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Biomedical Importance of Host Genetic Factors in Infectious Diseases

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1. Introduction

Tuberculosis, human immunodeficiency virus/acquired immunodeficiency syndrome and malaria are the three most profound cause of death worldwide. In developing country tuberculosis is a serious problem. It is estimated that one third of the world's population is infected with *M. tuberculosis*; however, only a minority (10%) of those infected ever develop clinical disease (Corbett et al., 2003). Such clinical diversity suggests that factors other than bacterial infection alone determine disease development. Tuberculosis (TB) is a significant disease affecting both humans and animals. Susceptibility to *Mycobacterium tuberculosis* is relatively higher in humans than other primates and guinea pigs. Cattle, rabbits and cats are susceptible to *M. bovis* and are quite resistant to *M. tuberculosis.*

Each year, 8.8 million patients are newly diagnosed with active TB and 1.6 million patients die of TB. The rapid spread of the human immunodeficiency virus has fueled the TB epidemic, especially in sub-Saharan Africa, where 28% of TB patients are HIV positive (WHO 2007). The current first-line treatment for TB is a multidrug regimen consisting of rifampin, isoniazid, pyrazinamide, and ethambutol (RIZE). Several major problems are associated with the currently available TB treatment. There is an increasing incidence of multidrug-resistant (MDR; resistance to at least rifampin and isoniazid) and extensively drug-resistant (XDR; MDR resistance plus resistance to a fluoroquinolone and an aminoglycoside) which is creating an alarming situation as far as treatment of the disease is concerned.

1.1 Causes of drug resistance

The emergence of drug resistance in *M. tuberculosis* in India has been associated with a variety of management, health provider and patient-related factors. These include, deficient or deteriorating TB control programs resulting in inadequate administration of effective treatment; poor case holding, administration of sub-standard drugs, inadequate or irregular drug supply and lack of supervision; ignorance of health care workers in epidemiology,

treatment and control; improper prescription of regimens; interruption of chemotherapy due to side effects; non-adherence of patients to the prescribed drug therapy; availability of anti-TB drugs across the counter, without prescription; massive bacillary load; illiteracy and low socio-economic status of the patients; the epidemic of HIV infection; laboratory delays in identification and susceptibility testing of *M. tuberculosis* isolates; use of non-standardized laboratory techniques, poor quality drug powders and lack of quality control measures; use of anti-TB drugs for indications other than tuberculosis.

1.2 Initial drug resistance in India

Indian Council of Medical Research (ICMR) undertook drug resistance studies during 1965-67 in nine urban areas of the country. However, this exercise was not a surveillance study and did not use strict sampling techniques, the centres being selected more for logistic considerations than for epidemiological reasons. Sputum specimens collected from all patients attending chest clinics were tested for drug susceptibility to streptomycin, Isoniazid, para amino salicyctic acid (PAS) and thioacetazone. The first study was on patients who had denied any history of previous treatment, while in the second study, patients with and without previous chemotherapy was included. The results showed that in the first study resistance to Isoniazid ranged from 11-20 per cent, to streptomycin from 8-20 per cent and to both drugs from 4-11 per cent. The second study showed resistance to Isoniazid to range from 15-69 per cent, to streptomycin from 12-63 per cent and to both drugs from 5-58 per cent. Further, the level of drug resistance was proportional to the duration of previous treatment.

1.3 Multi drug resistance in other countries

Resistance towards the responsible pathogens are also seen in developed countries. The situation has worsened often due to limited resource available to investigate and provide reliable susceptibility data on which rational treatments can be based as well as means to optimize the use of antimicrobial agents. The emergence of multi-drug-resistant isolates in tuberculosis, acute respiratory infections and diarrhea, often referred to as diseases of poverty, has had its greatest toll in developing countries. The epidemic of HIV/AIDS, with over 30 million cases in developing countries, has greatly enlarged the population of immuno compromised patients. The disease has left these patients at great risk of numerous infections and even greater risks of acquiring highly resistant organisms during long periods of hospitalization. This article discusses antimicrobial resistance in developing countries and the associated risk factors. Magnitude of resistance by regions Africa, America, Eastern Mediterranean, European, South East Asian, Western Pacific region has shown greater diversity in TB.

