Host genetics and tuberculosis: Theory of genetic polymorphism and tuberculosis

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ABSTRACT

Background and Objective: Tuberculosis (TB), the leading cause of morbidity and mortality by a single infectious agent, *Mycobacterium tuberculosis*, is still a major health problem in the world. To date, many studies have shown evidence of association between host genetic polymorphisms and TB susceptibility, including chemokine (C-C motif) ligand 2 (CCL-2)/monocyte chemoattractant protein1 (MCP-1), natural resistance-associated macrophage protein 1 (NRAMP-1)/ solute carrier protein 11A1 (SLC11A1), Immunity-related GTPase family M protein (IRGMI), interleukin (IL)-8, toll-like receptor (TLR), and nucleotide-binding oligomerization domain containing protein-2 (NOD-2) genes. Most of these genes participate in immune response, and their polymorphism can alter immunity and lead to genetic susceptibility to TB. **Materials and Methods:** This is a special article compiled with reference to various case-control studies, meta-analysis, and other research work on different genes and TB. The genes selected and a number of studies from different countries and ethnic groups for this article are shown below. The genes selected for the study are: NRAMP-1 (SLC11 A1), Vitamin D receptor, low molecular weight polypeptide/transporter with antigen processing, CCL-2/MCP-1, IRGM-1, IL-1, IL-8, IL-10, IL-12, TLR, NOD-2, human leukocyte antigen, mannose-binding lectin, major histocompatibility complex, tumor necrosis factor, P2X 7, epiregulin, SP110, and interferon gamma (IFN-gamma). **Results:** Genetic polymorphisms in different genes showed variable levels of significance in relation to TB. All these were proved by the researchers using appropriate statistical methods and tools. **Conclusions:** Based on different research works across the world, there is sufficient evidence to prove that TB is a genetically primed and determined infectious disease caused by *M. tuberculosis* and the genetic polymorphism is the mechanism that leads to progression from infection to TB disease. Why only 10–15% of the people infected with *M. tuberculosis* progress toward TB disease has continued to be an unresolved debate. Hence, for provoking thoughts and encouraging more research in the field of genetics and TB I formulated hypothesis and algorithms, and theory. Genetic susceptibility to TB has been substantiated based on the extensive literature review and the research findings that are well narrated.

KEY WORDS: Algorithm, genes, genetic polymorphism, theory, tuberculosis

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INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*. Patients suffering from smear-positive pulmonary TB (PTB) constitute the most important source of infection. The infection occurs most commonly through droplet nuclei generated by coughing, sneezing, etc. and inhaled via the respiratory route. The chances of getting infected depend on the duration, frequency of exposures, and the immune status of an individual.

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According to the annual report on global control of TB from the World Health Organization, about 9.4 million incident cases and 14 million prevalent cases occurred in 2009. Approximately 1.7 million people died of TB, including 0.38 million deaths among human immunodeficiency virus (HIV)-positive people and most cases were in the Southeast Asia, Africa, and Western Pacific regions(35%, 30%, and 20%, respectively).[1]

Entry and establishment of *bacilli* in the human body constitute infection.[2] It usually takes 6–8 weeks for the establishment and manifestation of infection. Lung TB spreads through droplets that enter via air breathing to lung alveoli, which evoke an inflammation response through accumulation of macrophages and neutrophils, which then migrate to regional lymph nodes to form a Primary Complex. The sub pleural lung lesion, lymphangitis, and hilar adenopathy together constitute a "primary complex." In most cases, the host's immune defenses overcome the primary infection that generally passes unnoticed.

Secondary bacillary multiplication that occurs at the regional lymph nodes causes bacillemia resulting in the implantation of seedlings of *bacilli* in different parts of the body. In few cases, the infections may develop into progressive primary forms of TB diseases such as meningitis and miliary TB. However, in a majority of the cases, the multiplication of the *bacilli* is contained by the host defense mechanism.

All those who get infected do not necessarily develop TB diseases. The lifetime risk of progression to the disease among those infected with TB is 10–15% that gets increased to 10% per year among those coinfected with HIV. Other determinants such as diabetes mellitus, the smoking of tobacco products, malnutrition, and alcohol abuse also increase the risk of progression from infection to TB disease.[3]

It is well-known that host genetic susceptibility, together with bacterial strains and environmental factors, play an important role in determining TB predisposition and drug response. Only about 10% of the infected individuals develop the clinical disease while most infected people carry the bacteria without overt symptoms.[4,5] To date, many studies have shown the evidence of an association between host genetic polymorphisms and TB susceptibility including chemokine (C-C motif) ligand-2 (CCL-2)/monocyte chemoattractant protein 1 (MCP-1), natural resistance-associated macrophage protein 1 (NRAMP-1)/solute carrier protein 11A1 (SLC11A1), IRGMI, interleukin (IL) 8, toll-like receptor (TLR), and nucleotide-binding oligomerization domain-containing protein 2 (NOD 2) genes.[6-11]

Most of these genes participate in immune response, and their polymorphism can alter immunity and lead to genetic susceptibility to TB.

In humans, NRAMP gene is expressed in macrophages, lymphocytes, and lung tissue. The gene encodes a protein that functions as a divalent ion channel.[12] Fe^{++} ion can inhibit the growth of *M. tuberculosis*.[13] When a mutation of NRAMP-1 gene yields a nonfunctional NRAMP-1 protein, there is an inhibition on the intracellular killing mechanism of *M. tuberculosis* in macrophages. Bellamy *et al*.[14] have reported in Gambia that polymorphism in 5'(GT)nINT4, D543, and 3'UTR of NRAMP1 enhance susceptibility to *M. tuberculosis*.

Many studies have revealed that of the people who are infected with TB, many are considered less susceptible due to the genetic and environment factors.[15,16] A study from Poland[17] and another study from Indonesia[18] found that INT 4 polymorphism is not associated with TB infection but is strongly correlated with autoimmunity; however, both D'543N and 3'UTR polymorphisms are associated with susceptibility to TB infection. Assessment of the contribution of the genetics of host resistance to human TB is one of the longstanding challenges of human genetics research, and TB has been considered as a complex disease with strong genetic components. There are several studies that provide strong data in support of genetic factors being involved in TB susceptibility.[5]

Host genetic factors such as human leukocyte antigen (HLA) and non-HLA genes that are associated with the susceptibility to TB, have been studied using various methods such as case–control studies, candidate gene approach, family-based and genome-wide linkage studies and will serve as genetic markers to predispose or predetermine development of the disease.[19]

Similarly, susceptibility to *M. tuberculosis* also has genetic variation.[19] HLA studies carried out in the Asian region, especially in India, demonstrated the association of HLA-DR2 and HLA-DQ1 antigens with susceptibility to PTB.[19] Various diallelic polymorphisms have been identified in the Vitamin D receptor (VDR) gene and these polymorphic variants have been demonstrated to be associated with the TB susceptibility or resistance.[19]

