, transporter 2, ATP binding cassette subfamily B member; ASAP1, ArfGAP with SH3 domain, ankyrin repeat and PH domain 1; CD53, CD53 molecule; SP110, SP110 nuclear body protein; GWAS, genome-wide association studies; IL6R, interleukin 6 receptor; IL10RA, interleukin 10 receptor subunit alpha; TLR2, toll-like receptor 2; TLR4, toll-like receptor 4.

Table 2. Representative host genetic variants associated with TB susceptibility in diverse population groups.

Gene	Population	Representative variant (SNP/Allele)	Reference
ASAP1	China	rs4733781	[20]
SP110	Mongolia	rs722555, rs1135791	[21]
TAP2	Tibet	rs3819721	[18]
TLR2	Moldavia	rs5743708	[7]
HLA	China/ Tibet	*HLA-DQA1* allele variants	[8,17]

SNP, single nucleotide polymorphism; TAP2, Transporter 2, ATP binding cassette subfamily B member.

in environmental factors, e.g., MTB exposure, nutritional status, and co-infections, can modulate the impact of genetic mutations on disease susceptibility. Furthermore, the diversity of circulating MTB strains in different regions can interact with host genetic factors, resulting in changes in disease outcomes [12]. This result highlights the importance of considering population diversity in TB genetic studies. Understanding these population-specific genetic susceptibilities can improve risk prediction models and support the development of targeted prevention and treatment strategies tailored to specific populations.

Existing literature has shown that TB susceptibility is shaped by complex interactions among the host's genetic variation, environmental factors, and pathogen diversity, highlighting the need for an integrated and multi-collective approach in future studies.

The distribution of the population hierarchy of TB-associated genetic variants is shown in Table 4 (Ref. [3,4,5,7,8,9,10,12,17,18,19,20,21,23,25,26,27]).

As shown in Table 4, studies conducted in Asian populations, particularly China and Tibet, mainly focused on *HLA* and GWAS, whereas studies in European populations focused on innate immune genes such as TLRs. Whereas multiethnic studies have investigated various genetic mechanisms, including cytokine-related pathways, GWAS-identified loci, and host-pathogen interactions.

Clinical Implications

The host's genetic susceptibility to TB has significant implications for both clinical practice and public health. Discovering genetic polymorphisms associated with disease risk offers opportunities to improve risk stratification, enable earlier diagnosis, and support better personalized approaches to TB management. These empirical findings suggest potential application in precision medicine, and genetic profiling can help identify individuals at high risk of disease progression.

One of the promising applications is building genetic risk prediction models. Combining GWAS with multiple susceptible loci identified by candidate genetic analysis will allow better identification of individuals at increased risk of developing ATB. In particular, this approach can be useful in high-burden environments, and targeted screening and prevention interventions can significantly reduce disease incidence [20]. Integration of population-specific variants and environmental factors can further improve the accuracy and applicability of the models.

In terms of molecular medicine, genetic variation in the immune pathway may serve as a biomarker for disease progression and treatment response. Polymorphisms that affect cytokine signaling, antigen presentation, or innate immune responses may impair affect the host's ability to regulate MTB, thereby directly influencing clinical outcomes. This suggests that genetic profiling of hosts may contribute to more precise and individualized treat-

Table 3. Summary of odds ratios for TB-associated genes.

Gene/Pathway	SNP	Risk allele	Population (s)	OR (95% CI)	Direction of association	Reference
HLA (*HLA-DQA1*)	rs9272785	T allele	Hong Kong Chinese	1.3 (1.05–1.68)	↑ Increased susceptibility	[17]
TLR (*TLR2*)	rs3804099	C allele	Moldavian	0.7 (0.53–0.91)	↓ Decreased susceptibility	[7]
IL-6 signaling (*IL6/IL6R*)	rs2228145	C allele	Multi-ethnic	0.94 (0.93–0.96)	↓ Decreased susceptibility	[4]
ASAP1	rs4733781	C allele	Xinjiang Muslim, Mongolian	1.2 (1.00–1.54)	↑ Increased susceptibility	[20,21]
SP110	rs722555	T allele	Mongolian	1.7 (1.16–2.60)	↑ Increased susceptibility	[21]
TAP2	rs13501	G allele	Tibetan	1.0 (0.80–1.35)	No statistically significant association	[18]
CD53	rs1418425	A allele	Multi-ethnic	1.6 (1.35–1.93)	↑ Increased susceptibility	[11]