2. Symptoms

Symptoms of tuberculosis include: a bad cough that lasts 3 weeks or longer, pain in the chest, coughing up blood or sputum (phlegm from deep inside the lungs). Other symptoms of active TB disease are weakness or fatigue, weight loss, no appetite, chills, fever and sweating at night.

3. Spread

TB spreads through the air from one person to another. The bacteria are put into the air when a person with active TB disease of the lungs or throat coughs or sneezes. People nearby may breathe in these bacteria and get infected. When a person breathes in TB bacteria, which may settle in the lungs and begin to grow. From there, they can move through the blood to other parts of the body, such as the kidney, spine, and brain. TB in the lungs or throat can be infectious. This means that the bacteria can spread to other people. TB in other parts of the body, such as the kidney or spine, is usually not infectious. People with active TB disease are most likely to spread it to people they spend time with every day. This includes family members, friends, and coworkers.

4. Diagnoses

4.1 Molecular diagnosis of *Mycobacterium*

During the past several years, many molecular methods have been developed for direct detection, species identification, and drug susceptibility testing of mycobacteria.

4.1.1 Direct detection of mycobacteria from specimens

Many mycobacterial species, including *M. tuberculosis*, grow extremely slowly in the laboratory and require 3–8 weeks of incubation on solid medium or at least 2 weeks in a radiometric liquid culture system (BACTEC). This slow growth often leads to delay in TB diagnosis. Nucleic acid amplification (NAA) methods allow for detection of mycobacterial DNA or RNA directly from the specimens before the culture results are available. The Food and Drug Administration (FDA) has approved two NAA tests for direct detection of *M. tuberculosis* from clinical specimens. These are the Enhanced *Mycobacterium tuberculosis* Direct Test (E-MTD; Gen-Probe, San Diego, CA) and the Amplicor *Mycobacterium tuberculosis* Test (Amplicor; Roche Diagnostic Systems, Inc., Branchburg, NJ).

4.1.2 Amplicor test

Based on PCR assay, Mycobacterium is amplified. After amplification, the amplicons are denatured to form single strands and added to a microtiter plate containing a bound, *M. tuberculosis* complex-specific oligonucleotide probe. An avidin-horseradish peroxidase conjugate then binds to the bound, biotin-labeled amplicons. The conjugate reacts with peroxide and 3, 39, 5, 59-tetramethylbenzidine in dimethylformamide to form a color complex. The results are measured with a photometer.

4.1.3 E-MTD

The E-MTD test is based on the transcription-mediated amplification system developed by Kwoh et al. (1989). In this assay, rRNA is released from the target cells by sonication, and a promoter-primer binds to the rRNA target. Reverse transcriptase is then used to copy rRNA to a cDNA-RNA hybrid. The initial RNA strand is degraded, and a second primer binds to the cDNA and is extended, leading to the formation of double-stranded cDNA, which is then transcribed by DNA-directed RNA polymerase to produce more rRNA molecules. The new transcripts serve as templates for reverse transcription and further amplification. The

RNA amplicons are detected with an acridinium ester-labeled DNA probe in a solution hybridization assay.

4.1.4 DNA probes

Commercial DNA probes are available for detection of mycobacterium. These are based on species-specific DNA probes that hybridize with rRNA released from bacteria. The probes are labeled with acridinium ester, and results are measured with a luminometer.

4.1.5 Line-probe assay

The Line Probe assay (LiPA; Inno-Genetics N.V., Zwijndrecht, Belgium) has been developed for rapid detection of RIF resistance. The test is based on the reverse hybridization method, and it consists of PCR amplification of a segment of the *rpoB* gene and denaturation and hybridization of the biotinylated PCR amplicons to capture probes bound to a nitrocellulose strip. The bound amplicons are then detected with alkaline phosphatase-conjugated streptavidin and BCIP/NBT chromogen, producing a color reaction.

4.2 TB skin test

The TB skin test may be used to find out if you have TB infection. You can get a skin test at any pathology laboratory. A technician will inject a small amount of testing fluid (called tuberculin or PPD) just under the skin on the under side of the forearm. After 48 hours, you must return to have your skin test read by the laboratory technician. You may have a swelling where the tuberculin was injected. The technician will measure this swelling and tell you if your reaction to the test is positive or negative. A positive reaction usually means that you have been infected by someone with active TB.

