REVIEW ARTICLE

Tuberculosis and Single Nucleotide Polymorphisms in the SP-A Gene

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SUMMARY

Tuberculosis (TB), is a primary global health concern, caused by Mycobacterium tuberculosis (MTB). Pakistan is ranked 5th among highly prevalent TB countries. Susceptibility to TB is affected by several biological variables, including age, gender, host genetics, and host immunity. Among these, host genetics is a key factor because it not only affects the probability of TB susceptibility but also aggravates its clinical manifestations. Understanding the contribution of host genetics in the protection, proneness, and progression of TB is of paramount importance. The host's innate immune system offers protective genes that promote uptake and clearance of MTB and detrimental genes that promote survival and progression of MTB. Surfactant protein A (SP-A) is an essential constituent of innate immunity involved in the host defense against various pathogens, particularly MTB. SP-A acts as a bridge between MTB and macrophages as it interacts with the glycoprotein located on the surface of MTB and mannose receptors present on the surface of alveolar macrophages, consequently enhancing the engulfment of MTB. This gene is also important in LTBI as it is involved in the progression of LTBI to active TB. A variety of single nucleotide polymorphisms (SNPs) are in the exonic and intronic regions of SP-A gene that may affect its expression hence MTB uptake into macrophages. SP-A polymorphisms have been investigated in various diseases but not specifically for TB and LTBI in the Pakistani population. This review is aimed at summarizing existing literature on SP-A gene polymorphisms and their impact on SP-A gene expression in pulmonary as well as extrapulmonary disorders. This study will assist in choosing candidate polymorphisms that can be further investigated in TB and LTBI patients from the Pakistani population. Total of 17 Studies were identified reporting 79 SPA gene polymorphisms including rs1059047, rs1136450, rs1059049, rs1059054, rs4253527, rs1136452, rs1914663, rs1059225, rs17880809, rs1965708, rs17886395, rs1059046, rs17879335, rs17881720 in pulmonary and extra pulmonary disorders. Conclusion: We conclude that rs1059047 is most commonly studied SNP that has a significant effect on expression of SP-A gene and is an appropriate candidate to be investigated in LTBI and active TB.

Keywords: *Latent Tuberculosis Infection, Mycobacterium Tuberculosis, Surfactant Protein A, Tuberculosis.*

How to cite this: *Subhan U, Tariq EB, Deeba F, Younis S. Tuberculosis and Single Nucleotide Polymorphisms in SP-A Gene. Life and Science. 2025; 6(2): 292-303. doi: http://doi.org/10.37185/LnS.1.1.494*

TB Prevalence

TB is an airborne bacterial infection spread by the inhalation of tiny aerosols from the cough and sneeze of an individual infected with MTB. TB is caused by the small bacillus pathogenic bacterium MTB that belongs to the family Mycobacteriaceae.[1] MTB was first identified in 1882 by Robert Koch and has a waxy, unusual coating on its surface due to mycolic acid and cord factor glycolipid making it impervious to gram staining. The MTB divides every 18-24 hours, and its physiology is extremely aerobic and non-motile. MTB mostly attacks the lungs, causing pulmonary TB (PTB), but it can also attack other parts of the body (kidney, spine, bones, nervous system, or brain), resulting in extra-pulmonary TB (EPTB).[2]

Globally, TB accounts for the deaths of 1.5 million

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Received: Oct 03, 2023; 1st Revision Received: May 08, 2024
2nd Revision Received: Sep 15, 2024; Accepted: Sep 22, 2024

individuals in 2023 (including co-infection of 161,000 people with HIV). TB is the 13th leading cause of death globally and the second most frequent infectious killer worldwide, after COVID-19.[3] The Eastern Mediterranean Region has a TB incidence rate of 14.4 cases per 100,000 people. In Pakistan, the annual prevalence of TB is 310 cases per 100,000 people.[4]

When an individual inhales MTB from an infected person, the infection occurs either as an asymptomatic latent TB infection (LTBI) or as a symptomatic active TB infection. LTBI refers to the condition when bacterial proliferation is restrained by host immune responses inside granulomas or other areas, where it can only persist in a dormant state, and the inflammatory response is decreased. When TB is latent, an individual does not feel ill or show symptoms of active TB.[5] According to WHO, 2-3 billion individuals are infected with LTBI while 5-10% of individuals experience reactivation in their lifetime.

