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Genetic susceptibility in tuberculosis

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ABSTRACT

The importance of host genetic factors in determining susceptibility to tuberculosis (TB) has been studied extensively using various methods, such as case-control, candidate gene and genome-wide linkage studies. Several important candidate genes like human leucocyte antigen/alleles and non-human leucocyte antigen genes, such as cytokines and their receptors, chemokines and their receptors, pattern recognition receptors (including toll-like receptors, mannose binding lectin and the dendritic cell-specific intercellular adhesion molecule-3 grabbing nonintegrin), solute carrier family 11A member 1 (formerly known as natural resistance-associated macrophage protein 1) and purinergic P2X7 receptor gene polymorphisms, have been associated with differential susceptibility to TB in various ethnic populations. This heterogeneity has been explained by host–pathogen and gene–environment interactions and evolutionary selection pressures. Although the achievements of genetics studies might not yet have advanced the prevention and treatment of TB, researchers have begun to widen their scope of investigation to encompass these practical considerations.

Key words: cytokine, gene polymorphism, human leucocyte antigen, solute carrier family 11A member 1, tuberculosis.

INTRODUCTION

Host genetic factors explain, at least in part, why some people resist infection more successfully than others and play a major role in determining differential susceptibility to major infectious diseases. The importance of host genetic factors on genetic susceptibility to various infectious diseases has been reviewed.[1–3] The association of host genetic factors with susceptibility or resistance to tuberculosis (TB) has been studied extensively using various methods, such as case–control studies, candidate gene approaches and family-based, genome-wide linkage analyses that have revealed several important candidate genes for susceptibility.[3–5] The present review provides information that supplements the existing reviews on human genetic susceptibility to TB.

HOST GENETIC FACTORS AND TUBERCULOSIS SUSCEPTIBILITY/RESISTANCE

Tuberculosis, caused by *Mycobacterium tuberculosis* infection, remains a major cause of morbidity and mortality around the world.[6] It is estimated that one-third of the world's population is infected with *M. tuberculosis*. Among those putatively infected only around 10% will ever develop clinical disease.[7,8] In 1926, the accidental administration of live *M. tuberculosis* (in place of Bacillus Calmette-Guérin) to babies in Lübeck, Germany left some babies unaffected but led to severe disease and death in others.[9] This indicates that the majority of the population has effective innate resistance to TB. On the other hand, twin studies show an increased concordance rate among monozygotes (60%) compared with dizygotes (20%) indicating a genetic component to susceptibility.[10]

The identification of host genetic factors, such as human leucocyte antigens (HLA) of major histocompatibility complex and other non-major histocompatibility complex genes/gene products that are associated with susceptibility or resistance to TB, may provide genetic markers to predict the development or predisposition to develop TB. Those HLA types that are associated with protection from TB will be useful in the development of a new epitope-based vaccine. Clarification of the role of these markers in the immune mechanisms underlying susceptibility or

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resistance to TB will be useful in understanding the immunopathogenesis of the disease.

HUMAN LEUCOCYTE ANTIGENS AND TUBERCULOSIS SUSCEPTIBILITY

Human leucocyte antigens, with its ever-increasing allelic diversity (2496 and 1032 class I and II alleles, respectively, as of June 2009),[11] is the most polymorphic loci in the human genome. HLA class I molecules present pathogenic peptides to CD8+ T cells, while class II molecules display them to CD4+ T cells. The search for genetic determinants associated with differential susceptibility to TB infection has long been sought in the HLA region, due to its prime role in antigen presentation and the generation of effective immune responses to curtail infection. A large number of HLA association studies[12–43] have been carried out and some are summarized in Table 1.

Racial differences in susceptibility to TB are well known. Several studies have shown an association between various HLA antigens and disease susceptibility in different ethnic populations.[12–17] Hypotheses have been proposed to explain this geographic variation. It seems likely that evolutionary selection pressures have given rise to frequent polymorphisms in the genes involved in resisting infectious pathogens and so contributed to marked differences in allele frequency at the same loci. When geographic variation in pathogen polymorphism is superimposed on host genetic heterogeneity, considerable variation may occur in allelic associations. Gene–environment interactions are likely to introduce another layer of complexity. The genes involved in the defence against infectious pathogens evolve more rapidly than others and excessive polymorphism in the human genome may result from selection pressures exerted by infectious diseases. The causative organism, *M. tuberculosis,* also has genetic variation. All these polymorphic forms might have evolved over time due to host–microbial interaction.[3]

ASSOCIATION OF HLA-DR2 WITH SUSCEPTIBILITY TO TUBERCULOSIS IN ASIAN POPULATIONS

Earlier studies on the serological determination of HLA-DR antigens in TB reported an association between progressive TB and HLA-DR2 in populations from India, Indonesia and Russia.[18–23] The association of HLA-DR2 with susceptibility to TB has been consistently observed across ethnic boundaries. Molecular typing of HLA-DR2 at the allelic level showed that the frequency of the allele DRB1*1501 was higher than that of DRB1*1502 in north Indian patients, and it has been suggested that the DR2 association was stronger in patients with drug failure.[22] Studies carried out in south Indian patients revealed the positive association of HLA-DRB1*1501[24,25] and HLA-DQB1*0601 (a subtype of HLA-DQ1) with susceptibility to pulmonary TB.[24] A meta-analysis to estimate the association between TB and HLA antigens based on reported case–control studies that used serological HLA typing indicated a lower risk of thoracic TB in carriers of HLA-B13, DR3 and DR7 antigens and a higher risk for HLA-DR8-positive individuals.[26] However, this analysis also suggested an inconsistent positive association between HLA-DR2 and thoracic TB.

