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Mycobacterial Diseases

ISSN: 2161-1068

Commentary

# Genetic Variations and their Effect on Active and Latent Tuberculosis

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## DESCRIPTION

*Mycobacterium tuberculosis* (*M. tb*) being a highly infectious disease, not everyone exposed to the bacteria develops TB. For some, the immune system controls the infection, leading to a latent form of TB, while others develop active disease. This variability in response is due to multiple factors, including genetics. Certain genetic variations can influence the effectiveness of immune responses, making some people more susceptible to active TB, while others are able to contain the bacteria in a dormant state, known as latent TB. Environmental factors, such as nutrition and exposure levels, also contribute to this variability. However, genetic predispositions, particularly in immune-related genes, are key determinants in whether TB remains latent or progresses to an active disease.

### Role of genetics in TB susceptibility

Although environmental factors like malnutrition, exposure, and HIV infection are significant contributors to TB risk, genetics can predispose certain individuals to the disease. Human susceptibility to TB is complex and involves various genes that interact with the pathogen and the immune system. Studies have revealed that genetic variations influence how the immune system recognizes and responds to *Mycobacterium tuberculosis*.

**Innate immunity and genetic factors:** The body's first line of defense against TB infection is the innate immune system, which consists of cells and proteins that react quickly to the presence of pathogens. Several key players in innate immunity are genetically influenced, by Pattern Recognition Receptors (PRRs) receptors recognize *M. tb* and trigger an immune response. Genetic variations in PRRs like Toll-like receptors (TLR2, TLR4, and TLR9) have been associated with altered immune responses, making some individuals more prone to TB. Mannose-Binding Lectin (MBL) protein recognizes carbohydrates on the surface of bacteria. Individuals with genetic variations leading to lower levels of MBL may have a compromised ability to recognize and clear *M. tb*, increasing their susceptibility to TB. Cytokines and chemokines proteins regulate immune responses. Genes encoding cytokines like IL-10, TNF-α, and IFN-γ are vital for controlling TB. Polymorphisms in these genes may lead to impaired immune responses, either making it easier for the bacteria to proliferate (increasing risk of active TB) or enabling the body to contain the infection (leading to latent TB).

**Adaptive immunity and genetic influence:** Once the innate immune system recognizes *M. tb*, the adaptive immune system, which includes T cells and B cells, works to eliminate the infection or keep it in check. Genetic differences in this system can affect how well an individual controls TB infection, such as, Human Leukocyte Antigen (*HLA*) genes help the immune system distinguish between the body's own proteins and those made by pathogens like *M. tb*. Variations in *HLA* genes have been linked to both increased and decreased susceptibility to TB. For example, certain *HLA* alleles may be better at presenting *M. tb* antigens to T cells, leading to more efficient immune responses, while others may be less effective. Vitamin D Receptor (*VDR*) gene is essential for immune function, and the *VDR* gene plays a important role in activating the immune response to TB. Variations in the *VDR* gene can lead to differing levels of susceptibility to TB, as some individuals with certain *VDR* gene polymorphisms may have a weakened ability to activate the immune system against the bacteria.

### Genetic susceptibility to latent TB

Understanding the genetics of TB susceptibility offers important implications for public health and treatment. Genetic insights can lead to better diagnostic tools to identify individuals at higher risk for TB. In addition, personalized treatment strategies, including targeted vaccines and immune-based therapies, can be developed for those with genetic predispositions to TB. While active TB is characterized by symptoms such as coughing, weight loss, and fatigue, latent TB presents no symptoms and remains dormant within the body. About one-quarter of the world's population is estimated to have latent TB, and only a small percentage will develop active disease. Understanding the genetics of latent TB is important, as some individuals have a higher likelihood of progressing to active TB than others.

**Host-pathogen interaction:** The transition from latent to active

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**Received:** 04-Sep-2024, Manuscript No. MDTL-24-34692; **Editor assigned:** 06-Sep-2024, Pre QC No. MDTL-24-34692 (PQ); **Reviewed:** 20-Sep-2024, QC No. MDTL-24-34692; **Revised:** 27-Sep-2024, Manuscript No. MDTL-24-34692 (R); **Published:** 03-Oct-2024, DOI: 10.35248/2161-1068.24.14.506

**Citation:** Kanareu V (2024). Genetic Variations and their Effect on Active and Latent Tuberculosis. Mycobact Dis. 14:506.

TB involves complex host-pathogen interactions, influenced by genetic factors. For instance, genes involved in immune regulation and inflammation play key roles in controlling latent TB infection. Studies suggest that polymorphisms in genes like Natural Resistance-Associated Macrophage Protein 1 (*NRAMP1*) and *P2X7* may affect the body's ability to maintain latent TB, potentially leading to reactivation.

**Immune system regulation:** Regulatory genes that manage immune system balance are also important. The balance between pro-inflammatory and anti-inflammatory cytokines, regulated by genes like *IL-10*, can determine whether TB remains latent or becomes active. Genetic variants that reduce the body's ability to control inflammation may increase the risk of reactivation.

# CONCLUSION

The interplay between genetic factors and TB susceptibility highlights the complexity of this disease. While genetic predispositions do not guarantee the development of TB, they play a significant role in determining an individual's risk of infection and progression. Future research in genetics likely to uncover more detailed mechanisms, offering hope for more effective TB control and prevention strategies tailored to individuals' genetic profiles.