TB Pathogenesis

MTB transmission potential is influenced by several factors, including host susceptibility, infectious droplet nuclei concentration, and duration of exposure. When these aerosols are inhaled by uninfected individuals, alveolar macrophages are the first cells to become infected. One or more outcomes may result from the consequent deposition of MTB in the lungs, including the instant removal of MTB from the body, direct beginning of active disease (primary disease), asymptomatic infection (LTBI), or the commencement of an active disease several years after LTBI (disease reactivation).

To eradicate pathogens, macrophages have lysosomes, which have hydrolytic enzymes. Under normal immune response, the lysosome fuses with the phagosome to form a phagolysosome in which the pathogen is dissolved with acids and finally eliminated.[6] But in the case of TB, the formation of phagolysosomes is restricted, and MTB remains protected inside the macrophages without being detected by the immune system and may reproduce at a slow rate. The infected macrophages then release these bacilli, and other macrophages will pick them up, which results in a large number of infected cells in the distal part of the lung, resulting in primary infection.[7] Three weeks after primary infection, cell-mediated immunity takes effect, and immune cells surround the site of infection, resulting in the development of a particular kind of lesion in the lungs known as a granuloma or tuberculoma.[8] Granuloma is an enlarged cellular aggregate that comprises macrophages and other inflammatory cells resulting in Ghon focus, in the center of the lungs within 2-6 weeks after infections.[9]

After the local infection occurs in macrophages and granulomas have been formed, the infection is no longer contained at the local site. There is a spillover of the infection to the regional lymph nodes in the lungs, leading to an immune reaction. The regional lymph nodes and infected granuloma are called Ghon complex. At this stage, either there is complete elimination of MTB or it goes to a quiescent state that is known as LTBI.[10] Primary infection is progressive, resulting in local progression of infection, which either leads to enlargement of Ghon focus, causing PTB, also known as TB pneumonia, or may disseminate widely in other organs of the body, such as the liver, brain, and other parts of the lungs, resulting in EPTB. Additionally, 5-10% of individuals develop secondary disease which represents the reactivation of a prior latent infection or prior dormant infection.[9] Reactivation of primary infection is influenced by many biological factors for example suppression of host immune system by co-infection with other pathogen (incidence of reactivation increases 10-100 times in HIV patients), immunosuppressant drugs (as in case of organ transplant), autoimmune diseases (administration of TNF-α blockers) and chronic renal failure.[11]

Human Genetics and TB Susceptibility

Susceptibility to TB is affected by several biological variables. Among these, host genetics clearly influences the probability of TB onset because most of the genes participate in immunological responses, and SNPs in these genes alter the immunity.[12] Host genetics explains why some individuals are more/less susceptible to TB infection. Several genome-wide association studies (GWAS) and genome-wide linkage studies provide evidence that host genetics strongly influences TB susceptibility. Several studies investigated that SNPs in pattern

recognition receptors (PRRs) and phagocytic receptors are involved in the recognition of MTB. Studies suggest that among these PRRs, SNPs in mannose receptors (MR), VDR (Vitamin D receptor), DC-SIGN (Dendritic Cell-Specific Intercellular adhesion Molecule-3-Grabbing Non-Integrin), TLRs (Toll Like Receptors), NOD1/NOD2 (Nucleotide-binding Oligomerization Domain Containing Protein 1 and 2), and CR1 (Complement Receptor 1) (CD11b/CD18) are associated with TB. Numerous studies have demonstrated that individuals possessing specific mutations in the genes encoding soluble C-type lectins, which serve as a primary defense mechanism against Mycobacterium tuberculosis (MTB) infection such as Surfactant Protein A (SP-A), Surfactant Protein D (SP-D), and Mannose-Binding Lectin (MBL) exhibit a significant association with tuberculosis (TB) infection.[13-26]