Associations with HLA gene polymorphisms appear insufficient to explain the range of variation in immune responses to vaccines and to infections by major pathogens like *M. tuberculosis*. A model derived from studies of twins in Gambia suggests that the cumulative effect of human non-HLA genes exceeds the contribution of HLA class II genes in immune responses to purified protein derivative of *M. tuberculosis* antigens.[27] In light of this, there has been a surge of interest in non-HLA genes and their role in the immune response against TB bacilli. Genome-wide linkage studies on sib pairs of families affected with TB have identified several candidate genes that are associated with susceptibility to TB.[4]

CYTOKINES AND RECEPTORS

The immune response to TB is regulated by interactions between lymphocytes with antigen-presenting cells and the cytokines secreted by these cell types. Although cytokines exhibit a low degree of genetic variation, an increasing number of association studies have implicated polymorphisms located on promoter regions or coding regions of cytokine genes as host factors influencing susceptibility to infectious diseases.[44,45] Mutations in these genes may result in altered transcription factor recognition sites, affecting transcriptional activation and altering the levels of cytokine production.[46,47] Selected association studies of cytokines and their receptors are presented in Table 2.

INTERFERON-γ AND ITS RECEPTORS

A874T polymorphism on the intron 1 of interferon (IFN)-γ gene, which is associated with the secretory capacity of IFN-γ, was reported to be associated with the development of TB among Sicilians, South Africans, Hong Kong Chinese and Spanish,[49–52] although this association was not found in Malawians[54] and in other populations from Houston,[55] West Africa,[56] South India[57] and China.[58] However, a recent meta-analysis reported a protective effect of the 874T allele on the development of TB (OR = 0.75; 95% CI: 0.63–0.89).[77] Several polymorphisms on the IFN-γ receptor 1 gene have been tested for their association with TB. Three[56,78,79] of seven studies[80–83] found an association between TB susceptibility and polymorphisms in the gene encoding the IFN-γ receptor 1 protein. Among these, the genotype of 56CC on the promoter region[56] and cytosine-adenine repeat polymorphism on intron 1[84] were reported to be associated with the development of TB. A recent study of 77 TB patients from Japan revealed that the *IFNG* + 874 AA genotype was strongly and independently predictive of a lower

Table 1 Selected studies that investigated the association between HLA and TB

Population	HLA antigen/allele	Nature of association	Sample size		Reference
			Control	TB	
Canadian	B8	Susceptibility	543	46	[12]
Indian	A2	Susceptibility	329	153	[28]
	B18	Protective			[28]
	A1-like supertype	Protective	—	235	[29]
	A3-like supertype	Susceptibility			[29]
	DR2	Susceptibility	—	25 families	[18]
			404	204	[21]
			289	153	[22]
			122	209	[23]
	DRw6	Protective	109	124	[30]
	DRB1*1501(DR2)	Susceptibility	87	126	[24]
			36	72	[25]
	DQ1	Susceptibility	122	209	[23]
	DQB1*0601(DQ1), *DRB1*1501-DQB1*0601*	Susceptibility	87	126	[24]
	DRB1*14(DR6), DQB1*0502 and *0503†	Susceptibility	—	114	[31]
Black American‡	B5 and DR5	Susceptibility	54	72	[14]
	DR6	Protective			[14]
Korean	DRB1*08032 and DQB1*0601†	Susceptibility	200	53	[32]
Italian	DR4 alone or along with B14	Susceptibility	1089	122	[33]
	A2+, B14-, DR4-	Protective			[33]
Indonesian	DR2 and DQw1	Susceptibility	64	101	[19]
	DQw3	Protective			[19]
Mexican	DRB1*1501, DQA1*0101, and DQB1*0501	Susceptibility	95	50	[34]
	DR4, DR8 and DQB1*0402	Protective			[34]
Venda, South African	DRB1*1302, DQB1*0301-0304, *DRB1*1101-1121-DQB1*05*	Susceptibility	117	95	[35]
Polish	DRB1*13	Protective	58	31	[36]
	DRB1*16	Susceptibility			[36]
	DQB1*05	Susceptibility	58	38	[37]
	*DRB1*1601-DQB1*0502, DRB1*04-DQB1*03 and DRB1*14-DQB1*05*	Susceptibility	125	61	[38]
	*DRB1*11-DQB1*03*	Protective			[38]
Cambodian	DQB1*0503	Susceptibility	49; 39§	78; 48§	[39]
	DQ β57 Asp/Asp	Susceptibility	107	436	[40]
Thai	DQB1*0502	Susceptibility	160	82	[41]
	DQA1*0601, DQB1*0301	Protective			[41]
Iranian	A26 and B27	Protective	108	44	[42]
	B17 and DR14	Susceptibility			[42]
	DRB1*07, DQA1*0101	Susceptibility	100	40	[43]
	DQA1*0301 and *0501	Protective			[43]
Soviet Union (six ethnic groups)	DR2	Susceptibility	984	643	[20]
	DR3	Protective			[20]

† denotes studies involving multi-drug-resistant TB patients.
‡ HLA-DR of 45 patients and 41 controls.
§ Study done in two stages.
HLA haplotypes are given in italics.
HLA, human leucocyte antigen; TB, tuberculosis.

likelihood of sputum conversion. Indeed, four of 56 patients with the *IFNG* + 874 AA genotype (7.1%) had not achieved culture negativity at 3 months. This study indicates that the presence or absence of this polymorphism could provide useful information on public health decisions, such as the duration of patient isolation as well as the clinical course of treated TB patients.[85]

IL-12 AND RECEPTORS

IL-12 is a heterodimeric protein (IL-12p70) composed of p40 and p35.[86,87] IL-12 is mostly produced by activated phagocytic cells (macrophages, monocytes and neutrophils) with significantly more IL-12p40 than IL-12p35 being secreted. Both the IL-12 receptors β1 and β2 belong to the gp130 cytokine receptor

Table 2 Selected studies that investigated the association between cytokine gene polymorphism and TB