OR, odds ratios; ↑ indicates a positive association with tuberculosis (TB) susceptibility (OR >1); ↓ indicates a negative association with tuberculosis (TB) susceptibility (OR <1).

Table 4. Population-stratified distribution of TB-associated genes.

Population	Gene category	Reference
Chinese (Han & general Chinese)	*HLA*-related	[8,17]
	GWAS loci (*ASAP1*, rs4331426)	[19,20]
Tibetan	*HLA*-related	[17]
	Antigen processing (*TAP2*)	[18]
Korean	Risk prediction genes	[23]
	HLA-related (*HLA-DRA*)	[25]
	Other susceptibility loci (*CLCN6*, *DOK7*)	[25]
	Transcription factor (*FOXO3*)	[26]
	Immune signaling (*CD247*)	[27]
Moldavian	*TLR* (innate immunity)	[7]
Taiwanese	GWAS loci (rs4331426)	[19]
Mongolian	*ASAP1/SP110*	[21]
Multi-ethnic	Cytokine-related (*IL-6*)	[3,4,5]
	GWAS loci	[9,10]
	Host–pathogen interaction	[12]

ment strategies. These biomarkers might also be useful for monitoring treatment response and predicting disease progression in clinical settings.

Furthermore, understanding interactions between host and pathogen at the genetic level could provide insights into the development of new therapies. Identifying key pathways in TB susceptibility, especially those associated with immunomodulatory and cell-mediated immunity, might provide host-led therapy that aims to enhance protective immune responses while minimizing immunopathology.

In particular, the population-specific nature of genetic susceptibility to TB highlights the need for customized approaches in clinical applications. Genetic risk models and biomarkers developed in one population may not be applied directly to another, thus highlighting the importance of incorporating population diversity into translational research and clinical implementation.

Despite these promising perspectives, some challenges persist. The clinical utility of many genetic markers remains limited owing to inconsistent findings, moderate effect size, large scale, and lack of validation in diverse populations. Therefore, further studies are needed to establish robust and reproducible genetic markers and translate these results into practical clinical tools.

Collectively, incorporating host genetic information into TB control strategies has practical potential in advancing precision medicine, improving disease prevention, and optimizing treatment.

Table 5 presents a summary of the reported host gene mutations associated with TB susceptibility identified in previous studies. These mutations include SNPs, *HLA* alleles, and other polymorphisms that may affect immune path-

Table 5. Host genetic variation associated with TB susceptibility and its functional implications.

Gene	SNP	Population	Reported effect (OR)	Functional implication	Impact on TB susceptibility
IL6/IL6R	rs2228145	Multi-ethnic	0.9	Altered cytokine signaling	Dysregulated inflammation
TLR2	rs3804099	Moldavian/others	0.7	Impaired pathogen recognition	Reduced innate immunity
HLA-DQA1	rs9272785	Chinese/Tibetan	1.3	Altered antigen presentation	Reduced T cell activation
ASAP1	rs4733781	Chinese/Mongolian	1.2	Impaired dendritic cell migration	Delayed immune response
CD53	rs1418425	Multi-ethnic	1.6	Immune cell signaling	Altered host–pathogen interaction
SP110	rs722555	Mongolian	1.7	Macrophage regulation	Impaired intracellular control
TAP2	rs13501	Tibetan	1.0	Antigen processing	Reduced antigen presentation

ways related to pathogen recognition, cytokine signaling, and antigen presentation, thus affecting host defense against MTB infection.

