



Influence of Genetic Polymorphism Towards Pulmonary Tuberculosis Susceptibility

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Tuberculosis (TB) still remains the major threat for human health worldwide. Several case-control, candidate-gene, family studies and genome-wide association studies (GWAS) suggested the association of host genetic factors to TB susceptibility or resistance in various ethnic populations. Moreover, these factors modulate the host immune responses to tuberculosis. Studies have reported genetic markers to predict TB development in human leukocyte antigen (HLA) and non-HLA genes like killer immunoglobulin-like receptor (KIR), toll-like receptors (TLRs), cytokine/chemokines and their receptors, vitamin D receptor (VDR) and SLC11A1 etc. Highly polymorphic HLA loci may influence antigen presentation specificities by modifying peptide binding motifs. The recent meta-analysis studies revealed the association of several HLA alleles in particular class II HLA-DRB1 with TB susceptibility and valuable marker for disease development especially in Asian populations. Case-control studies have found the association of HLA-DR2 in some populations, but not in other populations, this could be due to an ethnic specific association of gene variants. Recently, GWAS conducted in case-control and family based studies in Russia, Chinese Han, Morocco, Uganda and Tanzania revealed the association of genes such as *ASAP1*, *Alkylglycerol monooxygenase (AGMO)*, *Forkhead BoxP1 (FOXP1)*, *C-terminal domain phosphatase 1 (UBLCP1)* and intergenic SNP rs932347C/T with TB. Whereas, SNP rs10956514A/G were not associated with TB in western Chinese Han and Tibetan population. In this review, we summarize the recent findings of genetic variants with susceptibility/resistance to TB.

Keywords: *Mycobacterium tuberculosis*, genetic polymorphisms in TB, HLA genes, Non HLA genes, host genetics, cytokine and chemokine polymorphisms

INTRODUCTION

Tuberculosis (TB) remains a serious global health problem with approximately 5–10% latent tuberculosis infections (LTBI) individuals and among which 90–95% individuals will develop active tuberculosis infection. According to WHO Report 10.4 million new TB cases and 1.3 million deaths occurred in 2016 (1). Host genetic factors play an important role in determining inter-individual difference in susceptibility or resistance to infectious diseases including TB. However, the mechanisms involved in restriction of disease development in latent infection or lead to severe active disease are still largely unknown. Studies such as case-control, twin, candidate gene approaches, family-based and genome-wide association studies (GWAS) revealed the association of genetic factors with susceptibility or resistance to TB (2–8). Twin studies revealed higher

TB susceptibility rate in monozygotic twins than dizygotic twins or siblings (9, 10). Immune response to *Mycobacterium tuberculosis* (Mtb) involves several important genes such as human leukocyte antigen (HLA) and non-HLA genes like killer immunoglobulin-like receptor (KIR), toll-like receptors (TLRs), cytokine/chemokines and their receptors, vitamin D receptor (VDR), SLC11A1 and C-type lectins etc. Polymorphisms in these genes may regulate the expression and have a diverse influence on the susceptibility or protection against TB among particular families, ethnicities and races. The identification of host genetic markers will be useful to predict the development or predisposition to develop TB and understanding the immunopathogenesis of the disease. Moreover, protective HLA alleles to TB will be useful in new epitope based vaccine development. Several methodologies have been employed for genotyping different SNPs. The polymerase chain reaction (PCR) based methods has made possible to study HLA and non-HLA gene polymorphisms at DNA level. This molecular technology has gradually replaced the HLA serotyping and cellular typing methods which had several limitations compared to DNA based methods. The common methods are PCR based sequence specific primers (PCR-SSP), PCR based restriction fragment length polymorphism (PCR-RFLP), single-strand conformation polymorphism (PCR-SSCP), sequence-specific oligonucleotide (PCR-SSO) and single nucleotide polymorphism (PCR-SNP). Recently, exome sequencing, pyro-sequencing and next generation sequencing (NGS) technology has emerged as a simpler and more informative than classical molecular methods and employs DNA amplification followed by sequencing. In this review, we summarize the association of HLA and non-HLA gene polymorphisms in different ethnic populations and current advanced molecular methods for SNP genotyping.

GENETIC VARIANTS AND TB ASSOCIATION

Mendelian Susceptibility to Mycobacterial Diseases (MSMD)

Mendelian susceptibility to mycobacterial diseases is a clinical disorder in whom familial susceptibility to mycobacterial disease is observed. It is characterized by a narrow vulnerability to poorly virulent mycobacteria, such as bacillus Calmette-Guérin (BCG) vaccines and environmental mycobacteria. Only about half of patients with MSMD have an identified genetic cause. The pattern of heritability differs according to the gene affected and the specific genetic lesion. Nine genes are known to be responsible for MSMD. Seven of them are inherited in an autosomal recessive or autosomal dominant pattern IFNGR1 (OMIM 209950, 615978, 600263, 610424, 607948; 6q23.3), IFNGR2 (OMIM 614889; Chr21q22.11), STAT1 (OMIM 614892, 613796, 614162; Chr2q32.2), IL12RB1 (OMIM 614891, Chr19q13.11), IL12B (5q33.3), IRF8 (OMIM 614893-4; Chr16q24.1), ISG15 (OMIM 61626; Chr1p36.33), TYK2 (OMIM 611521, Chr19p13.2) and 2 less severe X-linked (IKBG/NEMO (OMIM 300636, ChrXq28) and CYBB (also known as p91-phox, OMIM 306400, 300545; ChrXp21.1-p11.4) recessive mutations

(11–19). The genes implicated in MSMD have frequently been studied through linkage and candidate gene studies which cumulatively indicate that genes involved in MSMD do not appear to account for non-familial cases of TB (20).

Candidate Gene Studies

Candidate gene studies includes SNPs in a specific gene, which implicated to association with particular disease.