5. National and international status

Tuberculosis (TB) is a major, global public health problem, particularly in sub-Saharan Africa, where the prevalence of TB is increasing dramatically with the rise of the HIV pandemic. One third of the world is infected by Mtb (*Mycobacterium tuberculosis*). (Raviglione et al., 1995). According to the World Health Organization, almost 8 million new cases of TB occur annually, with 2 million deaths attributed to the disease each year. There were globally an estimated 9.27 million new cases of tuberculosis (TB) and 1.3 million deaths in 2007 (WHO, 2009).

Uganda is one of the world's 22 highest burden countries with TB, with an estimated annual risk of tuberculosis infection of 3% and an annual incidence of new smear positive TB cases of 9.2 per 1000 in an urban setting (Guwatudde et al., 2003). Pakistan ranks 7th globally in terms of tuberculosis (TB) disease burden (Ansari et al., 2009).

TB is one of the leading causes of mortality in India killing more than 300,000 people every year. The Human Immunodeficiency Virus (HIV, the virus that causes AIDS) is the strongest risk factor for tuberculosis among adults. Tuberculosis is one of the earliest opportunistic diseases to develop amongst persons infected with HIV. HIV debilitates the immune system increasing the vulnerability to TB and enhancing the risk

of progression from TB infection to TB disease. An HIV positive person is six times (50-60% life time risk) more likely of developing TB disease once infected with TB bacilli, as compared to an HIV negative person, who has a 10% life-time risk. Since 1993, the Government of India has been implementing the WHO-recommended DOTS strategy via the Revised National Tuberculosis Control Programme (RNTCP). The revised strategy was pilot-tested in 1993 and launched as a national programme in 1997. By March 2006, the programme was implemented nationwide in 633 districts, covering 1114 million (100%) population.

India accounts for one fifth of the world's incident TB cases. The reported incidence in 2003 was 168 per 100,000 and in 2006 is nearly 175 per 100,000. Every year, nearly 2 million people die in India, and nearly 1 million cases are smear positive; An estimated 40% of the Indian population is latently infected with *M. tuberculosis*. A number of factors - cultural, social, political, economic and technical - have determined the nature of society's response to TB. It has been shown that most of the infectious TB cases in a rural community in South India. About three-fourths of them are worried about their sickness; and, about half of them actively seek treatment for their symptoms at rural medical hospital. The existing facilities deal with only a very small fraction of even these patients who are actively seeking treatment. The various study report carried out in India has shown increase in TB and MDR-TB . India is classified along with the sub-Saharan African countries to be among those with a high burden of TB.

5.1 Epidemiology

The aim of epidemiology is the determination of natural history of disease and measurement of its frequency.

5.1.1 Aims of epidemiology

- Describe the trends of disease.
- Evaluation of intervention
- Define the risk group
- Frequency, distribution, time, place and person

6. Available drugs

6.1 Fluoroquinolone- fluoroquinolone is a promising class of drugs for the treatment of TB

6.1.1 Moxifloxacin- Moxifloxacin is a broad-spectrum 8-methoxy fluoroquinolone with activity against both gram-positive and gram-negative bacteria, including anaerobes. It inhibits bacterial DNA gyrase, an enzyme that is essential for the maintenance of DNA supercoils.

6.1.2 Gatifloxacin: Like the other fluoroquinolones, gatifloxacin blocks the bacterial DNA gyrase, thereby preventing chromosomal replication.