Discussion

This review summarizes reported host gene mutations associated with susceptibility to TB, focusing on genes involved in susceptibility identified by innate immunity recognition, cytokine signaling, antigen presentation, and GWAS. Studies have shown that TB susceptibility is affected by multiple genetic factors, not by a single dominant variant. Although several variants showed significant associations with TB risk, their effects vary considerably among population groups, suggesting that host genetic background and environmental factors contribute to differences in disease susceptibility.

Congenital immune-related variants play an important role in susceptibility to TB, but their effects are not consistently reproduced across all population groups. Despite the association of *TLR2* rs5743708 with increased susceptibility to tuberculosis in multiple populations, the contribution of other *PRR*-related variants remains controversial. These differences could be explained by genetic background, environmental exposure, MTB lineage, and differences in sample size among studies.

Cytokine-related genetic variants showed a biologically plausible association with susceptibility to tuberculosis, with variants involved in the *IL-12*/*IFN-γ* axis being particularly prominent. However, the magnitude and direction of these associations differ among groups. Recent studies focusing on the *IL6R* variant suggest that altered cytokine signaling might influence the risk of TB; however, further validation is needed to determine whether these variants are causative factors or markers reflecting broader immune regulation.

GWAS research elucidated TB susceptibility beyond existing immune pathways by identifying gene loci such as rs4331426, *ASAP1*, and CD53. In contrast with candidate gene studies, GWAS provides an unbiased approach, but many of the identified gene loci are non-coding regions, thus necessitating functional validation. Therefore, genetic associations alone are insufficient to explain biological mechanisms and integration with transcriptome and functional genomic data is necessary.

This review's strength lies in its integration of different genetic findings into functional categories, thereby providing a comprehensive perspective on the contributions of different biological pathways to TB susceptibility. By comparing candidate gene studies with GWAS-based findings, this review highlights conserved genetic mechanisms and population-specific differences. Future studies should enhance the biological interpretation and clinical relevance of TB-related gene mutations by incorporating an integrated approach that combines greater multiethnic groups with genomics, transcriptomics, epigenomics, and functional analyses.

Limitations and Future Directions

In this review, we identified genetic variations associated with TB susceptibility in several functional categories, including innate immunity recognition, cytokine signaling, antigen presentation, and GWAS-derived susceptibility loci. However, interpreting these associations remains challenging owing to differences in study populations, genetic backgrounds, and experimental approaches. Despite significant progress in identifying host genetic polymorphisms associated with susceptibility to TB, some limitations persist. The lack of consistent replication of genetic associations between studies and population groups is a major challenge. Many of the reported associations have limited reliability and clinical applicability owing to their small effect sizes and inconsistent replication in independent cohorts. Furthermore, many studies have been conducted with specific populations, especially Asian cohorts, which might limit the generalizability of their results.

The heterogeneity of the study design, including differences in sample size, case definition, and analysis methods presents another limitation of the review. In many studies, small cohorts reduce statistical power and increase the probability of false-positive or population-specific out-

comes. Population stratification and unexplained confounding factors can further complicate the interpretation of genetic association outcomes. Collectively, these factors lead to significant variability throughout the study and complicate direct comparisons.

Functional interpretation of reported variants also remains a major challenge. Although several variants, such as *TLR2*, *IFNGR1*, *IL6R*, and *HLA*-associated polymorphisms, are associated with TB susceptibility, the biological mechanisms underlying these associations have not been comprehensively elucidated. Furthermore, the effectiveness of individual variants might vary depending on population background, MTB lineage, and environmental exposure.

The complex and multi-factor nature of TB susceptibility is also an important challenge. Because environmental factors, socioeconomic conditions, co-infections, pathogen diversity, all play an important role, genetic variation in the host alone cannot comprehensively explain disease outcomes. In particular, the interactions between the host's genetic variation and the different MTB lineages have not yet been fully explored. This result highlights the need for an integrated approach that considers host and pathogen factors simultaneously.