Human Leukocyte Antigen (HLA)

Human leukocyte antigen is the most polymorphic loci located in chromosome 6 of the human genome. Polymorphisms in Class I and Class II genes may alter the binding affinity of antigens which could lead to impaired antigenic presentation to CD4+ and CD8+ T-cells. Among the class I and class II alleles HLADRB1 is the most associated with TB susceptibility/protection. A meta-analysis conducted in China reported that DRB1*03 and DRB1*07 may provide protective effects against TB susceptibility (21). Another meta-analysis of 31 studies revealed the association of HLADRB1 *04, *09, *10, *15, and *16 with TB risk, particularly in East Asian population while HLADRB1* 11 associated with protective to TB (22). In Uganda study, HLA-DQB1*03:03 allele was associated with protection to TB (23). In contrary, Amazon Brazilian population DRB1*04:07:01, DRB1*04:11:01, and DRB1*04:92 of the HLA-DRB1*04 associated with susceptibility to TB (24). A recent study conducted among 682 TB patients and 836 healthy controls in Thailand reported that HLA-DRB1*09:01 and HLA-DQB1*03:03 alleles were associated with TB susceptibility in patients infected with modern Mtb strains and suggested strain specific susceptibility to TB (25). In general, meta-analysis and other recent studies suggested the inconsistent results among different ethnic groups this could be due to population heterogeneity and small sample size. Hence well-designed studies with larger sample sizes are needed to confirm HLA association in TB. Various HLA studies in different ethnic populations given in Table 1.

Toll Like Receptors (TLRs)

TLRs are pattern recognition receptors play an important role in host innate immune responses and activate adaptive immunity by inducing production of inflammatory cytokines and antimicrobial molecules by T helper (Th1) cells in response to Mtb infection (75–77). Different TLRs such as TLR-2, 4, 8, and 9 play an important role in Mtb infection (78). Among the 10 TLRs, TLR2 and TLR4 interact with mycobacterial lipoprotein and whole live Mtb to mediate immune responses (79, 80). Association with TB was reported in several studies and found diverse among various ethnic groups (81, 82). In a case-control study conducted in a South African population investigated 23 polymorphisms in TLR genes. The results suggested the association of TLR8 polymorphism (rs3761624A/G) with TB susceptibility in females compared to males. Whereas, inTLR1 (rs5743618G/T) and TLR8 (rs3764879C/G and rs3764880A/G) both sexes were associated with susceptibility to TB (83). A study conducted in Pakistani population, TLR8 “G” allele (rs3764880A/G) associated with susceptibility to TB and with

TABLE 1 | Association between HLA and TB in different ethnic population.

Ethnicity/Country	Allele/Haplotype	Association	Sample size		References
			HCs	TB	
Asian/India	HLA-DR2	Susceptibility	287	143	(26)
	HLAB*57	Protective in female HIV patients	682	238	(27)
	HLA-DRB1*1501 and DQB1*0601	Susceptibility	87	126	(28)
	DPB1*04	Protective			
	DRB1*1501	Susceptibility	46	20	(29)
	DRB1*1501-DRB5*0101-DQA1*0103-DQB1*0601(Haplotype)	Susceptibility			
	HLA-DR2	Susceptibility	289	153	(30)
	DRB1*1501 and DRB1*1502				
	A2	Susceptibility	329	153	(31)
	B18	Protective			
	HLA-DRB1*14, DQB1*0503 and DQB1*0502	Susceptibility	–	–	(32)
	DRw6	Protective	109	124	(33)
	DR2	Susceptibility	–	25	(34)
	A1- like supertype	Protective	289	235	(35)
	A3- like supertype	Susceptibility			
	HLA-DRB1*15	Susceptibility	178	210	(36)
	A*24-B*40-DRB1*15				
HLA-DRB1*16	Protection				
A*02-B*40-DRB1*16 and A*02-B40-DRB1*03					
Asian/India	HLA-DR2 DQ1	Susceptibility	122	209	(37)
	DRB1*1501(DR2)	Susceptibility (inverse correlation to lymphocyte proliferation response)	36	72	(38)
		Downregulation of perforin positive CTL and NK cells			(39)
	Haplotypes	Susceptibility to TB in HIV			(40)
	HLA-DRB1*1502-DPB1*0201				
	HLA-DQB1*0601-DPB1*0201				
	HLA-DRB1*1502-DQB1*0601-DPB1*0201				
	HLA-A11,1101	Protective to HIV and HIV-TB			(41, 42)
	HLA-B40, 4006	Susceptibility to HIV and HIV-TB			
	HLA-DR2	Susceptibility to HIV and HIV-TB			
	HLA-DRB1*1502	Susceptibility to HIV-TB			(41)
	HLA-DQB1*050301	Susceptibility to HIV and HIV-TB			
	HLA-DPB1*1501	Protective to TB and HIV-TB			
	HLA-DRB1*13, HLA-DRB5 and HLA-DQB1*06	Susceptibility to TB in HIV	50	50	(43)
	HLA DQB1*02	Protective to TB in HIV			
HLA-B*15	Susceptibility to TB in HIV				
HLA-B*51	Protective to TB in HIV				
Asian/China	HLA-DR,DQ	Susceptibility to bone TB	88	86	(44)
	HLA-DRB1 * 15	Susceptibility	90	74	(45)
	HLA-DRB1 * 11	Protective			
	DRB1 * 09	Susceptibility to PTB with type2 diabetes mellitus	46	123	(46)
	DQB1 * 05	Protective to PTB with type2 diabetes mellitus			
	DR1 and DR13.3	Protective to PTB	101	110	(47)

(Continued)