The human NRAMP-1, renamed as SLC11A1-solute carrier family 11, member 1 gene has several polymorphisms.[19] An association has been found between NRAMP-1 gene and TB susceptibility in populations as diverse as the West Africans, Koreans, and Japanese.[14,20] A case–control study conducted in the Gambia showed that NRAMP-1 polymorphisms were significantly associated with TB susceptibility.[21]

There is substantial evidence from studies on racial variations in susceptibility to TB that a complex interaction of genetic and environmental factors causes the development of clinical TB.[22,23]

M. tuberculosis is a facultative intracellular pathogen that utilizes the macrophage as its host cell. Resistance to *M. tuberculosis* involves a complex interaction between the bacteria and the host immune system. Cytokines are believed to play a key role in mycobacterial

resistance. Macrophages are activated by interferon-gamma (IFN-gamma), tumor necrosis factor (TNF) alpha, Vitamin D, and IL-6.[24]

In a well-matched case–control study for candidate gene,[14] several candidate gene polymorphisms have been typed, and associations have been detected for NRAMP-1VDR and mannose-binding lectin (MBL) gene variants.[14,23,25]

Results of the case–control study demonstrates that although NRAMP-1 gene is not the sole determinant of host TB susceptibility; it is an important mycobacteria susceptibility gene in humans as well as in mice.

Epidemiological evidence suggests a link between Vitamin D deficiency and susceptibility to TB[26,27] and Vitamin D has shown to have beneficial effect in cutaneous TB.[28] Vitamin D is an important immune regulatory hormone.[29] The active metabolite of Vitamin D; 1,25-dihydroxy Vitamin D3 (1,25-dihydroxy cholecalciferol), activates monocytes, stimulates cell-mediated immunity, and suppresses lymphocyte proliferation, immunoglobulin production, and cytokine synthesis.[30]

MBL is a calcium-dependent serum lectin. It interacts with the immune system by acting as an opsonin to promote phagocytosis and by activating the complement cascade. Three co-dominant single base substitutions in codons 52, 54, and 57 of the myoblast city gene result in reduced serum MBL concentrations. Heterozygote advantage may maintain MBL variant alleles at high frequency by conferring resistance to mycobacterial diseases.[31] In a case–control study in Gambia, it was found that the frequency of the common African variant MBL allele (codon 57) was lower among TB cases than controls.[14]

A link between polymorphisms in NRAMP-1 gene and susceptibility to TB has been demonstrated worldwide. Individuals with homozygous type mutation have an increased risk of developing TB. The candidate gene involved with susceptibility to TB in solute carrier family 11 member 1 (SLC11A1) formerly known as NRAMP-1 gene. NRAMP-1 plays a critical role in early innate macrophages responses to intracellular infections.[32,33] Its pleotropic effects include the activation of microbial responses including the production of reactive oxygen and nitrogen intermediates and proinflammatory cytokines.[33,34] Initial studies demonstrated an association between four different NRAMP-1 polymorphisms (5'CA, INT4, D543, and 3'UTR) and PTB.[14]

Natural mutant may occur randomly in NRAMP-1 gene but other risk factors such as socioeconomic status, duration of contact, underlying disease, and even other genes can increase susceptibility to TB. The homozygous pattern of NRAMP-1 gene polymorphisms might be associated with susceptibility to TB. This might be one of the reasons why the TB exposed health care workers did not develop TB, even after long periods of working with TB bacillus.[35]

So far, genetic studies of TB susceptibility have largely been focused on adult patients despite the fact that TB is highly prevalent among children. To study the host genetic components of pediatric TB susceptibility using a family-based control design,[36] it was found that allelic variants of the NRAMP-1 gene (alias SLC11A1) is significantly associated with TB disease in the pediatric patient population. Common alleles of the NRAMP-1 gene polymorphisms are risk factors for pediatric TB disease. NRAMP-1 influences the speed of progression from infection to TB disease.

There is evidence for host-environment-agent interaction from infection to disease in TB. Several studies support evidence to state that there is a major role for the host genetics interplay in TB. Based on this, a hypothesis is formulated that is entitled "TB is an infectious disease caused by *M. tuberculosis* primed and determined by genetic polymorphism."

Many lines of evidence support an important role of host genetic variation in TB susceptibility including animal models of the disease.[37-41]

Polymorphisms in the NRAMP-I gene have been found in a number of genetic studies to be risk factors for the development of TB among adult populations.[42] NRAMP-1 alleles have their highest impact on risk of TB diseases under conditions of low transmission/exposure of *M. tuberculosis*.

The human NRAMP-1 gene has been implicated in increased risk of TB disease by a number of studies. Polymorphisms in the 5' and 3'regions of NRAMP-1 gene have been linked or associated with TB disease susceptibility in Guinea-Conakry.[43-45] Gambia,[14,34,46-49] and South Africa[42] but not in Taiwan[50] or Morocco.[51]

All patients with clinical TB could be classified as fast progressors or primary TB disease cases. Segregation analysis has revealed that the common NRAMP-1 alleles were preferentially transmitted to TB patients.[46] Considering that only 10% of the individuals infected with *M. tuberculosis* advance to clinical forms of TB, the involvement of genes controlling the rate of progression rather than bonafide susceptibility to TB may offer an effective genetic control of disease risk. Gene-environment interactions are critical for the appropriate selection of efficient host responses and hence, genetic control mechanism. The NRAMP-1 effects are most pronounced in the absence of prior exposure to mycobacteria and NRAMP-1 is a modulator of the speed of progression from infection with *M. tuberculosis* to TB disease.

To identify the genes responsible for the difference in human susceptibility to TB, polymorphisms of three genes were investigated in a study,[52] namely NRAMP-1, MBL, and CD14 that encode the proteins crucial for the functions of macrophages.

MBL insufficiency due to polymorphisms in the MBL-2 gene causes an opsonization defect and predisposes to recurrent infections in children and adults.[53] The ethnicity may determine the association of MBL polymorphism with the resistance/susceptibility to TB.[52]

It is known that MBL binds mycobacteria strongly,[54] and it has thus been suggested that MBL may facilitate the uptake of mycobacterium by phagocytes. Since macrophages are the living environment for mycobacteria, high MBL serum levels could be a relative disadvantage for the host in relation to these bacteria.

The macrophage CD14 plays a pivotal role in innate immunity. It functions as a multifunctional receptor for bacterial cell wall components and enhances TLRs-mediated signaling.[55] Significant increase in CD14 has suggested a role of the CD14 molecule in the host mycobacterium interactions.

However, it is clear that the association of TB with various polymorphisms in SLC 11 A1 is a feature in many divergent population groups. The possibility remains that SLC 11 A1 is not the disease-associated gene but is in linkage disequilibrium (LD) with such a gene.

Some genes may facilitate hematogenous spread of *M. tuberculosis* that would lead to a greater association with extra-pulmonary TB (EPTB). Association of the common allele of MBL with both PTB and TB meningitis (TBM)[56] was reported that was stronger with TBM presumably because MBL is a serum lectin and, therefore, aided the blood-borne spread of *M. tuberculosis* resulting in TBM.