Cytokine	Location	SNP db number	Association Status	Sample size		Population	References
				Controls	TB		
IFN-γ	+874 (A/T)	rs2430561	Susceptibility	188	178	Pakistani	[48]
				97	45	Sicilian	[49]
				235	313	South African	[50]
				451	385	Chinese	[51]
				100+ 82 (PPD^-)	113	Spanish	[52]
			No association	50	81	Turkish	[53]
				913	514	Malawian	[54]
				174	240	African American	[55]
				64	161	Caucasian	[55]
				98	319	Hispanics	[55]
				594	667	West African	[56]
				188	166	South Indian	[57]
				111	183	Chinese	[58]
IL-12B	Intron 2	rs3212227	Susceptibility	117	106	Whites	[59]
				167	186	African American	[59]
			No association	188	166	South Indian	[57]
IL-12BR1	−2 (C/T)		Susceptibility	78	101	Moroccan	[60]
				197	98	Japanese	[61]
	−111 (A/T)		No association	151	115	Korean	[62]
IL-1B	−511 C/T	rs16944	Susceptibility	298	335	Gambian	[63]
				166	122	Colombian	[64]
	+3954 T/C	rs1143634	Protective			Colombian	[64]
			No association	400	400	Gambian	[65]
				106	358	Cambodian	[66]
				114	89	Gujarati Asians	[67]
IL-2	−330 (T/G)	rs2069762	Susceptibility	188	166	South Indian	[57]
	+160 (G/T)	rs2069763					
	330 G/+160 G		Protective	123	41	Iranian	[68]
			No association	188	166	South Indian	[57]
IL-4	−590 (T/C)	rs2243250	No association	123	41	Iranian	[68]
	−1098 (G/T)	rs2243248		123	41	Iranian	[68]
	−33 (C/T)	rs2070874					
IL-6	−174 (G/C)	rs1800795	No association	188	166	South Indian	[57]
				$54^{\dagger} + 81^{\ddagger}$	140	Colombian	[69]
			Susceptibility	123	41	Iranian	[68]
				$61^{\P} + 42^{\dagger\dagger} + 91^{\ddagger\ddagger}$		Canadian	[70]
IL-10	−1082 (G/A)	rs1800896	Susceptibility	106	358	Cambodian	[66]
						Sicilian	[71]
				80	128	Turkish	[72]
				$54^{\dagger} + 81^{\ddagger}$	140	Colombian	[69]
			No association	400	400	Gambian	[65]
				871	459	Korean	[73]
				100 + 125 (PPD^+) + 82 (PPD^-)	113	Spanish	[52]
				188	166	South Indian	[57]
TNF-α	−592 (A/C)	rs1800872	No association	111	183	Chinese	[58]
	−819 (C/T)	rs1800871					
	−308 (G/A)	rs1800629	No association	120	210	South Indian	[74]
	−238 (G/A) and −376 (G/A)	rs361525		106	358	Cambodian	[66]
	−308 (G/A)		Protective			Sicilian	[71]
	−308 A-238 G		Protective	430	135	Colombian	[75]
TGF-β	Codon 10 (+869 T/C)	rs1982073	No association	111	183	Chinese	[58]
				$54^{\dagger} + 81^{\ddagger}$	140	Colombian	[69]
	Codon 25 (+915 C/G)	rs1800471		110	101	Japanese	[76]

† Tuberculin skin test negative (TST^-).
‡ Tuberculin skin test positive (TST^+).
¶ Dene population.
†† Cree population.
‡‡ Caucasian population.
Haplotypes are given in italics.
IFN, interferon; SNP, single nucleotide polymorphism; SNP db, single nucleotide polymorphism database; TB, tuberculosis; TGF, transforming growth factor; TNF, tumour necrosis factor.

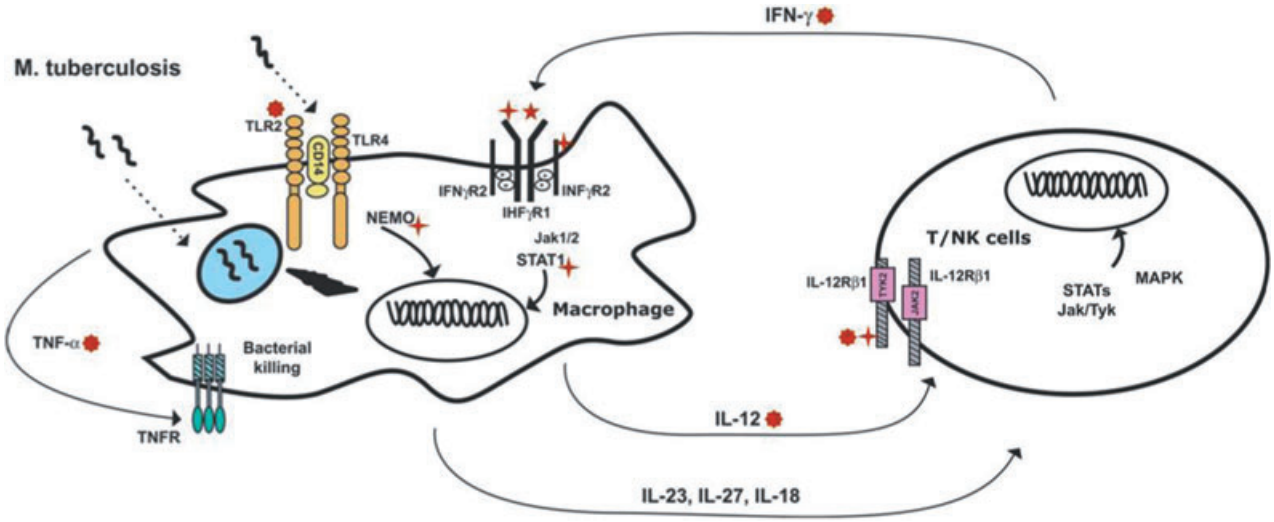

Figure 1 Schema of IL-12-dependent interferon-γ (IFN-γ) production pathway and reported mutations and polymorphisms associated with mycobacterial diseases. (✦) Genes with reported mutations predispose patients to severe non-tuberculous mycobacterial diseases, (★) genes with reported mutations predispose patients to TB, (●) genes with reported polymorphisms associated with clinical tuberculosis. IHF, integration host factor; MAPK, mitogen-activated protein kinase; NEMO, NF-κB essential modulator; NK, natural killer cells; STAT, signal transducers and activators of transcription protein; TLR, toll-like receptors;TNF, tumour necrosis factor; TNFR, tumour necrosis factor receptor; T/NK cells, natural killer T cells.

superfamily and are expressed primarily on T and natural killer cells, but they also are found on dendritic cells and B-cell lines. IL-12p40 binds mainly to IL-12Rβ1, while IL-12p35 binds to IL-12Rβ2. Expression of IL-12Rβ2 correlates most closely with IL-12 responsiveness.[88]

Several polymorphisms in promoter, introns and 3′UTR in the IL-12B gene have been reported to be associated with TB in various populations,[89–91] although results have been inconsistent.[57,59] Polymorphisms in the coding sequence of the IL-12 receptor β1 gene have been reported to be associated with TB in Moroccan and Japanese populations,[60,61,92] but, again, not in Koreans.[62]

Genes with reported mutations or polymorphisms in the IL-12-dependent IFN-γ pathway that predisposes patients to TB or non-tuberculous mycobacterial infection are summarized in Figure 1.