TABLE 1 | Continued

Ethnicity/Country	Allele/Haplotype	Association	Sample size		References
			HCs	TB	
	HLA-DR and DQ	Susceptibility	146	146	(48)
	HLA-DRB	Susceptibility	62	97	(49)
					(50)
	HLA-DRB1	Susceptibility	105	80	
	HLA-DRB1	Susceptibility	231	226	(51)
	HLA-DRB1, DQA1 and DQB1	Susceptibility	189	176	(52)
	HLA-DRB1*04 and HLA-DQB1*0201	Susceptibility	230	231	(53)
Asian/Korea	DRB1*0803 and DQB1*0601	Susceptibility	200	160	(54)
Asian/Combodia	HLA-DQB1*0503	Susceptibility	88	126	(55)
African/ SouthAfrica	DRB1*1302	Susceptibility	117	95	(56)
	DRB1*1302- DQB1*0602/3(Haplotype) DQB1*0301-0304(Phenotype) DQB1*0301- 0304/DRB1*1101-1121(Haplotype) DRB1*1101-1121-DQB1*05(Haplotype)				
African/Uganda	HLA-DQB1*03:03		42	43	(23)
Caucasian/ Mexico	DQA1*0101,DQB1*0501 and DRB1*1501	Susceptibility	95	50	(57)
	DQB1*0402, DR4 and DR8	Protection			
Caucasian/Iran	HLA-DRB1*07 and HLA-DQA1*0101	Susceptibility	100	40	(58)
	HLA-DQA1*0301 and 0501 A26 and B27 B17 and DR14	Protective Protective Susceptibility	108	44	(59)
Caucasian/Syria	DRB1*04 DRB1*11	Susceptibility Protective	209	147	(60)
Caucasian/ Portugal	HLA-DRB1*14	Susceptibility	82	92	(61)
Caucasian/Greek	HLA-A R ¹¹⁴ and HLA-DRβN ³⁷ (Aminoacid poly)	Susceptibility	46	86	(62)
	HLA-A S ⁷⁷	Protection			
Caucasian/Brazil	HLA-A*02 and HLA-B*18	Protection	224	112	(63) (24)
Canadian/Canada	B8 HLA-A*03 and HLA-DQB1*05:03	Susceptibility Susceptibility	543 -	46 -	(64, 65)
Black American/United states	B5 and DR5 DR6	Susceptibility Protection	54	72	(66)

(Continued)

TABLE 1 | Continued

Ethnicity/Country	Allele/Haplotype	Association	Sample size		References
			HCs	TB	
Italian/Italy	DR4 or along with B14 A2+,B14-,DR4-	Susceptibility Protection	1089	122	(67)
Indonesian/ Indonesia	DR2 and DQw1 DQw3	Susceptibility Protection	64	101	(68)
Polish/Poland	DRB1*13	Protection	58	31	(69)
	DRB1*16	Susceptibility	58	38	(70)
	DRB1*05	Susceptibility	125	61	(71)
	DRB1*1601-DQB1*0502, DRB1*04-DQB1*03 and DRB1*14-DQB1*05 DRB1*11-DQB1*03	Susceptibility			
Thai/Thailand	HLA-DQB1*0502HLA-DQA1*0601 and DQB1*0301	Susceptibility Protection	160 836	82 682	(72) (25)
	HLA-DRB1*09:01 and HLA-DQB1*03:03	Susceptibility			
Soviet Union (six Ethnic groups) / Russia	DR2	Susceptibility	984	643	(73)
	DR3	Protection			
Iraqi Arab	HLA-B18 and HLA-DR1	Susceptibility	40	105	(74)
	HLA-B5 and HLA-DR8	Protection			

bacterial load. Moreover, this study revealed a strong association among males (84). In contrary, cohort study from Hyderabad, India reported that “A” allele of TLR1-248 Ser/Asn (rs4833095 G/A) associated with TB protection and evoke a better immune response by activation of TNF- α production and transcription factor NF- κ B in Mtb lysate infected peripheral blood mononuclear cells (PBMC) and human embryonic kidney (HEK) cells *in vitro* (85). Another case-control study from Lucknow, India reported that TLR2 [rs5743708A/G (Arg753Gln) and rs5743704A/C (Pro631-His)] polymorphisms were not associated with tuberculous meningitis (86). Whereas, a Chinese cohort study observed association of TLR2 rs3804099 T/C with susceptibility to tuberculous meningitis rather than with susceptibility to pulmonary TB (87). Another study conducted in Connecticut revealed the mechanism of TLR2 rs574370 (R753Q) polymorphism. The results suggested that R753Q polymorphism alters TLR2 signaling which leads to impaired MyD88-TLR2 assembly, downregulated IRAK-1 phosphorylation, diminished activation of MAPKs and NF- κ B, and deficient induction of cytokines in macrophages infected with *M. Smegmatis* (88).

In Ghana study, screened exons of genes encoding TLR 1, 2, 4, and the adaptor molecule TIRAP. The results revealed a significant strong association of TLR1 “TT” genotype (rs3923647 A/T (His305Leu) with TB protection. This is supported by increased production of IFN- γ in BCG-stimulated PBMCs of “TT” genotype positive individuals (89). Another study screened the TLR and TIRAP gene markers to predict latent tuberculosis infection (LTBI) and active disease in a Chinese population. The analysis revealed the association of TLR2 “CC” genotype (rs3804100C/T) and TLR9 “TC” genotype

(rs5743836) with LTBI susceptibility and TLR2 “GA” genotype (rs5743708A/G), TLR4 “GG” genotype (rs7873784C/G) and TLR8 “CC” genotype (rs3764879C/G) with susceptibility to pulmonary TB (90). In a Vietnamese cohort study in TLR9 polymorphism, rs352142G/T was associated with meningeal TB while rs352143A/G was associated with pulmonary TB (91). It has been reported that TLR4 rs4986790A/G (Asp299Gly) and rs4986791C/T (Thr399Ile) SNPs were associated with susceptibility to pulmonary TB in an Iranian population (92). Moreover, in Croatian population “AA” genotype of TLR10 SNP rs11096957A/C was found an increased risk with TB (93).

Vitamin D Receptor (VDR)

Vitamin D (Cholecalciferol) exerts its pleiotropic effects through the vitamin D receptor (VDR) which is present in the majority of the immune cells, including macrophages, B and T lymphocytes, neutrophils and DCs (94, 95). Vitamin D deficiency has been reported to be associated with TB susceptibility (96–98). Moreover, influence of vitamin D receptor gene variants on vitamin D modulated innate and adaptive immune response against Mtb has been reported. Association of VDR polymorphisms to TB susceptibility reported in several studies (99–101). In South Indian population reported that TaqI “tt” genotype associated with susceptibility to pulmonary TB in female patients, while BsmI “Bb” and FokI “FF” genotypes in male patients (102, 103). In the same population, the promoter polymorphisms Cdx2 G/A and A1012G revealed that genotype “GG” of Cdx2 associated with protection and haplotype A-A (A allele of Cdx-2 and A allele of A1012G) with susceptibility to pulmonary tuberculosis (104). Moreover, role in immune