Furthermore, the GWAS approach identified susceptible loci, such as rs4331426, *ASAP1*, and *CD53*; however, the functional significance of many identified loci remains unclear. Most of the relevant SNPs are located in noncoding regions. Their role in gene regulation and immune response requires further investigation through functional and experimental studies [24]. Narrowing the gap between genetic association discovery and biological mechanisms remains an important challenge.

Future research should focus on large multiethnic cohort studies, which will help improve reproducibility and generalizability. An integrated approach combining genomics, transcriptomics, epigenomics, and metabolomics will be essential for understanding the biology of TB susceptibility. Furthermore, advanced computational methods, including machine learning, can help identify complex gene–gene and gene–environment interactions [28].

Finally, translating genetic findings into clinical practice remains a major challenge [29]. Research extending beyond identifying susceptibility locations is required. Solid validation studies and integration with existing clinical risk factors are needed for these findings to meaningfully contribute to TB risk prediction and personalized management.

Conclusion

TB remains a major global health issue, and a growing body of evidence highlights the important role of host genetic factors in determining susceptibility to MTB infection. This review has summarized the findings of current studies on genetic polymorphisms associated with TB, particularly those associated with cytokine signaling, innate immunity, antigen presentation, and genome-wide susceptibility loci.

Overall, TB susceptibility appears to be influenced by the complex interactions of several genetic variants in key immune pathways. Population-specific differences in genetic associations further highlight the importance of considering ethnic diversity in both genetic studies and clinical applications.

Despite significant progress, several challenges persist: Reproducibility of results is limited and the functional role of identified variants has not been comprehensively elucidated. Many TB-associated SNPs are located in noncoding regions and can influence transcriptional regulation and gene expression through mechanisms such as expression quantitative trait loci (eQTL) effects. Therefore, combining GWAS with transcriptomic data may help us determine the effects of these variants actually on the immune response.

Deeper understanding of genetic variation in hosts could potentially improve risk prediction, guide the development of new treatment strategies, and support the implementation of precision medicine in TB prevention and control. Ultimately, the application of these genetic insights to clinical practice requires coordinated efforts to incorporate research, clinical validation, and public health implementation.

Availability of Data and Materials

Not applicable.

Author Contributions

Conceptualization: SunK, HP; Literature search: MJ; Data curation: MJ, SohK, SoyK, JL, CK; Formal analysis: MJ, SohK, SoyK, JL, CK; Visualization: MJ; Writing—original draft: MJ; Writing—review and editing: SohK, SoyK, JL, CK, SunK, HP; Supervision: SunK, HP. All authors have read and agreed to the published version of the manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

We thank Busan Metropolitan City and Busan Techno Park for providing financial assistance for this study through the BB21 Plus Project.

Funding

This paper was supported by a research fund from the Catholic University of Pusan and University Innovation Support Project through the National Research Foundation of Korea funded (no fund number assigned).

Conflict of Interest

The authors declare no conflict of interest.

References

[1] World Health Organization. Global Tuberculosis Report 2025. World Health Organization: Geneva. 2025.

[2] Zargar AS, Borole K, Rai R. Correlation of polymorphism in Toll-Like Receptor (TLR1 and TLR2) genes with susceptibility of pulmonary tuberculosis in Doda region of India. The Indian Journal of Tuberculosis. 2024; 71: 41–47. https://doi.org/10.1016/j.ijtb.2023.03.018

[3] Smith CM, Baker RE, Proulx MK, Mishra BB, Long JE, Park SW, et al. Host-pathogen genetic interactions underlie tuberculosis susceptibility in genetically diverse mice. ELife. 2022; 11: e74419. https://doi.org/10.7554/eLife.74419

[4] Hamilton F, Schurz H, Yates TA, Gilchrist JJ, Möller M, Naranbhai V, et al. Altered IL-6 signalling and risk of tuberculosis: a multi-ancestry mendelian randomisation study. The Lancet. Microbe. 2025; 6: 100922. https://doi.org/10.1016/S2666-5247(24)00162-9