Many genetic research studies have revealed significant associations of innate immune modulators (TNF, IL-1β, IL6, 1L8, IL-10, 1L12, IL18, MCP-1, CCL5, CXCL10, iNOS, and NRAMP1) with increased risk of TB. After examining multiple pertinent studies, along with their findings and conclusions, there is substantial evidence to indicate that TB is a genetically predisposed and defined infectious disease caused by MTB. Furthermore, genetic variations are implicated in the progression from latent TB infection to active TB disease.[10,27-41]

Surfactant Proteins

Surfactant proteins are a group of specialized proteins from the collectin family that play a crucial role in the respiratory system, particularly the lungs. These host defense proteins have a critical function in maintaining alveolar homeostasis and immunity.[42] These proteins are primarily an intricate combination of lipids and proteins that coat the lungs' alveoli. Pulmonary surfactants help to decrease interfacial tension and prevent the collapse of alveoli during breathing, allowing for efficient gas exchange.[43]

There are four different subtypes of surfactant proteins (SPs), namely surfactant protein A, B, C, and D. All types of SPs are made by type II alveolar epithelial cells (AECs). SP-B and SP-C are lipophilic and small proteins, while SP-A and SP-D are hydrophilic and large molecules.[12] SP-B and SP-C are hydrophobic proteins critical for the surface tension-lowering properties of surfactant. SP-B is necessary for the development of surfactant-like particles, while SP-C helps to stabilize the surfactant film. SP-B interacts with phospholipids, the key surfactant component, and helps decrease surface tension within the alveoli. The alveoli can stay open during exhalation due to decreased surface tension, which stops lung collapse.[44] SP-C is embedded in the phospholipid layer of surfactant and helps stabilize the surfactant film at the boundary of liquid and air. SP-A and SP-D are similar constituents only produced by the lungs.[45] SP-A and SP-D have been attributed to the innate immunity in the lungs. Both surfactant proteins serve to promote the clearance of viruses and bacteria.[43] It is reported that SP-A is used as an opsonin and is essential for the respiratory system's innate immune response, enhancing the phagocytosis of microorganisms by immune cells. The modulation of surfactant metabolism and clearance is another role of SP-A.[46] Like SP-A, SP-D participates in the intrinsic immunological reaction. It recognizes and binds to specific carbohydrate sequences present on the surface of various microbes, facilitating their clearance by immune cells. Bourbon *et al.* reported that SP-D is an important modulator of lung surfactant lipid levels, and it has been postulated that SP-D might also contribute to the homeostasis of phospholipids at locations other than the lungs.[47] Moreover, SP-D is expressed in cardiac myocytes and endothelium, where it is thought to operate as a blocker of inflammatory signaling. SP-D also aids in surfactant homeostasis, modulation of inflammation, and lung defense against pathogens.[48]

These surfactant proteins (SP-A, SP-B, SP-C, and SP-D) work collectively to maintain optimal lung function by promoting efficient gas exchange, controlling surfactant metabolism, and contributing to respiratory immune defense. Chang at el., demonstrated that deficits in surfactant proteins might cause respiratory distress syndrome (RDS) in preterm newborns as well as other lung diseases.[49] Furthermore, surfactant protein gene mutations have been related to various types of lung disorders, such as interstitial lung disease, pulmonary fibrosis, and pulmonary tuberculosis (PTB).[50,51]

SP-A and its role in TB pathogenesis

Pulmonary surfactant protein A (SP-A), a kind of immune-reactive protein normally produced by type II alveolar epithelial cells, substantially impacts innate immunity, inflammatory processes, and hypersensitivity reactions. The primary structure of SP-A consists of a signal peptide sequence and four additional domains: a neck domain, a collagen-like domain, an N-terminal sequence necessary for oligomerization, and an evolutionarily conserved carbohydrate recognition domain (CRD) located at the C-terminus. The CRD is responsible for calcium-dependent ligand binding.[52] The SP-A gene is located on chromosome 10 (Chr10q22–23) and comprises six exons, four of which are coding, interrupted by a pseudogene-containing DNA segment of approximately 40 kb.[53] SP-A1 and SP-A2 are two functional proteins encoded by the SP-A gene. The SP-A molecule exhibits a hexameric structure, consisting of six heterotrimers arranged in a bouquet-like formation.[54] Further investigation is required to elucidate the mechanisms involved in the intracellular trafficking and secretion of newly synthesized SP-A.[55]