regulation of VDR gene variants also explored. It has been reported that Cdx2 “AA” and TaqI “tt” genotypes regulate the chemokine mediated inflammatory responses in T-cell subsets (105, 106). In addition, Cdx-2 “GG” genotype and “baT” haplotype are associated with a suppressed Th1 and increased IL-10 response and BsmI “BB,” TaqI “tt,” and the extended genotype “BBAAtt” shown to be associated with increased expression of VDR which in turn regulate the vitamin D₃ modulated macrophage phagocytosis and lymphoproliferative immune functions to culture filtrate antigen of Mtb in healthy controls (107, 108). These studies suggested the anti-inflammatory effect of vitamin D which could be beneficial to avoid tissue injury and faster recovery during active TB disease. Whereas, in north Indian study TaqI “Tt” and “tt” genotypes associated with tuberculous meningitis compared with controls and pulmonary TB patients (87). In a Gujarati Indian population living in London, the *FokI* ff genotype was strongly associated with PTB (109). In a study carried out in the Gambian PTB patients, the *TaqI* “t” genotype was found less frequently in patients, suggesting that this genotype may be associated with resistance (110). A study from Turkey reported that the BsmI “B” allele was overrepresented in TB patients compared with healthy controls (111), whilst other studies have described prevalence of the “BB” genotype in TB (112). A meta-analysis study with 29 studies revealed that homozygote for the mutant allele of the *ApaI* polymorphism and heterozygote for the *BsmI* polymorphism appeared to have a protective role on tuberculosis development in European populations. The same study also revealed that *FokI* ff genotype is associated with a significantly increased risk of tuberculosis in Chinese population (113). In Iranian population no such association was found. However, vitamin D deficiency was strongly associated with TB susceptibility (114). In Han Taiwanese population, TaqI (rs731236), BsmI (rs1544410) and vitamin D binding protein (VDBP) polymorphisms were studied and reported that TaqI “AA,” BsmI “GG,” and VDBP “AA+AC” genotypes were found risk for development of TB (115). A meta-analysis carried out in 32 studies showed that *FokI* polymorphism associated with TB susceptibility in Asian population, in contrary, no association was found in Caucasian and African populations (100). Another meta-analysis of 16 studies revealed that *FokI* polymorphism associated with TB risk in East Asian population among different ethnicities. This indicates the association of *FokI* polymorphism with TB risk in Asia. In contrast, no association was found in TaqI, BsmI and *ApaI* polymorphisms among different ethnicities (101). Moreover a meta-analysis including 34 studies confirmed that in East and Southeast Asian populations, the homozygote model (ff vs. FF) and the recessive model (ff vs. Ff + FF) of *FokI* polymorphism associated with TB risk (116).

Killer-Cell Immunoglobulin-Like Receptor (KIR)

Killer-cell immunoglobulin-like receptors are the regulatory molecules expressed on natural-killer (NK) cells. It mediates linking of innate and adaptive immune responses by the production of cytokines and modulate NK cell activity through

stimulatory/inhibitory signals generated when ligands binds with KIR molecules on NK cells (117). KIR molecules are highly polymorphic and its diversity associated with TB outcome in different ethnic populations (118–120). It has been reported that the genotype AH and FZ14 may associated with Mtb clearance and haplotype B and haplotype A associated with susceptibility and protection with pulmonary TB (121). In Chinese Han population, 15 KIR activating and inhibitory genes were studied. The results shown that stimulatory genes such as *2DS1*, *2DS3*, and *3DS1* associated with resistance to pulmonary tuberculosis (122). Similar protective association was observed in stimulatory *3DS1* gene in South African colored population (123). In Lur population of Iran investigated KIR as well as KIR-HLA combinations to TB susceptibility. They found a significant decrease in KIR3DS1 as well as KIR3DS1 with HLA-B Bw4Ile80 ligand frequencies in TB patients compared with controls. This suggested the combination of KIR3DS1+HLA-B Bw4LLe80 with susceptibility to TB in this population (124). Another study conducted in Iranian individuals on 17 KIR genes and their three major HLA class I ligand groups (-C1, -C2 and -Bw4: -B Bw4 (Ile80), -B Bw4 (Thr80) and -A Bw4) showed no significant association with pulmonary TB (125).

Solute Carrier Family 11A Member 1 (SLC11A1)

Solute carrier family 11A member 1 also known as natural resistance-associated macrophage protein 1 (NLRP1) is a member of proton-coupled divalent metal ion transporters. Polymorphisms in this gene have been associated with tuberculosis, leprosy and other inflammatory diseases (126). Studies conducted in Japanese, Koreans, West Africans and South Africans reported that 3′ untranslated region Asn543Asp (G to A at codon 543, resulting in an aspartic acid to asparagine change) and (TGTG) deletion in the 3′ untranslated region (1,729 + 55del4) (rs17235416) polymorphisms were associated with TB susceptibility (127–129). Moreover, in Gambian and Guineans intron 4 (469 + 14 G/C) (rs3731865) polymorphism and (CA)_n repeat polymorphism in the immediate 5′ region among Gambians, Japanese, South Africans and Americans have also been reported to TB risk (128–132). The heterozygosity of CAAA insertion/deletion polymorphism of 3′UTR polymorphism associated with protection against TB in HIV positive and negative individuals in Karonga district of northern Malawi (133). Meta-analysis conducted in 14 case-control studies revealed that 3′UTR Asn543Asp (rs17235409) and 5′ (GT)_n polymorphisms were associated with susceptibility to TB (134). Another meta-analysis in China studied 3′UTR TGTG ins/del, D543N, INT4 (single nucleotide G to C change in intron 4) and (GT)_n in the 5′ promoter region of *SLC11A1* gene. The analysis revealed that “A” allele carriers of D543N, TGTG ins/del, “C” allele carriers of INT4 and another allele carriers of (GT)_n were associated with TB risk. Analysis stratified by ethnicity, subgroup of Asians found more susceptible to TB while an increased risk of extra-pulmonary TB was found for D543N polymorphism (135). Other studies in Chinese populations reported that deletion of TGTG in 3′UTR polymorphism TGTG+/del genotype

associated with susceptibility to TB (53, 136). In contrary, studies conducted in Taiwanese, South Indian and Turkish population no significant association was found in TB (137–139).