[5] Zhang SX, Lu ZH, Wang MT, Shen YP, Duan L, Guan SY, et al. Assessing the association between the circulating levels of inflammatory cytokines and the risk of tuberculosis: A bidirectional two-sample mendelian randomization study. Infection, Genetics and Evolution: Journal of Molecular Epidemiology and Evolutionary Genetics in Infectious Diseases. 2023; 116: 105524. https://doi.org/10.1016/j.meegid.2023.105524

[6] Liu Q, Chen X, Dai X. The association of cytokine gene polymorphisms with tuberculosis susceptibility in several regional populations. Cytokine. 2022; 156: 155915. https://doi.org/10.1016/j.cyto.2022.155915

[7] Varzari A, Deyneko IV, Vladei I, Grallert H, Schieck M, Tudor E, et al. Genetic variation in TLR pathway and the risk of pulmonary tuberculosis in a Moldavian population. Infection, Genetics and Evolution: Journal of Molecular Epidemiology and Evolutionary Genetics in Infectious Diseases. 2019; 68: 84–90. https://doi.org/10.1016/j.meegid.2018.12.005

[8] Sanchez-Mazas A. A review of HLA allele and SNP associations with highly prevalent infectious diseases in human populations. Swiss Medical Weekly. 2020; 150: w20214. https://doi.org/10.4414/smw.2020.20214

[9] Bai H, Song M, Lei S, Jiao L, Hu X, Wu T, et al. Genome-wide association study of tuberculosis in the western Chinese Han and Tibetan population. MedComm. 2023; 4: e250. https://doi.org/10.1002/mco2.250

[10] Schurz H, Kinnear CJ, Gignoux C, Wojcik G, van Helden PD, Tromp G, et al. A Sex-Stratified Genome-Wide Association Study of Tuberculosis Using a Multi-Ethnic Genotyping Array. Frontiers in Genetics. 2019; 9: 678. https://doi.org/10.3389/fgene.2018.00678

[11] Omae Y, Toyo-Oka L, Yanai H, Nedsuwan S, Wattanapokayakit S, Satproedprai N, et al. Pathogen lineage-based genome-wide association study identified CD53 as susceptible locus in tuberculosis. Journal of Human Genetics. 2017; 62: 1015–1022. https://doi.org/10.1038/jhg.2017.82

[12] McHenry ML, Wampande EM, Joloba ML, Malone LL, Mayanja-Kizza H, Bush WS, et al. Interaction between M. tuberculosis Lineage and Human Genetic Variants Reveals Novel Pathway Associations with Severity of TB. Pathogens (Basel, Switzerland). 2021; 10: 1487. https://doi.org/10.3390/pathogens10111487

[13] Chen C, Wang J, Pan D, Wang X, Xu Y, Yan J, et al. Applications of multi-omics analysis in human diseases. MedComm. 2023; 4: e315. https://doi.org/10.1002/mco2.315

[14] Schurz H, Naranbhai V, Yates TA, Gilchrist JJ, Parks T, Dodd PJ, et al. Multi-ancestry meta-analysis of host genetic susceptibility to tuberculosis identifies shared genetic architecture. ELife. 2024; 13: e84394. https://doi.org/10.7554/eLife.84394

[15] Hall TJ, Mullen MP, McHugo GP, Killick KE, Ring SC, Berry DP, et al. Integrative genomics of the mammalian alveolar macrophage response to intracellular mycobacteria. BMC Genomics. 2021; 22: 343. https://doi.org/10.1186/s12864-021-07643-w

[16] Chen R, Wang X, Li Z, Dai Y, Du W, Wu L. Human Toll-like receptor 2 genetic polymorphisms with tuberculosis susceptibility: A systematic review and meta-analysis. Cytokine. 2023; 172: 156405. https://doi.org/10.1016/j.cyto.2023.156405

[17] Tang NLS, Wang X, Chang KC, Chan CY, Szeto NWS, Huang D, et al. Genetic susceptibility to Tuberculosis: Interaction between HLA-DQA1 and age of onset. Infection, Genetics and Evolution: Journal of Molecular Epidemiology and Evolutionary Genetics in Infectious Diseases. 2019; 68: 98–104. https://doi.org/10.1016/j.meegid.2018.12.014

[18] Du B, Hua D, Droma C, Zhang H, Qu J, Yang L, et al. Association between TAP2 and SEC14L2 polymorphisms and pulmonary tuberculosis risk in the Tibetan Chinese population. International Journal of Clinical and Experimental Pathology. 2017; 10: 11188–11194.

