INTERNATIONAL MULTIDISCIPLINARY JOURNAL FOR RESEARCH & DEVELOPMENT
SJIF 2019: 5.222 2020: 5.552 2021: 5.637 2022:5.479 2023:6.563 2024: 7,805
eISSN :2394-6334 https://www.ijmrd.in/index.php/imjrd Volume 12, issue 02 (2025)

THE INFLUENCE OF GENETIC FACTORS ON SUSCEPTIBILITY TO TUBERCULOSIS

Mirzakarimova Dildora Bakhodirovna

Department of Infectious Diseases

Andijan State Medical Institute

Abstract: Tuberculosis (TB) remains a leading infectious cause of morbidity and mortality worldwide. Although various environmental and socioeconomic factors contribute to TB risk, a growing body of evidence highlights the importance of genetic predisposition in host susceptibility to *Mycobacterium tuberculosis* infection [1]. This review summarizes current knowledge of the genetic variants associated with increased or decreased TB risk, highlights emerging genomic and transcriptomic approaches, and discusses the complex interplay between host genes and pathogen-related factors [2]. Understanding these genetic determinants can facilitate personalized risk assessments, inform vaccine development, and guide novel therapeutic strategies [3].

Keywords: tuberculosis, *Mycobacterium tuberculosis*, genetics, susceptibility, immune response.

Introduction

Tuberculosis (TB) is caused by the bacterium *Mycobacterium tuberculosis* (Mtb), which typically affects the lungs but can also infect other organs (extrapulmonary TB). Despite significant advances in diagnostic tools and therapeutic regimens, TB remains a major global health challenge, with an estimated 10.6 million new cases and 1.6 million deaths in 2021 alone 111.

Host defense against *M. tuberculosis* involves a coordinated immune response, primarily driven by cell-mediated immunity involving T-cells and macrophages 222. However, not all individuals exposed to Mtb become ill. While environmental and socioeconomic factors—such as overcrowding, malnutrition, and HIV co-infection—can predispose a person to infection, host genetic variability also plays a crucial role in determining whether infection progresses to active disease 333. This article explores the main genetic factors that influence TB susceptibility and discusses emerging directions for research [4].

Overview of Tuberculosis Susceptibility

The Role of the Immune Response

When Mtb enters the lungs, alveolar macrophages attempt to engulf and destroy the bacilli. A strong cell-mediated immune response, orchestrated by CD4+^++ and CD8+^++ T-lymphocytes, is critical for containing the pathogen within granulomas. However, certain genetic backgrounds may impair or overly modulate immune responses, allowing Mtb to survive or replicate unchecked.

Population Genetics

It has long been observed that TB prevalence and severity vary among different population groups, suggesting a hereditary component 444. Early twin studies demonstrated that monozygotic twins have higher concordance rates of TB compared with dizygotic twins, supporting a genetic contribution to host susceptibility.

Key Genetic Factors Associated with TB

NRAMP1 (SLC11A1)

One of the earliest and most widely studied genes implicated in TB susceptibility is **NRAMP1** (natural resistance-associated macrophage protein 1), also known as **SLC11A1**. This gene encodes a divalent cation transporter in macrophages that influences intracellular microbial replication [5].

Variations in NRAMP1 have been linked to altered control of intracellular pathogens, including Mtb, with certain polymorphisms correlating with heightened TB risk 555.

HLA Class II Genes

The human leukocyte antigen (HLA) system, particularly the **HLA class II** genes (e.g., HLA-DR, HLA-DQ), is central to antigen presentation. The specific HLA allele an individual carries can affect how Mtb antigens are presented to T-lymphocytes. Certain HLA-DR and HLA-DQ variants have been associated with either increased or reduced TB risk, indicating that immune recognition of mycobacterial peptides can be genetically driven 666.

Cytokine Genes (IL-10, TNF-α, IFN-γ)

Cytokines are key mediators of the immune response against Mtb. Polymorphisms in cytokine genes can modify immune signaling pathways. For instance:

- **IL-10**: Some variants lead to higher IL-10 production, potentially dampening the pro-inflammatory response needed to clear Mtb.
- **TNF-α**: This cytokine is critical for granuloma formation. Genetic variants resulting in lower TNF-α expression can impair granuloma maintenance.
- **IFN-γ**: Defects or downregulation in IFN-γ signaling diminish macrophage activation, thus increasing TB susceptibility 777.

TLR (Toll-Like Receptor) Genes

Toll-like receptors are essential for pathogen recognition. **TLR2**, **TLR4**, and **TLR9** have been studied in the context of TB. Mutations that alter TLR signaling can reduce the immune system's ability to sense and respond to Mtb, leading to an increased risk of developing active disease 888.

VDR (Vitamin D Receptor)

Vitamin D plays an immunomodulatory role, particularly in macrophage activation and the production of antimycobacterial peptides (such as cathelicidin). Variations in the **vitamin D receptor (VDR)** gene can affect an individual's ability to mount an effective immune response against Mtb. Several studies have demonstrated an association between certain VDR polymorphisms and increased TB susceptibility, although these findings can vary by ethnic group 999.

Genetic Approaches and Emerging Research

Genome-Wide Association Studies (GWAS)

GWAS has become a powerful tool to identify novel genetic loci associated with TB risk [6]. By scanning the entire genome in large populations, GWAS can uncover candidate genes and pathways that were not previously linked to TB. Several GWAS have highlighted regions on chromosomes 8q, 11p, and 18q, suggesting new avenues for research 101010.

Transcriptomic and Epigenetic Studies

- **Transcriptomics**: Examines gene expression profiles of infected versus non-infected individuals to reveal specific immunological signatures associated with TB resistance or progression.
- **Epigenetics**: Factors such as DNA methylation and histone modification can modulate immune gene expression without altering the underlying DNA sequence [7]. Epigenetic changes may help explain variable responses among individuals with similar genetic backgrounds 111111.

Host-Directed Therapies

Understanding the host genetic factors that modulate TB susceptibility paves the way for **host-directed therapies**. These strategies aim to boost the patient's immune response or correct genetic/epigenetic deficiencies [6]. For instance, targeting pathways governed by IFN-γ or TNF-α might enhance granuloma formation and bacterial clearance, potentially improving treatment outcomes when combined with standard anti-TB drugs.

Clinical Implications

1. **Personalized Medicine**: Genetic screening could identify individuals at higher risk, allowing for tailored preventive strategies (e.g., prophylactic treatment, enhanced monitoring).

2. **Vaccine Development**: Knowledge of protective genetic variants could guide the design of more effective vaccines or adjuvants to bolster specific immune pathways.

3. **Public Health Strategies**: Incorporating genetic data into TB control programs may improve resource allocation, focusing interventions in high-risk populations.

Despite these promising avenues, there is a need for large-scale, multi-ethnic studies to replicate findings and ensure that identified genetic markers have consistent predictive value [8]. Additionally, ethical considerations, such as genetic privacy and the potential stigmatization of high-risk groups, must be carefully addressed.

6. Conclusions

Genetic factors play a critical role in modulating host susceptibility to *Mycobacterium tuberculosis*. Variants in NRAMP1, HLA genes, cytokine genes, TLRs, and VDR, among others, can influence the immune response, shaping an individual's risk profile [9]. Emerging genomic and transcriptomic approaches are shedding light on previously unknown pathways and gene-environment interactions.

Moving forward, integrating genetic insights into clinical practice will require well-designed, ethically sound research, coupled with robust public health policies [10]. By unraveling the genetic underpinnings of TB susceptibility, clinicians and researchers can develop better prevention, diagnostic, and therapeutic strategies to combat this persistent global health threat.

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