Cytokines and Its Receptors

Cytokines and chemokines are produced from various immune cells in response to external stimuli. They mediate its action through binding with specific receptors and modulate the immune functions. Polymorphisms in promoter as well as coding region of these genes may alter their transcriptional activation and its production. Studies have reported the association of altered cytokines/chemokines with susceptibility to infectious diseases including TB (140, 141).

Interferon-Gamma (IFN- γ)

IFN- γ is a Th1 type cytokine plays an important role in Mtb infections (142). In intron polymorphism of IFN- γ +874A/T, “T” allele and “TT” genotype associated with protection to tuberculosis in Sicilian and South African populations while associated with susceptibility in Pakistani population (143–145). In Spanish and Hong Kong Chinese population allele “A” and “AA” genotype associated with susceptibility to TB (146, 147). In contrary, no association was found in Turkish, Malawian, African American, Caucasian, Hispanics West African, South Indian and Chinese populations (148–153). Moreover, a meta-analysis study from Brazil reported the association of allele “T” with TB (141). In addition, polymorphisms in IFN- γ receptor genes have been reported in different ethnic population, but the results were inconsistent (154–159). Recently, 22 gene polymorphisms were studied in IFNGR1 and IFNGR2 gene among Korean TB patients, in which four IFNGR1 variants (rs9376269C/G, rs9376268A/G, rs9376267C/T, rs56251346C/T) were marginally associated with the risk of TB but not statistically significant (160). Another study analyzed 20 genes involved in IFN- γ signaling such as *IFNG*, *IFNGR1*, *IFNGR2*, *IRF1*, *IL12A*, *IL12B*, *IL12RB1*, *IL12RB2*, *IL23A*, *IL23R*, *IL27*, *EBI3*, *IL27RA*, *IL6ST*, *SOCS1*, *STAT1*, *STAT4*, *JAK2*, *TYK2*, and *TBX21* in a Ghanaian population but no significant result was observed in TB (20).

Interleukin-12 (IL-12)

Interleukin-12 mainly involved in T-cells into Th1 cells and induce the production of INF- γ from T-cells and NK-cells. The intron 2 polymorphism +1188 of IL12B in south Indian population no significant association was observed (152, 161). Similarly, in African American and White ethnicities, no association was found in the 3’UTR polymorphism of IL12B (162). The study carried out in two West African populations and South and North Americans revealed the association of 3’UTR polymorphisms of IL12B with TB risk in African ancestry (163). In Moroccan population *IL12RB1* gene was studied which encodes beta 1 chain of the receptor for interleukin (IL)-12 and involved in Mendelian susceptibility to mycobacterial diseases. The study reported that two polymorphisms –2C→ T and –111A→ T were associated with TB risk (164). Another study reported that in haplotypes of *IL12RB1* gene “allele 2” R214-T365-R378 and “ATGG” haplotype of (641A/G, 1094T/C, 1132C/G, 1573G/A) associate with TB susceptibility in the

Japanese population and this variation may diminish receptor response to IL-12 and IL-23 which may lead to downregulation of IFN- γ mediated immunity (165, 166). Among five SNPs studied in *IL12RB1* gene lack of association was found in Korean population (167).

Tumor Necrosis Factor- α (TNF- α)

Tumor necrosis factor- α is an inflammatory cytokine which mediates the recruitment of immune cells at the site of infection for granuloma formation during Mtb infection. Among the various ethnic populations, the promoter gene polymorphisms of TNF- α [–238 (G/A), –308 (G/A), –376 (G/A), –592 (A/C) and –819 (C/T)] were not associated with TB risk in South Indian, Chinese and Cambodian populations (153, 168, 169). However, in Sicilian and Colombian populations protective associations were found in TNF- α –308 (G/A) and haplotype combination of –308A–238G polymorphisms (170, 171). In contrary, TNF- α [–308 (G/A)] variants associated with pulmonary TB susceptibility in Iranian population (92). In a meta-analysis study four TNF- α polymorphisms rs1800629G/A (–308G/A), rs1800630C/A (–863C/A), rs1799724 (–857C/T) and rs361525G/A (–238G/A) were analyzed among 18 studies. The results showed that in all study participants allele “G” and “GG” genotype of –308G/A and –238G/A polymorphisms were associated with pulmonary TB risk. When the analyses were performed among ethnicity –308G/A variant was associated with pulmonary TB in Asians, while –238G/A variant was associated with pulmonary TB in African individuals (172).

IL-2

In South Indian population IL-2–330 T/G and +160 G/T polymorphisms were studied; the results reported that “TT” genotype associated with protection toward pulmonary TB (152). The similar protective effect was observed in allele “T” and “TT” genotype was observed in IL-2–330 T/G polymorphism in Russian study (173). Whereas, the haplotype combination of IL-2 330 G+160 G associated with protection with TB in Iranian population (174).

IL-4

The promoter polymorphisms of IL-4–590T/C, –1098G/T, and –33C/T were studied in Iranian population and found no association to TB (174). In the 5’UTR variant IL4 rs2070874(C/T), “T” allele associated with two fold risk of TB in North Indians (175). In the South Indian study, the promoter IL-4-590C/T and VNTR polymorphisms were studied. The results revealed that –590 “T” allele associated with susceptibility and “CC” genotype with protection to pulmonary TB. The lack of association was observed in VNTR polymorphism (152, 176). The same promoter polymorphism of IL-4 allele “C” and “CC, “CT” genotypes associated with TB in Russian population (173).

IL-6

In Colombian and South Indian populations no significant association was found in the IL-6 promoter –174(G/C) polymorphism (152, 177) while in Iranian and Canadian populations allele “G” and “GG” genotype associated with

TB susceptibility (174, 178). Another study reported that the combinations of “TT-GG” of IFN- γ +874(T/A) and IL-6–174(G/C) polymorphisms associated with TB risk while combinations of “AA-GC” associated with protection to TB (179).