A review search of the literature systematically by means of meta-analysis[57] provided a qualitative summary estimate on the association with TB and the examination of some sources of study on heterogeneity. The summary odds ratios for studies with3'UTR, D'543 N, INT 4 and 5'(GT)n loci allele variants in the SLC11A1 gene were compared with their corresponding common alleles. The study concluded that polymorphisms of the four loci have no statistically significant association between the SLC11A1 variants and susceptibility to TB in subjects of European descent while they showed a statistically significant association in Asian subjects (in except the INT variant), African subjects (except the 3'UTR variant), and the population as a whole (except the INT4 variant).

In another meta-analysis study based on systematically reviewed and published studies on SLC11A1, polymorphisms, and TB susceptibility[7] quantitatively summarized associations of the most widely studied polymorphisms for 3'UTR, D'543 N, INT 4, and5'(GT)n, respectively. There was evidence of the association between SLC11A1 polymorphisms and TB susceptibility, supporting the hypothesis that NRAMP-1 (SLC11A1) gene might play on important role in the host defense in the development of TB.

The most widely studied SLC11A1 polymorphisms; 3'UTR, D'543N INT 4 and 5'(GT)n were identified, and their effects were summarized by means of a meta-analysis.[4,7-11,14,19,29,36,44,46,56-105] Significant associations with TB susceptibility were observed for all these four foci. A significant association has been observed for all populations (Africans, Asians, and Westerners) with at least one of the four loci.

The updated meta-analysis[57] based on 36 eligible studies until September 2010 did not present an ethnic-specific effect of SLC11A1 polymorphisms. Three ethnic groups were defined with respect to the distribution of the study population in the included studies, e.g. Asians, Africans, and Westerners (Europeans and Americans). Statistically significant or marginal associations with TB susceptibility were found for the four studied loci in all the three ethnic groups. A large number of included articles in the study make the evidence stronger to propose a consistent effect of SLC11A1 polymorphisms in the different populations. Moreover, the effects and role of polymorphisms of NRAMP-1 in the development of TB might not be disease type-specific.

A case–control study on sex- and age-dependent associations of SLC11A1 polymorphisms with TB in Chinese[58] showed the association of the polymorphisms SLC 6a (D'543N) and SLC 6b (3'UTR)of the SLC11A1 locus with TB. It also found a significant association with the 3'polymorphisms of SLC11A1 that was restricted to female patients and young patients.

Currently, the research hot spot is mainly on candidate predisposing genes of non-HLA such as VDR gene[59] NRAMP-1 gene[60] and mannose-binding protein (MBP).[61]

People with low Vitamin D content in serum face, higher risk of suffering from TB.[62] Vitamin D plays its role through VDR so that the polymorphism of genes may affect the activity and the subsequent mediated effect of VDR; it has been considered as a risk factor in a large number of clinical outcomes.[63]

VDR gene has many polymorphic loci and the most extensive research is focused on the Fok I and 3/noncoding regions (Taq I, Apa I, and Bsm I). This locus could be recognized and digested by the Fok I restriction end nuclease and thus, display polymorphism.

Many studies have shown evidence of the association between host genetics polymorphisms and TB susceptibility including CCL-2/MCP-1, NRAMP-1/SLC11A1, IRGM-1, IL-8, TLR, and NOD-2 genes.[7-11,64,65] Most of these genes participate in immune response and their polymorphisms may lead to increased genetic susceptibility to TB.

The genes for low molecular weight polypeptides (LMPs) and transporter with antigen processing (TAP) are located within the major histocompatibility complex (MHC)

Class II region of chromosome 6 between the HLA-DP and HLA-DQ loci and have been shown to play a critical role in the processing and presentation pathway for intracellular antigens.[66]

These data establish that MHC Class I antigen processing pathway that requires cleavage of antigen peptides by LMP2/LMP7 and transportation of peptide fragments into the endoplasmic reticulum by TAP 1/TAP 2 is vital for controlling *M. tuberculosis* infection and preventing the development of active TB.

A few of the polymorphisms (TAP 1 and TAP 2) have been studied to determine the predisposition toward TB in different ethnic groups that have revealed susceptibility to TB.[67,68]

LMP and TAP polymorphisms may differ among populations as reported by many studies. Significant association between LMP/TAP genes and TB was observed in a study where active TB patients and controls were compared.[69] The subjects containing LMP 7AA homozygote and CA heterozygote were found to be strongly associated with TB infection. Similarly, the TAP 1–2 polymorphisms also exhibited a significant relation to TB infection. Similar to the individual single-nucleotide polymorphism (SNPs), it was observed that haplotype B that carried LMP 7 and TAP 1–2 variations significantly increased the susceptibility to TB.[69]

The critical roles of the LMP/TAP genes are consistent with the observed association for TB. In a study, it was first reported a statistical association between alleles in TAP 2 region with PTB and tuberculoid leprosy susceptibility in the North Indian population.[67]

There is supporting evidence for the association between LMP gene polymorphisms and human susceptibility to TB disease. Evidence also supports the hypothesis that MHC Class I-mediated antigen presentation may play an important role in the host defense to TB.[69]

The majority of the population infected with *M. tuberculosis* maintains a latent state and do not convert to clinical disease, but do remain at risk of progressing to active TB later. Factors that can modulate progression to active TB include gender, anemia, smoking and alcohol consumptions as well as bacterial and host genetic factors.[70-72] Evidence from human and animal studies indicate that *M. tuberculosis* clearance in genetically regulated.[73] Twin studies, genome-wide linkage, and association analysis as well as candidate gene studies support the notions that human genetic factors play a role in the development of TB.[4] The majority of the genes that have been implicated so far are in immunological pathways.[74]

CCL-2/MCP-1 encodes the CCL-2/MCP-1 protein, a member of the CC cytokine subfamily that is characterized by two cysteine residue motif proximal to the amino terminus of the protein. The MCP-1 chemokine plays a key role in the granulomatous reaction in lung tissue and *M. tuberculosis* containment in mouse models occurs through interaction with the cognate receptor, chemokine (C-C motif) receptor-2 (CCR-2).[53] The chemokine MCP-1 was associated with severe TB and was proposed as a marker of disease severity.[75]

The 17q11–q21 chromosomal region encompassing MCP 1 was initially identified as a candidate for TB susceptibility in linkage analysis of multicase-TB and leprosy families from Brazil and the critical interval was subsequently refined to 17q11–12.[76]

To comprehensively evaluate the genetic risk of polymorphisms (D'543N, 3'UTR, TG ins/del, INT 4, [GT] n) in the SLC11A1 gene for TB, a total of 82 case–control studies in 35 articles were included.[77] The results showed that these four polymorphisms were associated with an increased risk of TB. The meta-analysis suggests that polymorphisms in the SLC11A1 gene contribute to TB (both PTB and EPTB), particularly in Asians.