Since MTB is primarily transmitted through the respiratory tract, SP-A is the first barrier for its entry in the cell. By acting on the mannose receptor on the surface of macrophages and the glycoprotein located on the cell wall of MTB, acts as a bridge between them and aid the uptake of MTB by macrophages.[56] MTB's surface may be recognized by SP-A and SP-D, which aids in triggering the immune response against the bacteria.[57] SP-A and SP-D can also regulate the role of immunological cells such as macrophages and dendritic cells, which can alter the immune response to MTB. SP-A and SP-D, for example, can improve macrophages' capacity to phagocytose MTB and increase the production of cytokines. Both surfactant proteins may also aid in preventing MTB spread from the lungs to the rest of the body.[58] Dissemination is an important phase in the transformation of latent TB infection to active TB. Some studies have found that levels of surfactant proteins are lower in persons with active TB, which might give rise to a weakened immune response and greater vulnerability to TB.[51] SP-A stimulates phagocytosis by the opsonization of microorganisms or by the functional upregulation of phagocyte receptor function.[59] SP-A induces the production of reactive oxygen intermediates and nitric oxide, stimulates chemotaxis and interaction between LPS and CD14, increase expression of scavenger receptor (SRA) and complement receptor (CR3), and modulate TLR function.[60] Comparative in vivo research between MTB-infected and uninfected macrophages, as well as research on active MTB-infected mice, has demonstrated that SP-A has a range of effects, though many processes still need to be extensively investigated.[61,62]

Polymorphisms in SP-A gene

Numerous SP-A polymorphisms in the sequence of the SP-A gene can lead to protein production with different structures and functions.[63] These variations can affect the SP-A levels in the serum, its ability to bind to pathogens, and its role in regulating immune responses in the lungs. Many SNPs have been recognized in the SP-A gene that can influence SP-A levels, activity, and susceptibility to lung disease. For instance, studies on genetic polymorphisms in SP-A have explored association with respiratory diseases such as allergic rhinitis, chronic obstructive pulmonary disease (COPD), community-acquired pneumonia (CAP), neonatal lung diseases, pulmonary edema, asthma, intestinal lung disease, and pediatric tuberculosis. Underlying mechanisms for these associations often lie in immunomodulation effects or alteration in the surfactant metabolism due to changes in SP-A gene expression triggered by these SNPs. The SP-A SNPs have also been investigated in non-respiratory diseases. For example, an association has been suggested between SP-A polymorphisms and autoimmune disorders, where aberration in the immune hemostasis may induce the onset of disease like systemic lupus erythematosus.

Several studies have investigated the association of SP-A1 and SP-A2 gene polymorphisms with various pulmonary and extra-pulmonary diseases, including allergic rhinitis, neonatal lung disease, r-UTI, cystic fibrosis (CF), high-altitude pulmonary edema, meningococcal disease, interstitial lung diseases, and pediatric tuberculosis in different populations. We have summarized information on SP-A1 and SP-A2 gene polymorphisms including SNP, location,

amino acid change, nucleotide change, expression level, receptor, disease, and population in table-1. In the SP-A1 gene following polymorphisms were found; rs1059047, rs1136450, rs1059049, rs1059054, rs1059050, rs1059052, rs1059053, rs1136452, rs4253527, rs4253528, rs1136451, rs4253527, rs1059057, rs1914663, rs1059225 and rs1617662. Furthermore, in SP-A2 following polymorphisms were identified including rs17880809, rs1965707, rs1965708, rs17886395, rs1059046, rs17879335, rs17881720, rs2271788, rs17878270, rs17886395 and rs1136452. The influence of these SNPs goes beyond the modulation of disease susceptibility. The overall picture emerging from these studies emphasizes the complexity and breadth of impact that SP-A genetic variation can have on disease susceptibility and gene expression, reaffirming the need for continued exploration in this area. SP-A gene polymorphisms can alter the structure of SP-A protein, impacting its ability to bind pathogens like MTB. These variations may modify immune cell signaling or phagocytosis efficiency, potentially enhancing or reducing the host's susceptibility to TB. Some polymorphisms enhance pathogen recognition, improve phagocytosis, stimulate inflammatory response, and promote bacterial clearance, leading to increased protection against TB, while others might have more nuanced effects. SP-A polymorphisms are related to TB susceptibility through their impact on the protein's function in innate immunity. Variants of SP-A can influence how effectively macrophages recognize and engulf M. tuberculosis, thereby impacting infection progression and immune response. For example, specific SP-A variants may enhance the immune response by increasing cytokine production, which aids in controlling TB infection.