IL-10

The promoter polymorphism of IL-10–1082(G/A) was studied in Cambodian and Sicilian populations, the results found that the allele “A” carriers was associated with TB risk, whereas in Turkish population the haplotype combinations “GCC” and “ACC” of IL-10–1,082 G/A,–819 C/T,–592 C/A polymorphisms were associated with susceptibility and protection to TB (169, 170, 180). In Colombian population “AA” genotype reported to be associated with pleural TB (177). In promoter IL-10–819C and–592C reported to be associated with TB risk in Turkish population (181). Another study reported that genotypes “GG” and “GA” of IL-10–1082 associated with TB (182). Moreover, the diplotype “AT/CC” of IL-10 (1800872/1800871) polymorphisms associated with TB risk in an Amerindian population (183). In contrary, no association was found in South Indian, Chinese, Turkish, Gambian and Spanish populations (152, 153, 161, 180, 184–186). Other candidate genes such as *chemokines*, *DC-SIGN* (*CD209*) and *Mannose binding lectin-2* (*MBL-2*) associated with TB given in **Tables 2–4**.

Mannose Receptor (CD206)

Mannose receptor or MRC1 is a type I transmembrane C-type lectin expressed on macrophages and dendritic cells. It recognizes ligands such as mannose-N-acetylglucosamine- and fucose-terminated glycoconjugates which includes lipoglycan and mannose-capped lipoarabinomannan (ManLAM). The binding of ManLAM leads to stimulation of a nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR- γ) and triggers anti-inflammatory immune response (222). Polymorphisms may affect the expression level and its structure and function which may lead to susceptibility to pulmonary tuberculosis. In Chinese population, six SNPs (G1186A, G1195A, T1212C, C1221G, C1303T, and C1323T) in exon 7 of the MRC1 gene was studied. Genotypic analysis revealed that the AG genotype of G1186A (rs34039386) polymorphism was significantly correlated with pulmonary tuberculosis (223). Another study investigated SNPs in exon 7 of MRC1 gene in 595 Chinese Uygur and 513 Kazak subjects. In the Uygur, the frequency of allele G ($P = 0.031$, $OR = 1.29$, $95\% CI = 1.02–1.62$) and AA genotype ($P = 0.033$, $OR = 1.64$, $95\% CI = 1.04–2.60$) for G1186A was lower in the pulmonary TB than healthy control and associated with pulmonary TB (224). Recent studies carried out in four functional MBL gene polymorphisms (HL, XY, PQ, and AB) found that individuals carrying BB/AB genotypes were associated with increased susceptibility to TB. Moreover, LYPB haplotype showed a significant association with increased risk of TB among Chinese population (225). Whereas, in Iranian Lur population MBL H allele and HH genotype significantly associated with increased susceptibility to TB (226).

IL-17

IL-17 is a potent pro-inflammatory cytokine produced by activated T-lymphocytes and has a critical role in the immunopathology of TB. During primary Mtb infection, IL-17 induces the expression of chemokines that promote cell recruitment and granuloma formation. A balance between Th1 and Th17 responses is essential to control bacterial growth and limit immunopathology. The response toward excessive IL-17 production may cause excessive neutrophil recruitment and tissue damage. Thus, regulated immune response is essential to promote anti-mycobacterial immunity and prevent excessive immunopathological consequences (227). In china, a meta-analysis carried out for IL-17A rs2275913, rs3748067 and rs3819024; and IL-17F rs763780 polymorphisms in case-control studies published up to July 2017 involving 4,961 TB patients and 5,435 healthy controls. The results revealed that the rs2275913 polymorphism was associated with decreased TB risk in Caucasians under the allelic model (A vs. G, $OR 0.69$, $95\% CI 0.49–0.96$; $p = 0.03$), heterogeneous model (AG vs. GG, $OR 0.67$, $95\% CI 0.47–0.93$; $p = 0.02$) and domain model (AA+AG vs. GG, $OR 0.64$, $95\% CI 0.44–0.93$; $p = 0.02$). Whereas, rs3748067 was associated with increased TB risk in Asians under the homogeneous model (TT vs. CC, $OR 1.36$, $95\% CI 1.03–1.79$; $p = 0.03$) and recessive model (TT vs. CT+CC, $OR 1.35$, $95\% CI 1.02–1.78$; $p = 0.03$) (228).

GENOME-WIDE ASSOCIATION STUDIES

Genome-wide association studies (GWAS) is a hypothesis-free methodology which powered to identify variants that have a frequency of $>5\%$. Five GWAS studies reported earlier, first study conducted in the Gambia and Ghana in 3,632 pulmonary TB patients and 7,501 healthy controls and confirmed that polymorphism in rs4331426 in Chr18q 11.2 was associated with pulmonary TB (5). Further, in Indonesian and Russian cohorts study identified the second variant associated with TB in rs2057178 on Chr11p13 in 13,859 PTB and 8,821 controls (6). The similar Chr11p13 variant association was studied in South African colored population, but not identified any loci associated with TB (229). The Russian study also identified a TB association in 11 SNPs in *ASAP1* gene in Chr8q24of5, 530 cases and 5,607 controls. Among the 11 SNPs, seven were more significant association with TB while these were found less common in Ghanaian and Gambian populations compared with Russian population. Moreover, this study demonstrated that “A” allele of SNP rs10956514 (A/G) alter *ASAP1* levels in dendritic cells (230). In a replication study conducted in 1115 western Chinese Han and 914 Tibetan population, no association was found in *ASAP1* rs10956514 (A/G) to TB risk (231). Family-based association tests (FBATs) performed in Morocco revealed significant association of 143 SNPs. Among them four SNPs were significantly associated with pulmonary TB during the replication phase with 317 TB and 650 healthy controls. These SNPs are rs916943C/T in the *AGMO* (alkylglycerol monooxygenase) gene, rs358793A/G located near the *WNT5A* (Wingless-Type MMTV Integration Site Family, Member 5A) gene, rs17590261C/T located near the *PCDH10* (Protocadherin

TABLE 2 | Association of DC-SIGN polymorphisms among different ethnic populations.