The VDR gene has been studied in several studies as a candidate locus due to genetic polymorphisms that affect the activity of the receptor and subsequent downstream Vitamin D-mediated effects. Among Asians, the Fok l FF genotype showed a pronounced positive association, a significant inverse association was observed for the Bsm1 Bb genotype and marginal significant associations were found for Taq 1 and Apa 1 polymorphisms. However, none of the polymorphisms was significantly related to TB among Africans or South Americans. The association of VDR polymorphisms with risk of TB observed support of the hypothesis that Vitamin D deficiency might play a role as a risk factor during development of TB.

The VDR is involved in a wide range of biological functions, including meditation of Vitamin D3, interactions with the immune system.[59,78-81] Among UK Gujarati Asians, the FF genotype was associated with an increase in TB susceptibility, particularly EPTB.[59]

In South Indians, the Taq1 and Fok 1 variants as well as two others, Bsm 1 and Apa 1 restriction fragment polymorphisms both in intron 8, were examined in a case–control study involving patients with spinal TB.[82] The Bsml Bb genotype was found to be elevated in patients, as was the FF. In a comparison study, the FF genotype was associated with active PTB among males[83] while in females, the TT genotype was associated with spinal TB.[84,85] Although VDR data appear to be in conflict across populations, this may be explained by the multiple roles of Vitamin D3[82] suggesting that higher utilization of Vitamin D3 for those with the FF genotype may result in lowered serum Vitamin D3, increasing risk for spinal TB.

As a member of the epidermal growth factor (EGF) family, epiregulin (EREG) is better known for its role in cell growth and homeostasis. Evidence supports a broader biological

role for EREG with evidence that it is involved in the macrophage response to *M. tuberculosis* infection.[86]

The polymorphism associated with TB is located within an intronic region of the EREG gene and is likely a genetic marker in LD with the functional and disease causative allele.

There is evidence to support the hypothesis that some strains of *M. tuberculosis* are more virulent than others.[87] This suggests that the causative variant of EREG may be associated with an impaired immune response to *M. tuberculosis* leading to more aggressive disease, prolonged bacteremia, and an increased chance of seeding to the meninges. This demonstrates a further significant interaction between host and bacterial genotypes and the development of TB. This provides the first evidence to suggest an important role for EREG in the human immune response to TB.

One of the first reports of an association between HLA and TB showed an increased frequency of HLA-B8 in Canada. Other studies showed an increased frequency of HLA-B5, B15, and DR 5 in the North American Black population, HLA-A2, and B5 in the Egyptian population and B27 in the Greek population.

A significantly increased frequency of HLA-DR2 was seen in the major studies those have revealed HLA-DR2 association with higher susceptibility to TB in Russia, China, and Canada. An increased frequency of HLA-DR2 and HLA-DQ1 was shown to be associated with the susceptibility to PTB in the Indian population. Molecular study has revealed that the allele DRB*1501 of HLA-DR2 was higher compared with DRB*1502 in North Indian patients. HLA-DRB1*1501, HLA-DQB1*0601 (a subtype of HLA-DQ1) and DPB1*02 were found to be positively associated with susceptibility to PTB in Indian patients.[19]

TB and HIV coinfections place an immense burden on healthcare systems and pose particular diagnostic and therapeutic challenges. Infection with HIV is the most powerful risk factor predisposing to *M. tuberculosis* infection and progression to active disease that increases the risk of latent TB reactivation 20-fold. TB is also the most common cause of acquired immune deficiency syndrome (AIDS)-related death. Thus, *M. tuberculosis* and HIV act in synergy, accelerating the decline of immunological functions and leading to subsequent death of untreated patients. TB is the largest single cause of death in the settings of AIDS.[88] Various lines of evidence indicate that inborn errors of immunity as well as genetic polymorphisms have an impact on the susceptibility to TB and HIV.[89]

Cell-mediated immunity is essential for the control of *M. tuberculosis* infection; activation of both CD4 and CD 8 T-cells seen in active TB in humans, as well as in mice after experimental infection.[90] T-cells recruited to the infected lung are thought to control infection by producing IFN-gamma in response to mycobacterial antigens presented by macrophages.[91,92] In turn, IFN-gamma activates macrophages to kill the intracellular bacteria through reactive nitrogen and oxygen intermediates[93] and by inducing phagosome formation.[94]

Maxine Caws *et al*. in a study,[95] on the influence of the host and bacterial genotype on the development of the disseminated disease with *M. tuberculosis*, provides evidence that *M. tuberculosis* genotype influences clinical disease phenotype and demonstrates a significant interaction between the host and bacterial genotypes and the development of TB.

Defining the contribution of host genetic polymorphisms to disease susceptibility based on studies has suggested that polymorphisms in several genes are associated with the development of PTB. Some of these genes with polymorphism that have been validated in multiple studies and may have an effect on gene functions including solute carrier family 11 member 1, SLC11A1, formerly NRAMP-1,[14,44,96-98] IFN-gamma,[99,100] TIRAP/MAL,[101] P2XA7[102,103] (Fernando *et al*., 2005), and CCL 2 or MCP-1.[73,104,105]

Studies provide evidence that *M. tuberculosis* genotype influences diseases phenotype. Also, there is evidence to support the association between the host and bacterial genotype in concert in *M. tuberculosis* disease.

Here arise certain important research questions:

- Why do not all *M. tuberculosis*-infected persons develop TB disease?
- Why do not all immune compromised and infected patients progress to TB disease?
- Even though the risk of developing TB in high among HIV-infected people, why do not all HIV-infected and AIDS patients develop TB?
- Why do not all patients with diabetes mellitus who are infected with *M. tuberculosis* develop TB?
- Why do not all family members and contacts of the patients with PTB develop TB disease?
- Why all health care providers attending to patients with PTB are not developing TB diseases?
- Why is there a difference in prevalence of the disease in different geographical areas and ethnic group?

If we go through the relevant scientific data for the answers, they will guide us to the genetic factors of both the host and the pathogen.

After perusing several well-documented research works, various salient observations and conclusions, there is sufficient evidence to prove that TB is a genetically primed and determined infectious disease caused by *M. tuberculosis* and the genetic polymorphism is the mechanism that leads to progression from infection to TB disease.