IL-1

Several studies on polymorphisms in the IL-1B gene, encoding the beta chain of IL-1, have been carried out. Studies in Gambian and Colombian populations[63,64] showed that the IL1B-511 C allele was associated with TB and that the IL1B + 3953 T allele was protective, while studies in Cambodia and a pilot case–control analysis of Gujarati Asians in west London found no association.[65–67] A few studies have looked at polymorphisms in the IL-1 receptor, but just one study found an association with pleural TB.[67]

IL-2

Polymorphisms in the IL-2 gene (–330 T/G and +160 G/T) are known to influence IL-2 levels. In a south Indian study, an increased frequency of –330 TT genotype was associated with protection against pulmonary TB. In addition, the GG haplotype (–330 G and +160 G) has been associated with susceptibility to pulmonary TB,[57] while no association was found with –330 T/G and +160 G/T polymorphisms in an Iranian population.[68]

IL-4

A single nucleotide polymorphism (SNP) at position –590 of the IL-4 promoter has been shown to be associated with increased promoter strength.[93] In a study conducted in south Indian TB patients, heterozygotes of the IL-4 –590 T polymorphism were found significantly more frequently in the patient group.[94] Significant negative associations at position –590 IL-4, the T allele and the T/T genotype were shown in Iranian patients with pulmonary TB and the C allele and T/C genotype were significantly increased, while no significant difference was observed in –1098 G/T and –33 C/T polymorphisms.[68] A variable number tandem repeat polymorphism in the IL-4 gene has been shown to be associated with many diseases. However, there was no significant association of this with TB in a south Indian population.[57] A Brazilian multicase TB family study found no association in guanine-thymine dinucleotide repeat in intron 3, and a 70-bp repeat in intron 2.[95]

IL-6

Analysis of the allele and genotype frequencies of IL-6 –174 (G/C) polymorphism revealed no significant

differences between controls and pulmonary TB patients in south Indian and Colombian populations.[57,69] In contrast to the above findings a significant positive association with position –174 G/G polymorphism has been shown in Iranian patients, where the G allele was significantly over represented and associated with high production of IL-6.[68] A study of Canadian aboriginal Dene and Cree cohorts showed a higher frequency of IL-6 –174G allele, which is associated with enhanced cytokine production,[70] compared with that of a Caucasian cohort[96] and this contributes to the high rates of TB among the Dene population. The Asian and African American populations studied had a similarly high frequency of the G allele.[96]

IL-10

Patients with TB have increased IL-10 production mainly during the anergic state. Polymorphism studies of the IL-10 gene showed that in the –1082 SNP, the G allele was more common in TB patients in Cambodia,[66] Sicily[71] and Turkey.[53] Ates *et al.*[72] found that IL-10 –1082 G/A alleles, or haplotypes containing these alleles, may influence the Th1/Th2 balance and play a role in TB susceptibility in a Turkish population. In Colombian patients, pleural TB was associated with SNP at both –1082 and +874.[69] No association with –1082 SNP was found in studies carried out in Gambia,[65] Korea,[73] Spain[52] and south Indian populations.[57] In Korea, the C allele at IL-10 –592 and the ht2 haplotype[73] were slightly protective; however, no such association was found in IL-10 –592 and –819 polymorphisms in a Chinese population.[58] Overall, there is a suggestion of an association of TB with IL-10, especially the –1082 SNP, but the differences in susceptibility are quite modest.

TUMOUR NECROSIS FACTOR-α

Tumour necrosis factor-α (TNF-α) is produced by macrophages, dendritic cells and T cells when stimulated or infected with *M. tuberculosis*.[97,98] In a murine model, the protective role of TNF-α in immunity against *M. tuberculosis* has been well documented. In mice deficient in TNF-α or the 55-kDa TNF receptor, *M. tuberculosis* infection resulted in rapid death, with a higher bacterial burden than that observed in control mice.[99,100] Furthermore, in the absence of TNF-α or the 55-kDa TNF receptor, the granulomatous response was deficient following acute *M. tuberculosis* infection in murine models.[101,102] However, whether TNF-α is beneficial or detrimental to the clinical course of human TB is still controversial. Although reports of severe disseminated TB in patients treated with anti-TNF agents[103,104] underscore the importance of TNF-α in host immunity against the tuberculous bacilli, TNF-α permits the multiplication of *M. tuberculosis* in human alveolar macrophages.[105] Moreover, high levels of TNF-α have been associated with clinical decline in patients with TB.[106] Microarray analysis using peripheral blood mononuclear cells from patients with extrapulmonary TB showed increased TNF-α production in peripheral blood mononuclear cells from patients who had recovered from extrapulmonary TB when stimulated with whole lysates of virulent *M. tuberculosis*, suggesting that higher secretion of TNF-α in humans could be associated with the haematogenous dissemination of *M. tuberculosis* to other organs.[107] The TNF-α –308 G/A polymorphism was found to protect against TB in Sicily;[71] and the –308A–238G haplotype was protective in Colombia.[75] Studies on TNF-α (–238 G/A, –308 G/A and –376 G/A) and TNF-β gene polymorphisms in Chinese, Cambodian and Indian TB patients revealed no association either with susceptibility or resistance to TB.[66,74] A recent meta-analysis including 10 studies found no significant association between –308 G/A on TNF-α gene and the development of TB.[77]

TRANSFORMING GROWTH FACTOR

Two main SNP have been described for transforming growth factor (TGF)-β1. The first SNP at –509 C-T is in linkage disequilibrium with +29 T-C, encoding leucine 10 to proline at residue 10 and is associated with increased TGF-β1 secretion.[108] The second SNP is located at +915 GC, and changes codon 25 arginine to proline. The TGF-β codon 10 polymorphism has been investigated in healthy controls and TB patients, and no significant differences were found in the TGF-β genotypes of the two groups.[58,69,76]

All these cytokine gene polymorphism studies have had a high degree of heterogeneity in their results, and the modest effects found in most studies make the putative influence of different cytokine SNP on TB susceptibility less credible.