DC-SIGN gene polymorphisms	Population/Country	Allele/haplotype	Association	Sample size		References
				HCS	TB	
–871(A/G)	South African	–871G	Protection	360	351	(187)
–336(A/G)		–336A				
–939(G/A)	Indonesian	GG vs. GA+AA	Protection			(188)
	Vietnamese		No association			
–336(A/G)	South Indian	–336GG	Susceptibility to PTB in HIV	157	107	(189)
	African	–336G	Protection	914	1,262	(190)
	Asian	–336GG	Susceptibility	3,610	3,539	(191)
	Asian	–336GG	Susceptibility	3,088	3,114	(192)
		–871G	Protection			
–336(A/G)	Spanish		No association	299	110	(193)
DC-SIGNR VNTR	Iranian		No association	161	171	(194)
–336(A/G)	West African		No association	347	321	(195)
139(A/G)						
–336(A/G)	Chinese		No association	2614	2598	(196)

DC-SIGN, Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin.

10) gene and rs6786408A/C in the *FOXP1* (ForkheadBox P1) gene TB (232). Moreover, this study confirmed the association of SNPs (rs2057178C/T, rs11031731A/G, rs4331426 A/G) with TB (5, 6, 230, 232). The biological significance of most of the identified SNPs are unknown, however *AGMO* rs916943 C/T and *FOXP1* rs6786408 A/C were involved in macrophage functions (232). In Uganda and Tanzania, GWAS was conducted in 267 HIV-positive individuals who developed active TB and 314 HIV patients without active TB symptoms. The study identified one SNP in rs4921437 C/T which located 51 kb downstream from 3'UTR of *IL-12B* gene and found to be associated with protection to TB (233). Further analysis reported that this SNP was in strong linkage disequilibrium (LD) with rs10515780 C/G variant and both are located in the intron of ubiquitin-like-domain-containing C-terminal domain phosphatase 1 gene (*UBLCP1*) and in an H3K27Ac histone active enhancer which are involved in the regulatory mechanism (233). Recent genome-wide association study (GWAS) of 6,465 *Mycobacterium tuberculosis* clinical isolates from more than 30 countries characterized genetic determinants of resistance to anti-tuberculosis drugs. This study identifies high-quality genome wide SNPs, indels and large deletions across all samples. Phenotypic analysis revealed that 31.2% of isolates were resistant to at least one drug, with 15.1% categorized as MDR-TB and 4.3% categorized as XDR-TB. It also identified drug resistance loci such as *folC*, *ubiA*, *thyX-hsdS.1*, *thyA*, *alr*, *ald* and *dfrA-thyA*, new epistatic relationships, such as *pncA* with *pncB2* and *thyA* with *thyX-hsdS.1*) and efflux pumps represented by the ABC transporters *rrrA* and *Rv2688c*. The novel genetic markers identified with resistance were SNPs in the *ethA* and *thyX* promoters. Besides SNPs, novels markers were found in small indels in *pncA* and *ald* and large deletions in prodrug activators such as *ethA* and *katG*. Most small indels were 1 bp in length and caused frameshifts and indels in *rpoB*, *pncA* and *embAB* promoter region were associated with MDR-TB and XDR-TB. It has been found that indels were distributed throughout the gene lengths; however, there was some evidence

of areas of higher density, such as the *pncA* region between codons 130 and 132 and the codon 427–434 region in *rpoB*. In large deletions in *katG*, *ethA* and *pncA* genes activate prodrugs and none are essential to Mtb survival. These deletions occurred independently in different phylogenetic tree and are likely offer an alternative route to resistance as compared to SNPs, across lineages and populations. This implies that regional variation should be considered to fully characterize genotype–phenotype relationships. The associations identified may enlighten the molecular mechanisms underlying drug resistance and help in the development of novel antibiotics (234). Overall, GWASs identified certain loci associated with TB susceptibility and protection which needs to be confirmed with other ethnicities.

CURRENT GENOTYPING METHODS

Newer sequencing methods such as pyro-sequencing, exome and whole-genome sequencing are able to detect rare variants with frequency <1% to TB susceptibility and gives higher resolution of SNP genotyping. Whole exome sequencing, is a transcriptomics technique for sequencing all of the protein-coding genes in a genome known as the exomes which constituting about 1-2% of the human genome. This method is effective in the study of rare Mendelian diseases. The major advantage is to identify genetic variants that alter protein sequences at a much lower cost. A pilot study was conducted to evaluate exome sequencing to detect markers for TB susceptibility between active TB and latent TB. They identified 1,611 SNPs different from latent TB using the Sure Select kit while 182 SNPs were identified in TB not in latent TB individuals using TruSight kit (235). However, this study needs to be done in larger sample size. Whole genome sequencing method is useful to study the frequency of different mutations with Mendelian disorders in whole human genome. Similarly, RNA-sequencing method useful for enhanced resolution of transcripts and transcript variants, but the cost of RNA sequencing relatively high.

TABLE 3 | Chemokine gene polymorphisms in various ethnic populations.

Chemokine gene polymorphisms	Population/Country	Allele/Haplotype	Association	Sample size		References
				HCs	PTB	
IL-8 -251 (T/A)	Whites/USA	-251 "A"	Susceptibility	107	106	(197)
	African American	-251 "T"	Protection	167	180	(183)
	Paraguayan South		No association	- 124	96	(198)
	Indian			320	127	(199)
MCP-1 (CCL2) -2518(G/A)	Gambian				360	
	Mexican	"GG" and "AG"	Susceptibility	518	435	(200)
	Korean			162	129	
-2362C	Brazilian		No association	-	627	(201)
	Moroccan	-2518GG	Protection	-	-	(202)
	West African	2362C	Protection	2300	2000	(203)
RANTES (CCL5) -403(G/A) -28(C/G) ln1.1 (T/C)	Chinese	A-C-T, G-C-C (Haplotype) Diplotypes (-403&ln1.1) GA/TT; GG/TC	Susceptibility	465	412	(204)
	Tunisian	-28GG G-G, A-C (Haplotypes) AG/GC (diplotypes) Of-403&-28		150	168	(205)
	South Indian	A-C-C (haplotype) G/A-T/C (diplotype)	Protection	213	212	(206)
	North Indian	-403G/A	Susceptibility	215	215	(207)
	Sudanese	-28G		206	191	(208)
	Mexican Korean		No association	518	435	(200)
	MIP-1α (CCL3) -459(C/T)					
MIP-1β (CCL4) Rs1634514(T/A) Rs1719144(G/A)	Brazilian	rs1634514T rs1719144A	Susceptibility	-	627	(201)
	Brazilian	rs2015086C rs2015070A rs14304A	Protective	-	627	(201)
CCL18 rs2015086(T/C) rs2015070(G/A) rs14304(G/A)						
IP-10 (CXCL10) -135(G/A) -1447(A/G) -872(G/A)	Chinese		Susceptibility No association	176	240	(209)