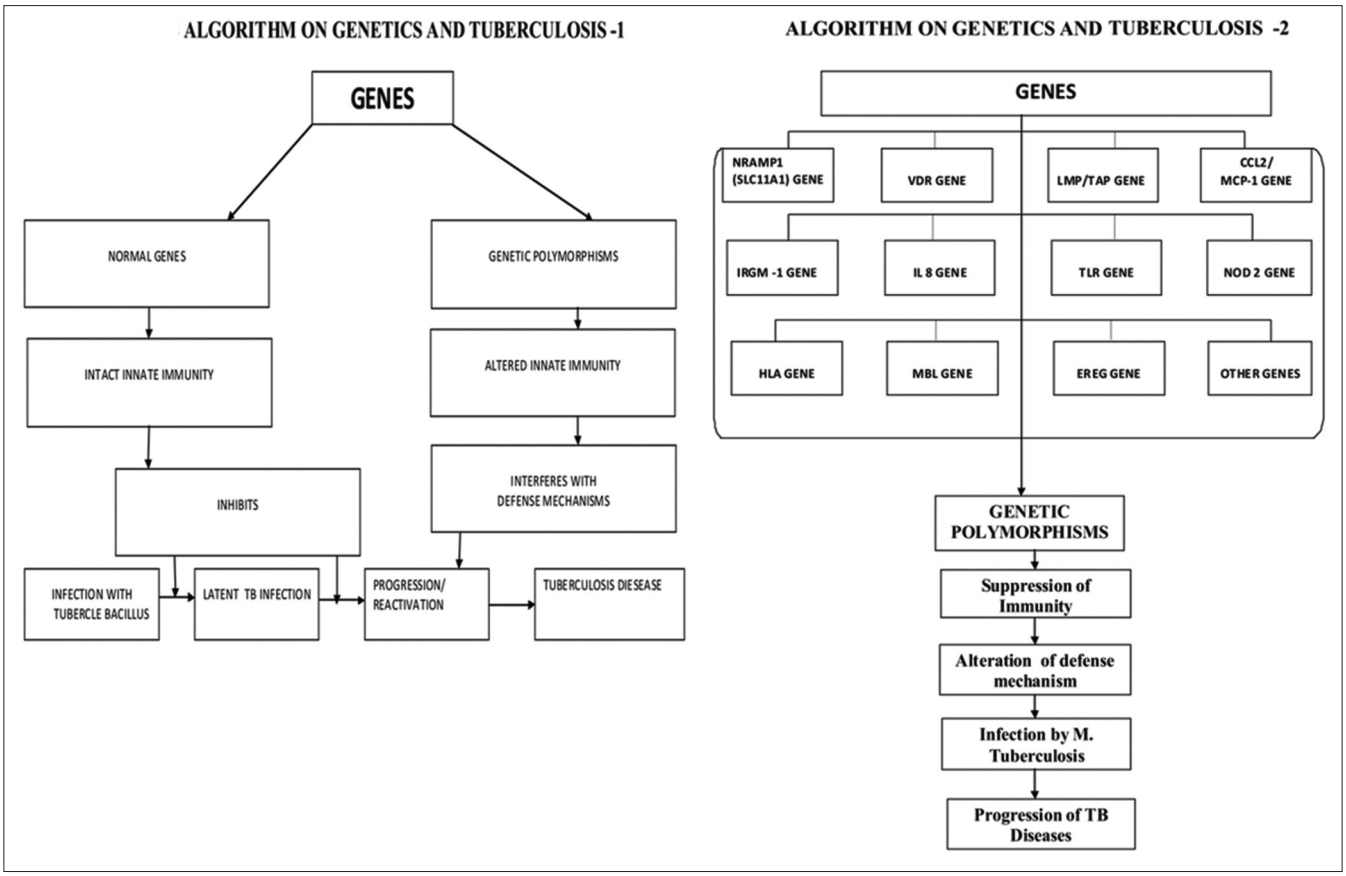

Figure 1: Algorithm 1 and 2

The proposed hypothesis and algorithms of "Genetic Polymorphism and TB" is given in Figure 1.

According to this theory, TB is an infectious disease caused by *M. tuberculosis*, primed and determined by genetic polymorphism. The *M. tuberculosis* is not the only determining factor toward progression. Genetic factors play a major role in the pathogenesis. In addition, genetic factors influence the immune responses of an individual. Polymorphisms in the different genes can influence and modulate the immune responses and that is why all *M. tuberculosis* infected people are not progressing to TB disease.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. WHO. Global TB Control Report; 2010.
2. Grosset J, Truffpt-Permot C, Cambau E. Bacteriology of tuberculosis. In: Reichmann LB, Herschfield ES, editors. Tuberculosis – A Comprehensive International Approach. 2nd ed. New York: Marcel Dekker; 2000. p. 157-85.
3. Central TB Division. Managing the Revised National Tuberculosis Control Programme in Your Area: A Training Course Modules (1-4). New Delhi: Central TB Division, Ministry of Health and Family Welfare, Nirman Bhavan; New Delhi, India. 2000. p. 1-4.
4. Comstock GW. Tuberculosis in twins: A re-analysis of the Prophit survey. Am Rev Respir Dis 1978;117:621-4.
5. Schurr E. Is susceptibility to tuberculosis acquired or inherited? J Intern Med 2007;261:106-11.
6. Feng WX, Mokrousov I, Wang BB, Nelson H, Jiao WW, Wang J, *et al*. Tag SNP polymorphism of CCL2 and its role in clinical tuberculosis in Han Chinese pediatric population. PLoS One 2011;6:e14652.
7. Li X, Yang Y, Zhou F, Zhang Y, Lu H, Jin Q, *et al*. SLC11A1 (NRAMP1) polymorphisms and tuberculosis susceptibility: Updated systematic review and meta-analysis. PLoS One 2011;6:e15831.
8. King KY, Lew JD, Ha NP, Lin JS, Ma X, Graviss EA, *et al*. Polymorphic allele of human IRGM1 is associated with susceptibility to tuberculosis in African Americans. PLoS One 2011;6:e16317.
9. Ma X, Reich RA, Wright JA, Tooker HR, Teeter LD, Musser JM, *et al*. Association between interleukin-8 gene alleles and human susceptibility to tuberculosis disease. J Infect Dis 2003;188:349-55.
10. Ma X, Liu Y, Gowen BB, Graviss EA, Clark AG, Musser JM. Full-exon resequencing reveals toll-like receptor variants contribute to human susceptibility to tuberculosis disease. PLoS One 2007;2:e1318.
11. Austin CM, Ma X, Graviss EA. Common nonsynonymous polymorphisms in the NOD2 gene are associated with resistance or susceptibility to tuberculosis disease in African Americans. J Infect Dis 2008;197:1713-6.
12. Gruenheid S, Gros P. Genetic susceptibility to intracellular infections: Nramp1, macrophage function and divalent cations transport. Curr Opin Microbiol 2000;3:43-8.
13. Blackwell JM, Goswami T, Evans CA, Sibthorpe D, Papo N, White JK, *et al*. SLC11A1 (formerly NRAMP1) and disease resistance. Cell Microbiol 2001;3:773-84.
14. Bellamy R, Ruwende C, Corrah T, McAdam KP, Whittle HC, Hill AV. Variations in the NRAMP1 gene and susceptibility to tuberculosis in West Africans. N Engl J Med 1998;338:640-4.
15. Kim J, Chung YD, Park DY, Choi S, Shin DW, Soh H, *et al*. A TRPV family ion channel required for hearing in *Drosophila*. Nature 2003;424:81-4.
16. Zhang W, Shao L, Weng X, Hu Z, Jin A, Chen S, *et al*. Variants of the