IκB KINASE-γ (NEMO)

Nuclear factor-κB (NF-κB) has attracted scientific attention due to its unusual regulation, the wide variety of stimuli that activate it, and the diverse genes and biological responses that it controls.[109–111] Its interaction with the inhibitor of NF-κB (IκB) regulates its cytoplasmic retention and, in turn, NF-κB activities.[112,113] The IκB kinase complex (IKK) regulates IκB phosphorylation, leading to its ubiquitination and proteosome degradation, liberating NF-κB to enter the nucleus and initiate its programme of gene transcription. IKK is composed of three subunits: IKKα and IKKβ serve as the catalytic components, while IKKγ (NEMO) is the structural scaffolding that supports the IKK complex.[110,114,115] Mutations in IKBKG gene-coding IKKγ (NEMO) protein cause the syndrome of anhidrotic ectodermal dysplasia with immunodeficiency.[116] Several reports of mycobacterial diseases including miliary TB in these patients suggest that dysfunction of IKKγ (NEMO) increases ssusceptibility to mycobacteria.[117–119]

Table 3 Association of selected chemokine and chemokine receptor gene variants with TB

Chemokine	Location	Association	Sample size		Population	References
			Controls	TB		
IL-8	–251 (T/A) (rs4073)	Susceptibility	107	106	Whites	124
			167	180	African American	124
		No association	124	127	South Indian	125
			320	360	Gambian	126
CXCR-1 exon2	+2607 G/C	No association	107	106	Whites	124
CXCR-2 exon 11	+785 C/T		167	180	African American	124
MCP-1 (CCL2)	–2518 (G/A) (rs1024611)	Susceptibility	518†	435	Mexican	131
			162	129	Korean	131
		No association		627	Brazilian	123
	–362C	Protective			West African	127
RANTES (CCL5)	–403 G/A (rs2107538), –28 C/G (rs2280788) & In1.1 T/C (rs2280789)	Susceptibility			Chinese	128
	–403 G/–28 C (haplotype) & GG/CC (diplotype)	Protective	157	76	Caucasian	129
MIP-1α (CCL3)	–459 (C/T)	No association	518*	435	Mexican	131
			162	129	Korean	131
MIP-1β (CCL4)	rs1634514 (T/A)	Susceptibility		627	Brazilian	123
	rs1719144 (G/A)					123
	rs1719147 (G/A)					
CCL18	rs2015086 (T/C)	Susceptibility		627	Brazilian	123
	rs2015070 (G/A)					123
	rs14304 (G/A)					
IP-10 (CXCL10)	–135 (G/A)	Susceptibility	176	240	Chinese	130
	–1447 (A/G)	No association				
	–872 (G/A)					

† Total 518 Mexican population comprises 334 healthy tuberculin-positive and 176 healthy tuberculin-negative subjects.

IP, interferon-gamma inducible protein; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; RANTES (CCL5), regulated upon activation normal T cell expressed and secreted; TB, tuberculosis.

CHEMOKINES AND RECEPTORS

Chemokines are small molecular mass chemotactic cytokines (8–14 kDa) that mediate constitutive recruitment of leucocytes from the blood into tissues. During infection, mycobacteria induce increased expression of CC-chemokine that includes monocyte chemoattractant protein-1 (MCP-1, CCL2), macrophage inflammatory protein-1α (MIP-1α, CCL3), MIP-1β (CCL4), and regulated upon activation normal T cell expressed and secreted (RANTES, CCL5) and CXC chemokine subfamily members, such as IFN-γ-inducible protein-10 (IP-10) (CXCL10) and CXCL8 (IL-8).[120–122] The 17q11.2 chromosomal region has been linked to susceptibility to TB and includes genes encoding for several chemokines that may contribute to immunity against TB.[123] The associations of selected chemokine and chemokine receptor gene variants with TB are presented in Table 3.

IL-8

IL-8 (CXCL8) gene polymorphism is associated with susceptibility to human TB, and decreased CXCL8 secretion occurs in HIV-infected patients with miliary TB. In a well-designed study, Ma *et al.*[124] showed an association between the –251 promoter polymorphism of IL-8 and lack of association of its receptor genes +2607 G/C in exon 2 of CXCR-1 and +785C/T in exon 11 of CXCR-2 to human TB susceptibility in two distinct ethnic groups in the USA. However, in south Indian[125] and Gambian population no such association was seen with –251 and +781 polymorphisms.[126]

MONOCYTE CHEMOATTRACTANT PROTEIN–1

Monocyte chemoattractant protein-1, a chemoattractant for monocytes and T lymphocytes, is the central component of the granulomatous response. The G allele of the MCP-1 promoter polymorphism at position –2518 relative to the ATG transcription start codon has been associated with susceptibility to TB in Mexican and Korean populations.[131] Persons bearing the GG genotype of MCP-1 –2518 promoter polymorphism produce high concentrations of MCP-1, which inhibits production of IL-12p40 in response to *M. tuberculosis* and promotes active pulmonary TB. In a group of infected individuals from Mexico, this polymorphism (–2518 G) was five times more prevalent in

patients with active TB than in those who remained healthy. However, the same variant was previously reported not to be associated with TB in a Brazilian cohort.[123] In the Ghanaian population,[127] eight additional MCP-1 polymorphisms were genotyped. Among them MCP-1 –362C was associated with resistance to TB in a case–control study (OR = 0.83, $P_{corr} = 0.00017$) and in affected families (OR = 0.7, $P_{corr} = 0.004$).