Table-1: Surfactant Protein A polymorphisms

SNP	Location	Amino acid change	Nucleotide Change	Expression level	Receptor	Disease	Population	References
Polymorphism in SP-A1 gene								
rs1059047	Exon_1	Ala19Val	T1101C	Decrease SP-A transcriptional levels in human lung tissue	C1q, TLR2, CD14, TLR4, SIRP-a, and CD91/calreticulin	Allergic rhinitis	Chinese population	64
rs1136450	Exon_1	Val50Leu	C1193G					
rs1059049	Exon_2	Thr66Met	A201G					
rs1059054	Exon_2	Arg85Cys	C51T					
rs1059050	Exon_2	Ile66Met	A51G	N/A				
rs1059052	Exon_2	Asn73Asp	A51G	N/A				
rs1059053	Exon_2	Val81Ile	A51G	N/A				
rs1136452	Exon_2	Ala91Pro	C51G	N/A				
rs4253527	Exon_4	Trp219Arg	C/T	N/A				
rs4253528	Exon_4	Term242Arg	C724T	N/A				
rs1059047	Exon_1	Val19Ala	T1101C	N/A	LPS, CD14, TLRs	Neonatal Lung Disease	General population	65
rs1136450	Exon_1	Val50Leu	G1193C	N/A				
rs1136451	Coding exon	Pro62Pro	A256G	N/A				
rs4253527	Exon_2	Arg219Trp	C/T	N/A				
rs1059057	Exon_6	Thr133Thr	A133G	N/A				
rs1059047	Exon_1	Ala19Val	C1101T	High serum and low urine SP-A	TLR2, TLR4	r-UTI	Chinese women	66
rs1136450	Exon_1	Leu50Val	C1193G	N/A				
rs1136451	Exon_2	Pro62Pro	A256G	N/A				

rs1059057	Coding Sequence Variant	Thr133Thr	A133G	N/A				
rs1059047	Exon_1	Ala19Val	C1101T	N/A	CFTR	Cystic Fibrosis (CF).	Pennsylvania	67
rs1136450	Exon_1	Leu50Val	C1193G	N/A				
rs1136451	Exon 5	Pro62Pro	A256G	N/A				
rs1059057	Exon_4	Thr133Thr	G133A	N/A				
rs4253527	Exon_4	Arg219Trp,	C/T	N/A				
rs1059047	Exon_1	Val19Ala	C1101T	Homozygous increase and heterozygous decrease SP-A level	β2-adrenoceptor	High-Altitude Pulmonary Edema	Chinese HAN	68
	Exon 2	His39His	C1162T	N/A				
rs1136450	Exon 2	Leu50Val	C1193G	N/A				
	Intron B	C1416T	N/A	N/A				
	Exon 3	G1544A	N/A	N/A				
	Exon 5	Tyr184Tyr	T3138C	N/A				
	Exon 5	Asp202Asp	T3192C	Non redundant SNPs				
rs1136451	Exon 5	Pro216Pro	T3234C					
rs1059047	Exon 1	Val19Ala	T1101C	The SP-A expression is restricted to the lower respiratory tract and SP-A2 is over expressed generally throughout the airway	SIRPα	Meningococcal Disease	Finland	69
rs1136450	N/A	Val50Leu	G1193C	N/A				
rs4253527	N/A	Arg219Trp	C/T	N/A				
rs1136452	N/A	Ala91Pro	G51C	N/A				
	N/A		140 Silent C/T	N/A				
rs1059047	Exon_1	Ala19Val	C1101T	Lower BAL fluid SP-A levels and. In scleroderma, higher serum levels of SP-A	CD14	Interstitial lung diseases	General population	70
rs1136450	Exon_2	Leu50Val	C1193G					
rs4253527	Exon_4	Arg219Trp	C/T					
rs1136452	Exon_2	Pro91Ala	G51C					
rs1914663	Intron	N/A	N/A	Increase Serum levels of SP-A (The T allele), susceptibility factor to TB	N/A	Pediatric tuberculosis	Han Chinese population	71
rs1059225	3’UTR	N/A	N/A		N/A			
rs1617662	3’UTR	N/A	N/a	N/A	N/A			
rs4253527	Exon-4	Arg219Trp	C/T	N/A	N/A			
Polymorphism in SP-A2								
rs17880809	Exon_1	Asn9Thr	A/C					64