natural resistance-associated macrophage protein 1 gene (NRAMP1) are associated with severe forms of pulmonary tuberculosis. Clin Infect Dis 2005;40:1232-6.
17. Dubaniewicz A, Jamieson SE, Dubaniewicz-Wybieralska M, Fakiola M, Nancy Miller E, Blackwell JM. Association between SLC11A1 (formerly NRAMP1) and the risk of sarcoidosis in Poland. Eur J Hum Genet 2005;13:829-34.
18. Nugraha J, Anggraini R. NRAMP1 polymorphism and susceptibility to lung tuberculosis in Surabaya, Indonesia. Southeast Asian J Trop Med Public Health 2011;42:338-41.
19. Selvaraj P. Host genetics and tuberculosis susceptibility. Curr Sci 2004;86:115-21.
20. Selvaraj P, Kurian SM, Uma H, Reetha AM, Narayanan PR. Influence of non-MHC genes on lymphocyte response to *Mycobacterium tuberculosis* antigens and tuberculin reactive status in pulmonary tuberculosis. Indian J Med Res 2000;112:86-92.
21. Bennett S, Lienhardt C, Bah-Sow O, Gustafson P, Manneh K, Del Prete G, *et al*. Investigation of environmental and host-related risk factors for tuberculosis in Africa. II. Investigation of host genetic factors. Am J Epidemiol 2002;155:1074-9.
22. Cheepsattayakorn A, Cheepsattayakorn R. Human genetic influence on susceptibility of tuberculosis: From infection to disease. J Med Assoc Thai 2009;92:136-41.
23. Bellamy R, Ruwende C, Corrah T, McAdam KP, Thursz M, Whittle HC, *et al*. Tuberculosis and chronic hepatitis B virus infection in Africans and variation in the Vitamin D receptor gene. J Infect Dis 1999;179:721-4.
24. Armstrong JA, Hart PD. Response of cultured macrophages to *Mycobacterium tuberculosis*, with observations on fusion of lysosomes with phagosomes. J Exp Med 1971;134(3 Pt 1):713-40.
25. Bellamy R, Ruwende C, McAdam KP, Thursz M, Sumiya M, Summerfield J, *et al*. Mannose binding protein deficiency is not associated with malaria, hepatitis B carriage nor tuberculosis in Africans. QJM 1998;91:13-8.
26. Davies PD. A possible link between Vitamin D deficiency and impaired host defence to *Mycobacterium tuberculosis*. Tubercle 1985;66:301-6.
27. Bellamy RJ, Hill AV. Host genetic susceptibility to human tuberculosis. In: Chadwick DJ, Cardew G, editors. Genetics and Tuberculosis. Chichester: John Wiley and Sons; 1998. p. 23, 30.
28. Macrae DE. Calciferol treatment of lupus vulgaris. Br J Dermatol Syph 1947;59:333-8.
29. Manolagas SC, Yu XP, Girasole G, Bellido T. Vitamin D and the hematolymphopoietic tissue: A 1994 update. Semin Nephrol 1994;14:129-43.
30. Denis M. Killing of *Mycobacterium tuberculosis* within human monocytes: Activation by cytokines and calcitriol. Clin Exp Immunol 1991;84:200-6.
31. Garred P, Harboe M, Oettinger T, Koch C, Svejgaard A. Dual role of mannan-binding protein in infections: Another case of heterosis? Eur J Immunogenet 1994;21:125-31.
32. Mulero V, Searle S, Blackwell JM, Brock JH. Solute carrier 11a1 (Slc11a1; formerly Nramp1) regulates metabolism and release of iron acquired by phagocytic, but not transferrin-receptor-mediated, iron uptake. Biochem J 2002;363(Pt 1):89-94.
33. Brown DH, Miles BA, Zwilling BS. Growth of *Mycobacterium tuberculosis* in BCG-resistant and -susceptible mice: Establishment of latency and reactivation. Infect Immun 1995;63:2243-7.
34. Awomoyi AA, Marchant A, Howson JM, McAdam KP, Blackwell JM, Newport MJ. Interleukin-10, polymorphism in SLC11A1 (formerly NRAMP1), and susceptibility to tuberculosis. J Infect Dis 2002;186:1808-14.
35. Farnia P, Pajand O, Anoosheh S, Tabarsi P, Dizaji MK, Mohammed F, *et al*. Comparison of NRAMP1 gene polymorphism among TB health care workers and recently infected cases; assessment of host susceptibility. Tanaffos 2008;7:19-24.
36. Malik S, Abel L, Tooker H, Poon A, Simkin L, Girard M, *et al*. Alleles of the NRAMP1 gene are risk factors for pediatric tuberculosis disease. Proc Natl Acad Sci U S A 2005;102:12183-8.
37. Lavebratt C, Apt AS, Nikonenko BV, Schalling M, Schurr E. Severity of tuberculosis in mice is linked to distal chromosome 3 and proximal chromosome 9. J Infect Dis 1999;180:150-5.
38. Mitsos LM, Cardon LR, Fortin A, Ryan L, LaCourse R, North RJ, *et al*. Genetic control of susceptibility to infection with *Mycobacterium tuberculosis* in mice. Genes Immun 2000;1:467-77.
39. Sánchez F, Radaeva TV, Nikonenko BV, Persson AS, Sengul S, Schalling M, *et al*. Multigenic control of disease severity after virulent *Mycobacterium tuberculosis* infection in mice. Infect Immun 2003;71:126-31.