6.2 Diarylquinolines. Diarylquinolines have been identified in a process of screening various compounds for potential anti-TB activity.
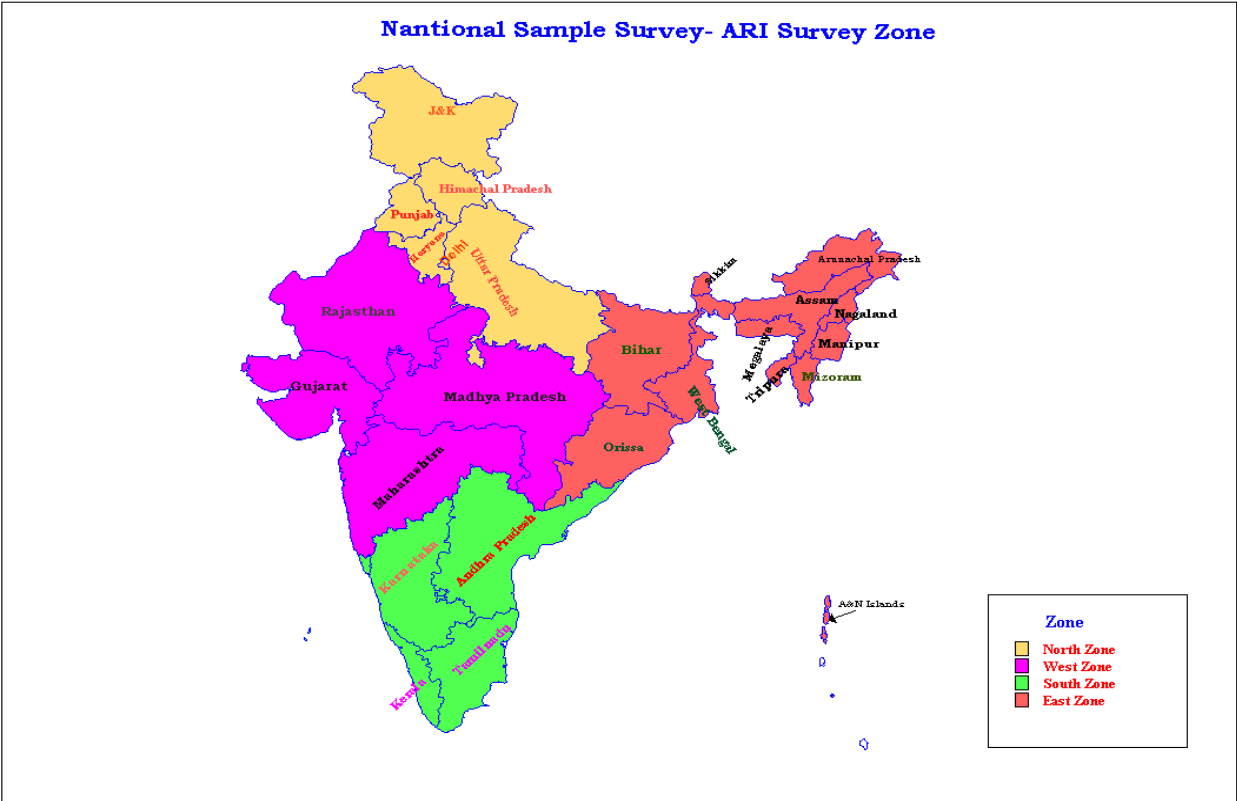
Fig. 1. Estimation of annual risk of Tuberculosis in different regions of India 2000-2003
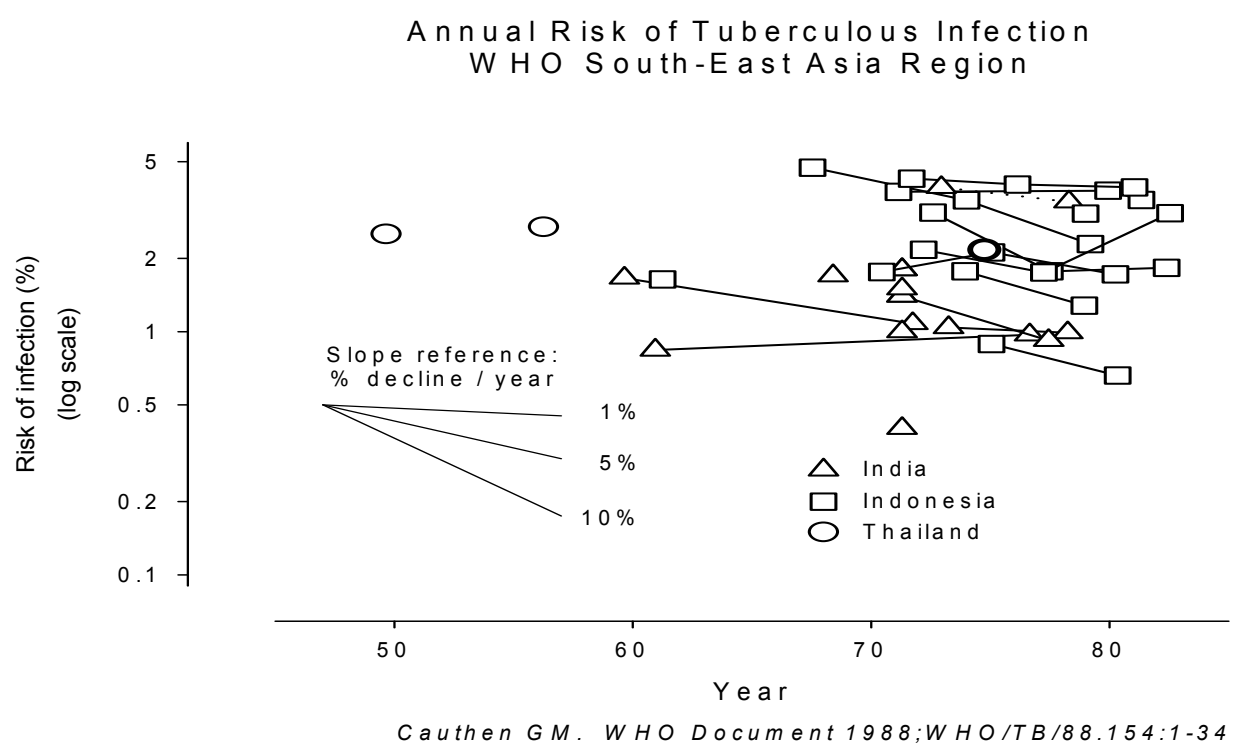(From National TB Institute Bangalore).