rs1965708	Exon_4	Lys223Gln	C667A	Decrease SP-A transcriptional levels in human lung tissue	C1q, TLR2, CD14, TLR4, SIRP-a, and CD91/calreticulin	Allergic rhinitis	Chinese population	
rs17886395	Exon_2	Pro91Ala	G271C	N/A				
rs17880809	Exon_1	Asn9Thr	A/C	Decrease serum SP-A	LPS, CD14, TLRs	Neonatal Lung Disease	General population	66
rs17886395	Exon_2	Ala91Pro	G271C					
rs1965707	Coding Sequence Variant	Ser140	C420T	N/A				
rs1965708	Exon_5	Gln223Lys	C667A	Overexpressed				
rs17880809	Exon_1	Asn9Thr	A/C	N/A	TLR2, TLR8	r-UTI	Chinese women	65
rs17886395	Exon_2	Pro91Ala	G271C	N/A				
rs1965707	Coding Sequence Variant	Ser140Ser	C450T	N/A				
rs1965708	Exon_5	Lys223Gln	C667A	High serum and low urine SP-A				
rs1059046	Exon_1	Asn9Thr	C26A	BAL SP-A level increased in early disease, decreased as disease progresses	CFTR	Cystic Fibrosis (CF).	Pennsylvania	67
rs17886395	Exon_2	Pro91Ala	C271G	N/A				
rs1965707		Ser140Ser	C450T	N/A				
rs1965708	Exon_5	Gln223Lys	C667A	N/A				
rs1965707	Exon 6	Ser140Ser	T271C	N/A	β2-adrenoceptor	High-Altitude Pulmonary Edema	High-altitude native (HAN)	68
rs1965708	Exon_6	Gln223Lys	C667A	Increase serum SP-A level				
rs17880809		Asn9Thr	A/C	N/A	SIRPα	Meningococcal Disease	Finland	69
rs1965708	CRD	Gln223Lys	C667A	N/A				
rs17880809	Exon_1	Thr9Asn	A/C	N/A	CD17	Interstitial lung diseases	General population	70
rs1965708	Exon_4	Lys223Gln	C667A	N/A				
rs17879335	3’UTR	N/A	N/A	Decrease Serum levels of SP-A (The G allele), a resistance factor to TB	N/A	Pediatric tuberculosis	Han Chinese population	71
rs17881720	3’UTR	N/A	N/A		N/A			
rs2271788	5’UTR	N/A	N/A	-	N/A			
rs17878270	5’UTR	N/A	N/A	N/A	N/A			
rs17886395		Ala91Pro	G271C	N/A	N/A			

rs1965708	Exon-Missense mutation	Lys223Gln	C667A	N/A	N/A				
N/A	Intron 3	C1382G	N/A	N/A	β2-adrenoceptor	High-Altitude Pulmonary Edema	High-altitude native (HAN)	68
N/A	Intron 3	T1492C	N/A	N/A				
rs1136452	Exon 4	Ala91Pro	G1649C	N/A				
N/A	Exon 4	Arg94Arg	A1160G	N/A				
N/A	Exon 5	Phe114Phe	C2474T	N/A				
N/A	Exon 5	Gln120Pro	C2491A	N/A				