MACROPHAGE INFLAMMATORY PROTEIN-1α (CCL3) AND REGULATED UPON ACTIVATION NORMAL T CELL EXPRESSED AND SECRETED (CCL5)

Macrophage inflammatory protein-1 and RANTES are involved in the recruitment of T cells to the site of inflammation, activation of T cells[132] and formation of the tuberculous granuloma.[133] Functional polymorphisms were studied in the CCL5 gene and TB in a Hong Kong Chinese population.[128] This work analysed three SNP in the CCL5 genes (–403 G/A, –28 C/G and In1.1 T/C). Two risk haplotypes of CCL5, A-C-T and G-C-C, at positions –403, –28 and In1.1, respectively, were identified. Furthermore, combining the genotypes of CCL5–403 and In1.1, two diplotypes GA/TT and GG/TC showed strong association with TB. Another study conducted in a Caucasian population[129] found that –403 G and –28 C alleles, either separately or combined as G-C haplotype and GG/CC diplotype, may be related to protection against pulmonary TB. By contrast, the –403 A and –28 G alleles, the G-G or A-C haplotypes and the G/G-G/G and A/A-C/C diplotypes may confer susceptibility to pulmonary TB. The study in Mexican and Korean populations did not report significant linkage or association between CCL5 and pulmonary TB. The promoter polymorphism in RANTES –471(A/T), and MIP-1α–459(C/T) alleles or genotypes were not associated with TB.[126]

INTERFERON GAMMA-INDUCIBLE PROTEIN-10

Interferon gamma-inducible protein, CXCL10, in addition to its chemotactic properties, is also involved in the stimulation of natural killer cells and T cell migration in *M. tuberculosis* infection.[134] A promoter SNP in CXCL-10 (–135 G/A) showed a moderate association with TB, but other SNP (–1447 A/G, –872 G/A) were not associated with TB in a Chinese population.[130]

SOLUTE CARRIER FAMILY 11A MEMBER 1

Solute carrier family 11A member 1 (SLC11A1), formerly known as natural resistance-associated macrophage protein 1 (NRAMP1), is a human homologue of the mouse gene (Nramp1), in which a single non-conservative amino acid substitution was found to control susceptibility to leishmania, salmonella and mycobacteria in inbred mouse strains.[135] SLC11A1 activates microbicidal responses in the infected macrophage, and it is therefore important in the early innate response to mycobacterial infection. Its exact function is unclear, but the fact that it is known to localize to the late endosomal membrane,[136] and that it is a bivalent cation antiporter, and has led to speculation that at least part of its role in containing early mycobacterial infection is through the regulation of cytoplasmic cation levels, especially iron.[137,138] While iron is an essential mycobacterial nutrient, it is also required by the cell to generate reactive oxygen and nitrogen intermediates. Divalent cations are also essential cofactors for enzymes, such as superoxide dismutase and catalase, which neutralize the cytotoxic effects of the oxidative burst in macrophages.[139] The function of SLC11A1 as well as the advantage to host or bacterium of divalent cation transport is therefore in dispute.

The SLC11A1 gene and its association with TB have been extensively studied. The Asn543Asp polymorphism has been reported as a genetic susceptibility factor to TB in Japanese, Korean and Gambian populations.[140–142] In addition, the associations between TB and (TGTG) deletion in the 3′ untranslated region (1729 + 55del4) (rs17235416) in Korean, Gambian and South African populations,[141–143] between a single nucleotide change in intron 4 (469 + 14 G/C) (rs3731865) and TB in Gambian and Guineans,[144] and between a (CA)n repeat polymorphism in the immediate 5′ region and TB among Gambians, Japanese, South Africans and Americans have also been reported.[140,142,143,145,146] However, an inverse relationship or lack of the above correlations has also been reported among the various racial groups.[66,140,144,147,148] Finally, a recent meta-analysis including 14 case–control studies showed that 3′UTR, D543N (rs17235409) and 5′(GT)n were associated with the development of TB, although racial variation existed (Table 4).

SLC11A2 (NRAMP2), another member of the SLC11A family of membrane transporters, is an iron transporter,[150,151] upregulated by dietary iron deficiency and expressed in many cells and tissues. Although the strong association between TB and iron overload in black South Africans has attracted attention,[152] the association between TB and polymorphisms in SCL11A2 was not found in South Africans.[143]

VITAMIN D RECEPTOR

In the prechemotherapy era, TB was treated with vitamin D supplements, vitamin D-rich diets, and sunlight was the basis of the sanatorium movement.[153] Susceptibility to TB has been associated with vitamin D_3 deficiency.[154,155] Several polymorphisms were found in the gene of the vitamin D receptor (VDR).[156] Studies from different populations have determined the differential susceptibility or resistance to TB. A study carried out in 202 pulmonary TB patients and 109 controls from a south Indian

Table 4 Odds ratios and 95% confidence intervals of studies on 3′UTR, D543N, INT4 and 5′(GT)n loci allele variant on SLC11A1 gene and TB[149]

Polymorphisms	Odds ratio (95% confidence interval)			
	Overall	Asians	African descents	European descents
3′UTR	1.33 (1.08–1.63)	1.46 (1.10–1.94)	1.20 (0.86–1.68)	1.81 (0.66–4.93)
D543N	1.67 (1.36–2.05)	1.65 (1.29–2.12)	1.69 (1.14–2.50)	1.79 (0.72–4.47)
INT4	1.14 (0.96–1.35)	0.91 (0.66–1.25)	1.50 (1.17–1.91)	0.87 (0.61–1.22)
5′(GT)n	1.32 (1.03–1.68)	1.86 (1.33–2.62)	1.31 (1.05–1.64)	1.02 (0.35–2.99)

population showed a significantly higher frequency of the *Taq*I tt genotype in female pulmonary TB patients and *Bsm*I (rs1544410) Bb and FF genotypes in male patients.[157,158] In a Gujarati Indian population study involving 126 pulmonary TB patients and 116 controls, the *Fok*I (rs10735810) ff genotype was strongly associated with pulmonary TB.[155] In a Gambian study carried out in 408 pulmonary TB patients and 414 controls, the *Taq*I (rs731236) tt genotype was found less frequently in patients, suggesting that this genotype may be associated with resistance to TB.[159]