40. Pan H, Yan BS, Rojas M, Shebzukhov YV, Zhou H, Kobzik L, *et al*. Ipr1 gene mediates innate immunity to tuberculosis. Nature 2005;434:767-72.
41. Gruenheid S, Pinner E, Desjardins M, Gros P. Natural resistance to infection with intracellular pathogens: The Nramp1 protein is recruited to the membrane of the phagosome. J Exp Med 1997;185:717-30.
42. Hoal EG, Lewis LA, Jamieson SE, Tanzer F, Rossouw M, Victor T, *et al*. SLC11A1 (NRAMP1) but not SLC11A2 (NRAMP2) polymorphisms are associated with susceptibility to tuberculosis in a high-incidence community in South Africa. Int J Tuberc Lung Dis 2004;8:1464-71.
43. Cervino AC, Lakiss S, Sow O, Hill AV. Allelic association between the NRAMP1 gene and susceptibility to tuberculosis in Guinea-Conakry. Ann Hum Genet 2000;64(Pt 6):507-12.
44. Gao PS, Fujishima S, Mao XQ, Remus N, Kanda M, Enomoto T, *et al*. Genetic variants of NRAMP1 and active tuberculosis in Japanese populations. International Tuberculosis Genetics Team. Clin Genet 2000;58:74-6.
45. Ryu S, Park YK, Bai GH, Kim SJ, Park SN, Kang S. 3′UTR polymorphisms in the NRAMP1 gene are associated with susceptibility to tuberculosis in Koreans. Int J Tuberc Lung Dis 2000;4:577-80.
46. Greenwood CM, Fujiwara TM, Boothroyd LJ, Miller MA, Frappier D, Fanning EA, *et al*. Linkage of tuberculosis to chromosome 2q35 loci, including NRAMP1, in a large aboriginal Canadian family. Am J Hum Genet 2000;67:405-16.
47. Ma X, Dou S, Wright JA, Reich RA, Teeter LD, El Sahly HM, *et al*. 5′ dinucleotide repeat polymorphism of NRAMP1 and susceptibility to tuberculosis among Caucasian patients in Houston, Texas. Int J Tuberc Lung Dis 2002;6:818-23.
48. Delgado JC, Baena A, Thim S, Goldfeld AE. Ethnic-specific genetic associations with pulmonary tuberculosis. J Infect Dis 2002;186:1463-8.
49. Søborg C, Andersen AB, Madsen HO, Kok-Jensen A, Skinhøj P, Garred P. Natural resistance-associated macrophage protein 1 polymorphisms are associated with microscopy-positive tuberculosis. J Infect Dis 2002;186:517-21.
50. Liaw YS, Tsai-Wu JJ, Wu CH, Hung CC, Lee CN, Yang PC, *et al*. Variations in the NRAMP1 gene and susceptibility of tuberculosis in Taiwanese. Int J Tuberc Lung Dis 2002;6:454-60.
51. El Baghdadi J, Remus N, Benslimane A, El Annaz H, Chentoufi M, Abel L, *et al*. Variants of the human NRAMP1 gene and susceptibility to tuberculosis in Morocco. Int J Tuberc Lung Dis 2003;7:599-602.
52. Druszczynska M, Strapagiel D, Kwiatkowska S, Kowalewicz-Kulbat M, Rózalska B, Chmiela M, *et al*. Tuberculosis bacilli still posing a threat. Polymorphism of genes regulating anti-mycobacterial properties of macrophages. Pol J Microbiol 2006;55:7-12.
53. Saunders BM, Britton WJ. Life and death in the granuloma: Immunopathology of tuberculosis. Immunol Cell Biol 2007;85:103-11.
54. Nadesalingam J, Dodds AW, Reid KB, Palaniyar N. Mannose-binding lectin recognizes peptidoglycan via the N-acetyl glucosamine moiety, and inhibits ligand-induced proinflammatory effect and promotes chemokine production by macrophages. J Immunol 2005;175:1785-94.
55. LeBouder E, Rey-Nores JE, Rushmere NK, Grigorov M, Lawn SD, Affolter M, *et al*. Soluble forms of Toll-like receptor (TLR)2 capable of modulating TLR2 signaling are present in human plasma and breast milk. J Immunol 2003;171:6680-9.
56. Hoal-Van Helden EG, Epstein J, Victor TC, Hon D, Lewis LA, Beyers N, *et al*. Mannose-binding protein B allele confers protection against tuberculous meningitis. Pediatr Res 1999;45(4 Pt 1):459-64.
57. Li HT, Zhang TT, Zhou YQ, Huang QH, Huang J. SLC11A1 (formerly NRAMP1) gene polymorphisms and tuberculosis susceptibility: A meta-analysis. Int J Tuberc Lung Dis 2006;10:3-12.
58. Leung KH, Yip SP, Wong WS, Yiu LS, Chan KK, Lai WM, *et al*. Sex- and age-dependent association of SLC11A1 polymorphisms with tuberculosis in Chinese: A case control study. BMC Infect Dis 2007;7:19.
59. Wilkinson RJ, Llewelyn M, Toossi Z, Patel P, Pasvol G, Lalvani A, *et al*. Influence of Vitamin D deficiency and Vitamin D receptor polymorphisms on tuberculosis among Gujarati Asians in West London: A case-control study. Lancet 2000;355:618-21.
60. Li HT, Zhang TT, Huang QH, Lv B, Huang J. Meta-analysis on NRAMP1 gene polymorphisms and tuberculosis susceptibility in East-Asia population. Zhonghua Liu Xing Bing Xue Za Zhi 2006;27:428-32.
61. Denholm JT, McBryde ES, Eisen DP. Mannose-binding lectin and susceptibility to tuberculosis: A meta-analysis. Clin Exp Immunol 2010;162:84-90.