Fig. 2. Annual risk of Tuberculosis infection in South East Asia region.
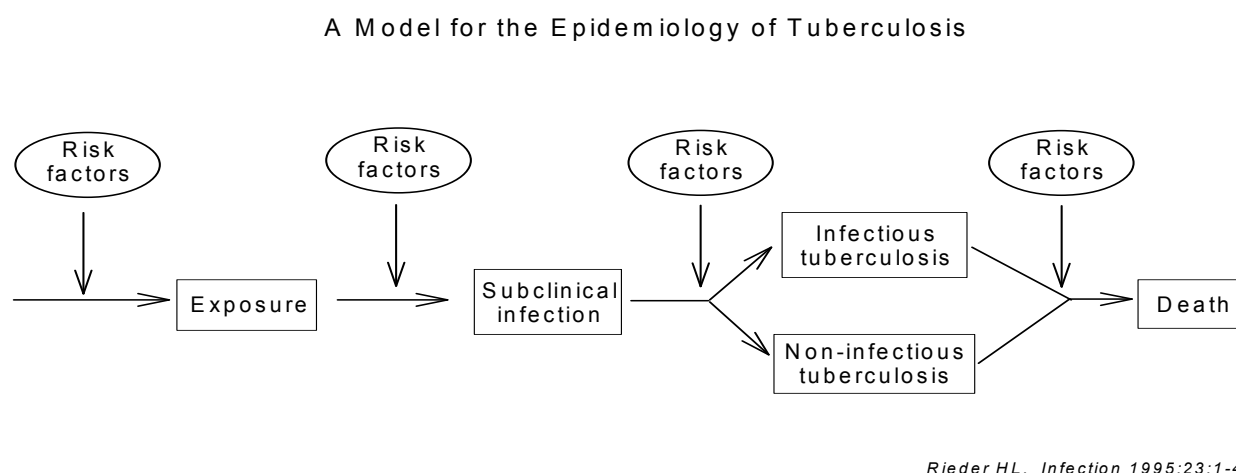
A Model for the Epidemiology of Tuberculosis

Rieder HL. Infection 1995;23:1-4

Fig. 3. Model of epidemiology of Tuberculosis.

6.2.1 TMC207: it inhibits the mycobacterial ATP synthase enzyme

6.2.2 PA-824. Activated: PA-824 inhibits the synthesis of proteins and cell wall lipids.

6.3 Nitroimidazopyrans: Nitroimidazopyrans have been derived from the bicyclic nitroimidazofurans that were originally developed for cancer chemotherapy but also exhibited activity against tuberculosis.