HOST GENETICS AND TUBERCULOSIS TREATMENT

Studies have studied the clinical impact of genetic factors in TB treatment. In china, anti-tuberculosis drug-induced hepatotoxicity (ATDH) was studied. The *in vivo* study shown to be associated with silent information regulator 1 (SIRT1), however the SNPs rs7069102C/G, rs2273773C/T, rs4746720C/T were not associated with ATDH (236). Some studies reported the bioavailability of TB drugs among different gene variants of Solute Carrier Organic Anion Transporter Family, Member 1B1 (SLCO1B1). Rifampicin activity depends on its concentration against Mtb. The study evaluated multidrug intensive-phase therapy in 72 adults with PTB from Africa, North America and Spain. The results were compared with 16 healthy controls from North America. Another study conducted in

60 TB patients of South African populations. Both the study results revealed that SNPs rs4149032C/T and rs11045819A/C were associated with lower concentrations and bio-availability of rifabutin (237, 238). In African 35 HIV positive TB patients, reduced rifabutin concentration was observed in SNPs rs4149032C/T, rs4149056C/T and rs2306283C/T, while 30% increased concentration of rifabutin was observed in heterozygous rs11045819 "AC" genotype compared to those with the homozygous rs11045819 "CC" genotype. The results suggested that SLCO1B1 polymorphisms may serve as a biomarker for the response to TB treatment (239). A GWAS conducted in Ethiopian patients with drug induced liver injury (DILI) and 354 anti-tuberculosis drug (ATD) tolerant patients and correlated with several SNPs. The replication phase was conducted in 27 DILI cases and 217 ATD tolerant individuals. The results shown association of the seven SNPs,

TABLE 4 | Association of MBL gene polymorphisms in different ethnic populations to TB.

MBL2	Population/Country	Allele/Haplotype	Association	Sample size		References
				HCS	PTB	
Exon1 (Codon 52, 54 and 57)	South Indian	Mutant homozygous	Susceptibility	109	202	(210)
Exon 1, codon-52 -221Y/X	Chinese	Heterozygous	Susceptibility	198	125	(211)
	South Indian	O/O genotype YA/YA diplotype	Susceptibility Susceptibility to TB in HIV	146	148	(212)
Codon 54, 57	Turkish	AB genotype	Protection	99	27	(213)
Exon 1 -550(H/L) -221(X/Y) +4(P/Q)	Italian	HYA-HYA (Haplotype) LYB-LYD (Haplotype)	Protection Susceptibility	288	277	(214)
Exon 1 Codon54(A/B) -221(Y/X)	Indian	B' allele	Protection	392	286	(215)
Exon 1 Codon57(A/C)	Brazilian	X/Y genotype 'O' allele 'C' allele and 'AC' genotype	Susceptibility Susceptibility Susceptibility	148	155	(216)
Exon1 codon 54(A/B) +4 (P/Q)	Chinese	54 'B' allele +4 'P/Q'	Susceptibility No association	1190	1106	(217)
rs7096206(C/G)	Chinese	'CG' genotype 'TC' genotype 'TC' genotype	Susceptibility	216	205	(218)
rs6695096(T/C) rs2273346(T/C)			Susceptibility Susceptibility	419	503	(219)
-550 (H/L) Codon 52 (A/B) +4 (P/Q) -221 (X/Y)	Chinese	HL genotype HPYA, LPXA, LQYA & LPYB (Haplotypes)	Protection Susceptibility	453	151	(136)
Exon 1 (Codon 54 and 57)	Turkish		No association	50	50	(139) (220)
Exon1 Codon 52,54 and 57	West Africa		No association	2346	2010	(221)

MBL, Mannose binding lectin.

such as rs10946737A/G, rs10946739C/T (close to FAM65B), rs320035A/G, rs393994C/T, rs320003A/G, rs319952C/T (close to AGLB4), and rs7958375A/G (close to CUX2) with ATD-induced liver toxicity (240). Polymorphisms in *CYP2E1* gene and its association with drug-induced liver disease (DILI) were studied in Indonesian TB patients. The results observed the association of rs3813867 "GG" genotype with an increased risk of DILI incidence (241). Polymorphism of NAT2 is associated with large inter-individual and inter-racial differences in the toxicity and efficacy of isoniazid. A study reported the safety and efficacy of a pharmacogenetics-based standard TB therapy for latent TB infection (LTBI) using NAT2 genotyping. This polymorphism shown to confer reduced acetylation of isoniazid, which results in higher drug levels and stratifying therapy based on NAT2 status reduces adverse outcomes (242). These studies suggested that host genetics play an important role in TB therapy and newer approaches needs to be emerge like host-directed immune-therapy, which have the potential to shorten the TB treatment, prevent resistance by promoting autophagy, antimicrobial peptide production by macrophages and other effector mechanisms. Several agents are in evaluation in phase II trials that could improve TB treatment outcome (243).

CONCLUSION

Genetic factors involved in TB pathogenesis are polygenic, these factors may be helpful to identify disease markers for

development or predisposition to TB. Overall, studies suggested that genetic markers identified in one population not consistent with other population due to ethnic variation. Moreover, these controversial results may also due to sample size and large degree of heterogeneity in study design. In addition, the biological functions of most of the identified markers using different methodologies have remained unknown. Hence, well designed work with large sample size and improved methodologies like exome sequencing, pyrosequencing and next generation sequencing (NGS) may provide high resolution information needed to provide a consistent genetic marker for TB disease. Moreover, genetic factors may play an important role in TB therapy and newer approaches needs to emerge to shorten the TB treatment.

AUTHOR CONTRIBUTIONS

MH contributed to the review of literature, drafting and revising the manuscript, concept and design. PS and RB contributed to conception of idea, design and revision of the manuscript.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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