62. Singh SP, Mehra NK, Dingley HB, Pande JN, Vaidya MC. Human leukocyte antigen (HLA)-linked control of susceptibility to pulmonary tuberculosis and association with HLA-DR types. J Infect Dis 1983;148:676-81.
63. Liu ZQ, Song CX, Hu XL, Li L, Shi GL. Study of HLA-DR.DQ genes associated with tuberculosis of the bone and joint. Chin J Antituberculosis (Chin) 2000;22:130-2.
64. Feng WX, Mokrousov I, Wang BB, Nelson H, Jiao WW, Wang J, *et al*. Tag SNP polymorphism of CCL2 and its role in clinical tuberculosis in Han Chinese pediatric population. PLoS One 2011;6:e14652.
65. York IA, Rock KL. Antigen processing and presentation by the class I major histocompatibility complex. Annu Rev Immunol 1996;14:369-96.
66. Lewinsohn DM, Grotzke JE, Heinzel AS, Zhu L, Ovendale PJ, Johnson M, *et al*. Secreted proteins from *Mycobacterium tuberculosis* gain access to the cytosolic MHC class-I antigen-processing pathway. J Immunol 2006;177:437-42.
67. Rajalingam R, Singal DP, Mehra NK. Transporter associated with antigen-processing (TAP) genes and susceptibility to tuberculoid leprosy and pulmonary tuberculosis. Tissue Antigens 1997;49:168-72.
68. Gomez LM, Camargo JF, Castiblanco J, Ruiz-Narváez EA, Cadena J, Anaya JM. Analysis of IL1B, TAP1, TAP2 and IKBL polymorphisms on susceptibility to tuberculosis. Tissue Antigens 2006;67:290-6.
69. Wang D, Zhou Y, Ji L, He T, Lin F, Lin R, *et al*. Association of LMP/TAP gene polymorphisms with tuberculosis susceptibility in Li population in China. PLoS One 2012;7:e33051.
70. Flynn JL, Chan J. Immunology of tuberculosis. Annu Rev Immunol 2001;19:93-129.
71. Möller M, de Wit E, Hoal EG. Past, present and future directions in human genetic susceptibility to tuberculosis. FEMS Immunol Med Microbiol 2010;58:3-26.
72. Lienhardt C, Bennett S, Del Prete G, Bah-Sow O, Newport M, Gustafson P, *et al*. Investigation of environmental and host-related risk factors for tuberculosis in Africa. I. Methodological aspects of a combined design. Am J Epidemiol 2002;155:1066-73.
73. Berrington WR, Hawn TR. *Mycobacterium tuberculosis*, macrophages, and the innate immune response: Does common variation matter? Immunol Rev 2007;219:167-86.
74. Vannberg FO, Chapman SJ, Hill AV. Human genetic susceptibility to intracellular pathogens. Immunol Rev 2011;240:105-16.
75. Hasan Z, Cliff JM, Dockrell HM, Jamil B, Irfan M, Ashraf M, *et al*. CCL2 responses to *Mycobacterium tuberculosis* are associated with disease severity in tuberculosis. PLoS One 2009;4:e8459.
76. Blackwell JM, Black GF, Peacock CS, Miller EN, Sibthorpe D, Gnananandha D, *et al*. Immunogenetics of leishmanial and mycobacterial infections: The Belem Family Study. Philos Trans R Soc Lond B Biol Sci 1997;352:1331-45.
77. Meilang Q, Zhang Y, Zhang J, Zhao Y, Tian C, Huang J, *et al*. Polymorphisms in the SLC11A1 gene and tuberculosis risk: A meta-analysis update. Int J Tuberc Lung Dis 2012;16:437-46.
78. Gao L, Tao Y, Zhang L, Jin Q. Vitamin D receptor genetic polymorphisms and tuberculosis: Updated systematic review and meta-analysis. Int J Tuberc Lung Dis 2010;14:15-23.
79. Hewison M, O'Riordan JL. Immunomodulatory cell differentiation effects of the Vitamin D. In: Feldman D, Glorieux FH, Pike JW, editors. Vitamin D. San Diego: Academic Press; 1997. p. 447-62.
80. Provvedini DM, Tsoukas CD, Deftos LJ, Manolagas SC. 1,25-dihydroxyvitamin D3 receptors in human leukocytes. Science 1983;221:1181-3.
81. Rook GA, Steele J, Fraher L, Barker S, Karmali R, O'Riordan J, *et al*. Vitamin D3, gamma interferon, and control of proliferation of *Mycobacterium tuberculosis* by human monocytes. Immunology 1986;57:159-63.
82. Selvaraj P, Kurian SM, Chandra G, Reetha AM, Charles N, Narayanan PR. Vitamin D receptor gene variants of BsmI, ApaI, TaqI, and FokI polymorphisms in spinal tuberculosis. Clin Genet 2004;65:73-6.
83. Selvaraj P, Chandra G, Kurain SM, Reetha AM, Narayanan PR. Association of Vitamin D receptor gene variants of Bsml, Apal and Fokl polymorphisms with susceptibilityor resistance to pulmonary tuberculosis. Curr Sci 2003;84:1564-8.
84. Selvaraj P, Narayanan PR, Reetha AM. Association of Vitamin D receptor genotypes with the susceptibility to pulmonary tuberculosis in female patients and resistance in female contacts. Indian J Med Res 2000;111:172-9.
85. Selvaraj P, Kurian SM, Chandra G, Reetha AM, Charles N, Narayanan PR. Vitamin D receptor gene variants of BsmI, ApaI, TaqI, and FokI polymorphisms in spinal tuberculosis. Clin Genet 2004;65:73-6.
86. Thuong NT, Hawn TR, Chau TT, Bang ND, Yen NT, Thwaites GE, *et al*. Epiregulin (EREG) variation is associated with susceptibility to tuberculosis. Genes Immun 2012;13:275-81.
87. Nicol MP, Wilkinson RJ. The clinical consequences of strain diversity in *Mycobacterium tuberculosis*. Trans R Soc Trop Med Hyg 2008;102:955-65.
88. Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, Raviglione MC, *et al*. The growing burden of tuberculosis: Global trends and interactions with the HIV epidemic. Arch Intern Med 2003;163:1009-21.
89. Möller M, Hoal EG. Current findings, challenges and novel approaches in human genetic susceptibility to tuberculosis. Tuberculosis (Edinb) 2010;90:71-83.
90. Cooper AM. T cells in mycobacterial infection and disease. Curr Opin Immunol 2009;21:378-84.
91. Lazarevic V, Flynn J. CD8+ T cells in tuberculosis. Am J Respir Crit Care Med 2002;166:1116-21.
92. Orme IM, Roberts AD, Griffin JP, Abrams JS. Cytokine secretion by CD4 T lymphocytes acquired in response to *Mycobacterium tuberculosis* infection. J Immunol 1993;151:518-25.
93. Chan J, Flynn J. The immunological aspects of latency in tuberculosis. Clin Immunol 2004;110:2-12.
94. Chackerian AA, Alt JM, Perera TV, Dascher CC, Behar SM. Dissemination of *Mycobacterium tuberculosis* is influenced by host factors and precedes the initiation of T-cell immunity. Infect Immun 2002;70:4501-9.
95. Caws M, Thwaites G, Dunstan S, Hawn TR, Lan NT, Thuong NT, *et al*. The influence of host and bacterial genotype on the development of disseminated disease with *Mycobacterium tuberculosis*. PLoS Pathog 2008;4:e1000034.
96. Fitness J, Floyd S, Warndorff DK, Sichali L, Malema S, Crampin AC, *et al*. Large-scale candidate gene study of tuberculosis susceptibility in the Karonga district of Northern Malawi. Am J Trop Med Hyg 2004;71:341-9.
97. Shaw MA, Collins A, Peacock CS, Miller EN, Black GF, Sibthorpe D, *et al*. Evidence that genetic susceptibility to *Mycobacterium tuberculosis* in a Brazilian population is under oligogenic control: Linkage study of the candidate genes NRAMP1 and TNFA. Tuber Lung Dis 1997;78:35-45.
98. Søborg C, Andersen AB, Range N, Malenganisho W, Friis H, Magnussen P, *et al*. Influence of candidate susceptibility genes on tuberculosis in a high endemic region. Mol Immunol 2007;44:2213-20.
99. Rossouw M, Nel HJ, Cooke GS, van Helden PD, Hoal EG. Association between tuberculosis and a polymorphic NFkappaB binding site in the interferon gamma gene. Lancet 2003;361:1871-2.
100. Lio D, Marino V, Serauto A, Gioia V, Scola L, Crivello A, *et al*. Genotype frequencies of the +874T-->A single nucleotide polymorphism in the first intron of the interferon-gamma gene in a sample of Sicilian patients affected by tuberculosis. Eur J Immunogenet 2002;29:371-4.
101. Khor CC, Chapman SJ, Vannberg FO, Dunne A, Murphy C, Ling EY, *et al*. A mal functional variant is associated with protection against invasive pneumococcal disease, bacteremia, malaria and tuberculosis. Nat Genet 2007;39:523-8.
102. Li CM, Campbell SJ, Kumararatne DS, Bellamy R, Ruwende C, McAdam KP, *et al*. Association of a polymorphism in the P2X 7 gene with tuberculosis in a Gambian population. J Infect Dis 2002;186:1458-62.
103. Fernando SL, Britton WJ. Genetic susceptibility to mycobacterial disease in humans. Immunol Cell Biol 2006;84:125-37.
104. Casanova JL, Abel L. Genetic dissection of immunity to mycobacteria: The human model. Annu Rev Immunol 2002;20:581-620.
105. Flores-Villanueva PO, Ruiz-Morales JA, Song CH, Flores LM, Jo EK, Montaño M, *et al*. A functional promoter polymorphism in monocyte chemoattractant protein-1 is associated with increased susceptibility to pulmonary tuberculosis. J Exp Med 2005;202:1649-58.