A family-based study conducted in a West African population and consisting of 417 TB patients and 722 controls proposed that VDR haplotypes, rather than individual alleles or genotypes, are responsible for the association between TB and VDR variants.[160] Moreover, another study of the Venda people in South Africa comprising 95 pulmonary TB patients and 117 controls showed that the F-b-A-T haplotype provided protection against TB.[35] In a recent large-scale genetic analysis of native South Americans, the *Fok*I F allele was reported to be associated with protection against infection and *Taq*I t allele with protection against active disease.[161] VDR gene polymorphisms have been associated with the time to sputum culture and auramine stain conversion during anti-TB treatment. In a Peruvian community with a high incidence of TB, the conversions were significantly faster among participants with the *Fok*I FF genotype and *Taq*I Tt genotype.[162] Another similar study involving 249 TB patients and 352 controls from South Africa reported that the *Apa*I (rs7975232) AA and *Taq*I T allele containing genotypes were predictive of a faster response to treatment.[163]

A recent study of 166 pulmonary TB patients and 206 controls from south India showed a significantly decreased frequency of Cdx-2 (rs17883968) G allele and G/G genotype and an increased frequency of A-A haplotype (A allele of Cdx-2 and A allele of A1012G (rs4516035)) in pulmonary TB patients compared with controls. This suggests that the Cdx-2 G/G genotype may be associated with protection and A-A haplotype with susceptibility to TB.[164] It emphasizes the need for large family-based studies that will address differential susceptibility. VDR results have confirmed the importance of investigating haplotypes instead of individual SNP.

PATTERN RECOGNITION RECEPTORS

One of the first lines of immune defence is the recognition and uptake of microorganisms by professional phagocytes: macrophages and dendritic cells. On the surface of phagocytic cells are several different pattern recognition receptors, which, in the absence of adaptive immunity, bind to different patterns on microbes to promote phagocytosis and activate signalling that leads to cytokine production, antigen presentation and the development of adaptive immunity. These pattern recognition receptors include toll-like receptors (TLR), scavenger receptors, the complement receptors, mannose-binding lectin (MBL), the dendritic cell-specific intercellular adhesion molecule-3 grabbing nonintegrin, called DC-SIGN, and others. Several of these have been shown to mediate the phagocytosis of *M. tuberculosis*,[165] and have been studied to determine whether different polymorphisms might affect TB susceptibility.[166]

TOLL LIKE RECEPTORS

The human TLR are pattern recognition molecules that play important roles in early innate immune recognition and inflammatory responses.[60,167–170] In addition to their critical roles in innate immunity, TLR are essential in the orientation of the adaptive immune response through the induction of the Th1 immune response.[171]

TLR 2

Among the 10 human TLR, TLR2 plays a key role in the immune responsiveness to peptidoglycans,[172,173] to lipoteichoic acid of Gram-positive bacteria,[174] to mycobacterial lipoproteins[175] and to leptospiral LPS.[176] The fact that TLR2-deficient mice are highly susceptible to *M. tuberculosis* infection[177,178] suggests that TLR2 is one of the indispensable receptors in the immunity against *M. tuberculosis* infection. In addition, several SNP studies confirmed the crucial roles of TLR2 in the development of TB. Arg753Gln (rs5743708) and Arg677Trp polymorphisms located in the intracellular domain of the TLR2 were reported to be associated with TB in Turkish and Tunisian populations, respectively.[179,180] In addition, the genotype of 597CC is associated with susceptibility to TB as a whole (OR = 2.22; 95% CI: 1.23–3.99), with TB meningitis (OR = 3.26; 95% CI: 1.72–6.18), and with miliary TB (OR = 5.28; 95% CI: 2.20–12.65).[181] Furthermore, a highly polymorphic guanine-thymine dinucleotide

repeat in the 100 bp upstream of the TLR2 translational start site was reported to be associated with TB in Koreans.[182,183]

TLR 4

TLR4, initially identified as the mediator of LPS inflammatory responses,[184] can also interact with both heat-labile soluble mycobacterial factor and whole viable *M. tuberculosis* to initiate innate responses.[185,186] The fact that TLR4 mutant mice, C3H/HeJ, showed a reduced capacity to eliminated *M. tuberculosis* with lower production of TNF-α, IL-12p40 and MCP-1 suggests a possible role for TLR4 in the human defence system against *M. tuberculosis*.[187] However, the association between clinical TB and the Asp299Gly (rs4986790) polymorphism in the TLR4 gene, which causes hyporesponsiveness to LPS, was excluded in a Gambian population.[188] In addition, the small study to test whether Asp299Gly increases chance of developing active TB among HIV-infected individuals in Tanzania failed to reach statistical significance.[120]

TLR8

In a large study carried out in Indonesian and Russian populations, four sequence polymorphisms (rs 3764879, rs 3788935, rs 3761624 and rs 3764880) in the TLR8 gene on chromosome X showed evidence of an association with TB susceptibility in men across different populations.[189]

MANNOSE-BINDING LECTIN

Mannose-binding lectin belongs to a family of proteins called the collectins, which possess both collagenous regions and lectin domains. This protein consists of multimers of an identical polypeptide chain of 32 kDa. There are two human MBL genes, but MBL1 is a pseudogene and the functional MBL2 gene encodes MBL protein. Inter-individual variations in the serum MBL levels are mainly due to the presence of three common point mutations in exon1 of MBL2 gene at the codons 52 (rs5030737), 54 (rs1800451) and 57 (rs1800450). MBL plays an important role in host defence against pathogens. Upon binding with certain carbohydrate moieties, such as terminal N-acetylglucosamine or mannose on various pathogens, MBL activates complement via specific protease and acts directly as an opsonin using the C1q receptor on macrophages. Mutations at codons 52, 54 and 57 lead to low or near absent serum MBL levels in heterozygotes and homozygotes, respectively.

Several groups have studied MBL genotypes and TB, following a suggestion that MBL deficiency might have had an evolutionary advantage by reducing the capacity of mycobacteria to invade macrophages in the absence of MBL, so leading to resistance to TB.[190] A study carried out in South Africa suggested that MBL-54 heterozygotes may have protection against tuberculous meningitis[191] and a study carried out in 202 pulmonary TB patients and 109 control subjects of a south Indian population revealed an increased genotype frequency of MBL functional mutant homozygotes (including codons 52, 54 and 57) in pulmonary TB compared with control subjects.[192] However, studies in China,[193] Poland,[194] Turkey,[195] Malawi,[54] Tanzania[196] and Gambia,[197] found no association.