C1q: Complement component 1q, TLR2: Toll-like Receptor 2, CD14: Cluster of differentiation 14, SIRP-α: Signal Regulatory protein α, LPS: lipopolysaccharides, CFTR: Cystic Fibrosis Transmembrane Conductance Regulator, CRD: Carbohydrates recognition domain, 3' UTR: 3' untranslated region, 5'UTR: 5' untranslated region, BAL: Broncho-alveolar Lavage

Association of SP-A SNPs with TB and LTBI

There are few investigations into the potential correlation between SNPs in the SP-A gene and their implications on TB susceptibility. These studies have been summarized below. A case-control study was conducted to explore genetic variations in the SP-A1 and SP-A2 genes and susceptibility to TB in the Ethiopian population. This study encompassed 181 Ethiopian families comprising a total of 226 individuals afflicted with TB (consisting of 119 males and 107 females). The PCR-RFLP technique was utilized for investigating genetic variations. This extensive analysis scrutinized nine SNPs located within the exonic region of SP-A1 and SP-A2. The outcome of this study revealed a statistically significant association between SP-A1 alleles 307A and 776T, and SP-A2 alleles 751C and 355C with TB.[72]

A case-control study was conducted to investigate the correlation of SNPs in SP-A1 and SP-A2 genes encoding pulmonary SP-A with the susceptibility to PTB in the Han population in China. This study included 248 patients with active PTB and a control group consisting of 124 normal individuals. Genetic polymorphisms were analyzed using sequence-specific PCR (SSP-PCR). Results showed that the G and T alleles at aa91 and aa140 in SP-A2 were significantly higher in the active PTB patients than in the control group suggesting that the two loci aa91 and aa140 are related to PTB in the Han population in China and the G allele at aa91 and T allele at aa140 may be risk factors for PTB in the Han population in China.[73]

Another case-control study aimed to investigate the association of polymorphisms in CRD of SP-A1 and SP-A2 with PTB in the Indian population. This study encompassed a case group comprising 7 individuals for SP-A1 and 8 for SP-A2, while a control group comprised 10 individuals for SP-A1 and 8 for SP-A2. To achieve specific amplification, two rounds of PCR were carried out. The first round of PCR resulted in the amplification of complete SP-A1 and SP-A2 genes, followed by dilution to 1:50 and 2nd round of nested PCR of smaller fragments of the genes. This extensive analysis scrutinized seven SNPs (4 exonic and 3 intronic) and revealed that SNPs in SP-A1 C1416T (Intronic) and A1660G (redundant) while SP-A2 C1382G and Ala91Pro (non-redundant) are associated with PTB susceptibility.[74]

Conclusion

Depending upon the different research studies in different populations, it is concluded that TB is a genetically primed infectious disease, and genetic polymorphisms are the main reasons that lead to the progression of MTB infection from a latent state to an active disease. It is still unpredictable why 5-10% of infected individuals progress towards active TB and what factors are involved in its progression. Future studies on the immunological mechanisms and genetic susceptibility of TB are of paramount importance because they will help to clarify the pathogenesis of MTB, detect susceptible populations, explore anti-tuberculosis methods, and lead to the development of vaccines against TB.

In conclusion, this review emphasizes the important role of the SP-A gene and its variations in influencing how the body responds to TB and latent TB infection (LTBI). Among the different genetic changes studied, the variation rs1059047 was found to be the most common and has a significant impact on how the SP-A gene functions. This makes it a key candidate for

further research, especially in the context of TB and LTBI in the Pakistani population. Understanding how these genetic factors affect the body's defense against TB could lead to better strategies for preventing and treating the disease.

Acknowledgement: We acknowledge the resources provided by the National University of Medical Sciences.

Conflict of Interest: The authors declare no conflict of interest

Grant Support and Financial Disclosure: None

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Author Contributions

US: Manuscript writing for methodology design and investigation, data acquisition, curation, and statistical analysis,
EBT: Validation of data, interpretation, and write-up of results
FD: Revising, editing, and supervising for intellectual content
SY: Conception and design of the work