[19] Lee SW, Lin CY, Chuang TY, Huang HH, Kao YH, Wu LSH. SNP rs4331426 in 18q11.2 is associated with susceptibility to tuberculosis among female Han Taiwanese. Journal of Microbiology, Immunology, and Infection = Wei Mian Yu Gan Ran Za Zhi. 2016; 49: 436–438. https://doi.org/10.1016/j.jmii.2014.11.007

[20] Wang X, Ma A, Han X, Litifu A, Xue F. ASAP1 gene polymorphisms are associated with susceptibility to tuberculosis in a Chinese Xinjiang Muslim population. Experimental and Therapeutic Medicine. 2018; 15: 3392–3398. https://doi.org/10.3892/etm.2018.5800

[21] Cui X, Yuan T, Ning P, Han J, Liu Y, Feng J, et al. Polymorphisms in the ASAP1 and SP110 Genes and Its Association with the Susceptibility to Pulmonary Tuberculosis in a Mongolian Population. Journal of Immunology Research. 2022; 2022: 2713869. https://doi.org/10.1155/2022/2713869

[22] Phelan J, Gomez-Gonzalez PJ, Andreu N, Omae Y, Toyo-Oka L, Yanai H, et al. Genome-wide host-pathogen analyses reveal genetic interaction points in tuberculosis disease. Nature Communications. 2023; 14: 549. https://doi.org/10.1038/s41467-023-36282-w

[23] Hong EP, Go MJ, Kim HL, Park JW. Risk prediction of pulmonary tuberculosis using genetic and conventional risk factors in adult Korean population. PloS One. 2017; 12: e0174642. https://doi.org/10.1371/journal.pone.0174642

[24] Ai JW, Zhang H, Zhou Z, Weng S, Huang H, Wang S, et al. Gene expression pattern analysis using dual-color RT-MLPA and integrative genome-wide association studies of eQTL for tuberculosis suscepitibility. Respiratory Research. 2021; 22: 23. https://doi.org/10.1186/s12931-020-01612-9

[25] Kim SS, Park M, Park S. Replicated Association Study between Tuberculosis and CLCN6, DOK7, HLA-DRA in Korean. Biomedical Science Letters. 2020; 26: 238–243. https://doi.org/10.15616/bsl.2020.26.3.238

[26] Park S, Kim SS, Jin HS, Cho JE. Replication Study of Association between Forkhead Box O3 (FOXO3) Polymorphisms and Tuberculosis in Korean Population. Biomedical Science Letters. 2020; 26: 42–46. https://doi.org/10.15616/bsl.2020.26.1.42

[27] Ju Y, Kim SS, Lee KE, Park S, Jin H. Association of the Genetic Polymorphisms for CD247 Gene and Tuberculosis Case. Biomedical Science Letters. 2020; 26: 22–27. https://doi.org/10.15616/bsl.2020.26.1.22

[28] Reicher L, Shilo S, Godneva A, Lutsker G, Zahavi L, Shoer S, et al. Deep phenotyping of health-disease continuum in the Human Phenotype Project. Nature Medicine. 2025; 31: 3191–3203. https://doi.org/10.1038/s41591-025-03790-9

[29] Thomas L, Raju AP, Mallayasamy S, Rao M. Precision Medicine Strategies to Improve Isoniazid Therapy in Patients with Tuberculosis. European Journal of Drug Metabolism and Pharmacokinetics. 2024; 49: 541–557. https://doi.org/10.1007/s13318-024-00910-7