DENDRITIC CELL-SPECIFIC INTERCELLULAR ADHESION MOLECULE-3 GRABBING NONINTEGRIN

Dendritic cell-specific intercellular adhesion molecule-3 grabbing non-integrin, is a lectin present on macrophages and monocyte-derived dendritic cells that recognizes many pathogens, including *M. tuberculosis* through the cell wall lipoglycan, manlam.[198] Two variants (–871G (rs735239) and –336A (rs4804803)) have been identified in the promoter region of CD209, the gene for DC-SIGN, and the –336A allele has been shown to increase its expression. In a South African study, consisting of 351 TB patients and 360 controls, these two variants were associated with a lower risk of developing TB, and the alternate nucleotides with an increased risk (–871A OR = 1.85 (95% CI: 1.29–2.66); –336G OR = 1.48 (95% CI: 1.08–2.02)).[199] The protective allele, –871G, was present in 21% and 38% of Asians and Europeans, respectively, but was absent in Africans; it has been postulated that this could contribute to the putative increased TB susceptibility in this ethnic group.[199] A subsequent study from Colombia found no significant association between TB and the –336 allele, although the frequency of this allele was very low in the population studied.[65] A recent study carried out in south India revealed no significant association of –336 allele with TB.[200] Although DC-SIGN is an attractive candidate for influencing TB susceptibility, further studies are needed to prove an association.

SURFACTANT PROTEINS AND COMPLEMENT RECEPTOR-1

Lung surfactant proteins (SP), such as SP-A and SP-D, are collagen-containing calcium-dependent lectins called collectins, and are structurally similar to MBL. They recognize many pathogens via their lectin domains and activate immune cells through their collagen region. SP-A is a multichain protein encoded by the SFTP-A1 and SFTB-A2 genes, and several polymorphisms in the SFTP-A2 gene were found to be associated with susceptibility to TB in Ethiopia,[201] Mexico[202] and India.[203] The complement receptor-1 (CR1) present on the surface of the macrophages is associated with phagocytosis of various microorganisms, including *M. tuberculosis*. A large-scale study in Malawi revealed that homozygotes in one of five CR1 polymorphisms (Q1022H) are associated with increased TB risk. The SNP causes an amino acid

change that alters ligand binding, perhaps reducing the phagocytosis of *M. tuberculosis*.[54]

THE PURINERGIC P2X7 RECEPTOR

Purinergic P2X7 receptors are cationic channels present on the cells in the blood and immune systems, and are highly expressed on macrophages.[204] The P2X7 receptor is activated by extracellular ATP, which causes their cation-selective channel to open, leading to an influx of calcium and induction of the caspase cascade, resulting in apoptosis and mycobacterial killing. A polymorphism with a 1513 A-C (rs3751143) change that causes the glutamic acid at residue 496 to be replaced by alanine, was not associated with pulmonary TB in a case–control study in Gambia;[205] however, this study identified five SNP and in one, at –762, the presence of a C showed significant protection against TB. It was suggested that the C at –762 could affect the level of P2X7 expression by altering the binding of a transcription factor. A study of two cohorts of Southeast Asian refugees in Australia found no association of the 1513 SNP with pulmonary TB, but, surprisingly, found a strong association between the C polymorphism and extrapulmonary TB.[206] Furthermore, *in vitro* studies showed that the ATP-mediated killing of mycobacteria was absent in macrophages from patients homozygous for the 1513 C allele, and impaired in macrophages from heterozygous subjects. There was a strong correlation between the capacity for mycobacterial killing and ATP-induced apoptosis.

CONCLUSIONS

The development of TB or other mycobacterial diseases is the result of a complex interaction between the host and pathogen influenced by environmental factors. Susceptibility to TB in humans appears to be highly polygenic with many loci implicated but only minority of these convincingly proven. Heterogeneity of genetic and allelic association is frequently observed when comparing results between populations and has many causes, including epistasis, wherein one gene interferes with or prevents the expression of another gene located at a different locus. Although susceptibility to TB is determined by many different genes, each having small effects, and the genes may be different in different populations, the great majority of susceptibility genes are as yet not identified.

Genetic susceptibility or resistance to TB infection is determined by pathogen as well as host factors. In line with this, a west African Ghana population study revealed that autophagy gene variant immunity-related GTPase M (IRGM) 2261T was associated with protection from TB caused by *M. tuberculosis* but not by *M. africanum* strains.[207] The high prevalence of IRGM 2261TT in the Ghanaian population and the relative protection that it confers from TB caused by *M. tuberculosis* Euro-American lineage substantiates that lineages have become differentially adapted to different ethnicities with allelic variations conferring traits associated with certain infection phenotypes.[208] These studies suggest the potential role of pathogen factors as well as host factors in the immunopathogenesis of TB and investigations in this direction are warranted.

At this point in time, however, we should admit that the achievements of genetics studies might not as yet have advanced the prevention and treatment of TB. So far, the major target of genetic studies on TB patients has been to elucidate the immunopathogenesis of TB through the research focused on the human genes associated with susceptibility to or the clinical manifestation of TB. However, researchers began to widen the scope to more practical fields, such as VDR gene polymorphisms associated with sputum culture and auramine stain conversion during anti-TB treatment,[163] association of *IFNG* + 874 AA genotype with a lower likelihood of sputum conversion,[85] as well as genetic trait associated with the response to Bacillus Calmette-Guérin vaccination[209] or anti-TB drug-induced hepatitis.[210] In fact, IFN-γ treatment or bone marrow transplantation were successfully used in patients with disseminated non-tuberculous mycobacterial infection, based on knowledge of the genetic mutations of specific patients.[211] These studies highlight the potential role of immunogenetics in the clinical management of TB and warrant investigations aimed at the replication of significant findings in large cohorts, enabling translation of research findings to the clinical setting. We believe that, in the near future, genetic studies will be no longer just 'curiosities' but may well be the leading edge of a major weapon against TB.

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