6.3.1 OPC-67683: OPC-67683 is a mycolic acid biosynthesis inhibitor.

6.4 Diamines

6.4.1 SQ109: SQ109 inhibits mycobacterial cell wall synthesis.

6.5 Pyrroles: In the search for compounds with activity against mycobacteria and fungi, several pyrrole derivatives have been developed.

7. Genetic polymorphisms and tuberculosis

The genetic contribution of the host plays a significant role in determining susceptibility to developing the active form of tuberculosis and severity of infection (Comstock, 1978; Schurr, 2007). Several genes of host immune response appear to play role in tuberculosis. Genetic polymorphisms and tuberculosis have been identified in several genes of host. A number of genes have been identified that play important role in tuberculosis (Fernando & Britton, 2006; Hoal, 2002). Several candidate gene studies and genome-wide linkage association studies (Bellamy et al., 2000; Jamieson et al., 2004; Miller et al., 2004; Cooke et al., 2008; Berrington & Hawn, 2007) have been performed for investigation of their role in disease risk.

Infectious disease has profound impact on human evolution. Tuberculosis is a multifactorial disorder in which the environment interacts with host-related factors, contributing to the overall phenotype. Improved understanding of the individuals balance between degrees of exposure and inherited genetic susceptibility to infection, as well as the respective effects of environmental and host-related factors will improve the understanding in the development of disease. Several host genes have been proven to contribute to active tuberculosis (TB) (Pesut, 2009). In human genome different types of variations are reported such as copy number variations (CNV), microsatellite repeats (SSR) and single nucleotide polymorphisms (SNP). Among these SNPs is the most common type of variations. Presence of polymorphisms affects either structure or level of gene products.

SNP description alone will not be sufficient to describe susceptibility to tuberculosis in a broad diverse population, and thus, functional gene studies need to be done. A real challenge is to associate candidate genes with a biologically plausible mechanism that explains the epidemiological data for tuberculosis in which only 10% of the infected individuals will develop tuberculosis. Lienhardt et al., (2002) stated that host-related and environmental factors for tuberculosis have usually been investigated separately using different study designs. Joint investigation of the genetic, immunologic, and environmental factors at play in susceptibility to tuberculosis represents an innovative goal for obtaining a better understanding of the pathogenesis of the disease. Host genetic susceptibility has been suggested as one of the most important explanations for inter-individual differences in tuberculosis (TB) risk. Multi-drug-resistant tuberculosis (MDR TB) is caused by strains of the tuberculosis bacteria resistant to the two most effective anti-tuberculosis drugs available-isoniazid and rifampicin. MDR TB can only be diagnosed in a specialized laboratory.

8. Genetic polymorphisms in tuberculosis pathogenesis

8.1 Tumor necrosis factor-alpha (TNF-α) polymorphisms

The host genetic factor plays a significant role in determining susceptibility to developing the active form of tuberculosis (Schurr, 2007). Several host immune response genes appear to play role in tuberculosis. Tumor necrosis factor-α (TNF-α) and lymphotoxin-α (LT-α), genes located within the MHC III region of chromosome 6, shows close linkage to the HLA class I (HLA-B) and class II (HLA-DR) genes (Nedwin et al., 1985) and play role in the pathogenesis of tuberculosis due to its role in the formation and maintenance of granulomas. It also plays a major role in host defense to *M. tuberculosis* by its synergistic action with interferon-γ (IFN-γ) to activate macrophages and thereby affects disease perpetuation (Mohan et al., 2001). Elevated serum TNF-α (sTNF-α) levels have been reported in advanced tuberculosis patients compared to those with mild tuberculosis and healthy controls. Several promoter polymorphisms region of TNF-α and the intron-1 polymorphism of LT-α, have been associated with altered levels of TNF-α (Sharma et al., 2008; 2010). Some of these polymorphisms have also been studied in several ethnic groups. Correa Paula et al. (2005) detected TNF-α gene polymorphisms (-308 and -238) in controls and patients of several diseases [systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), primary Sjogren's syndrome (SS), and tuberculosis (TB)]. TNF -308G was associated with TB and -308 GG genotype was protective for autoimmunity. TNF-238A allele was protective for autoimmunity but a susceptibility factor for TB. Haplotype -308A-238G have

been reported as a protective factor for TB, but susceptibility factor for RA, SLE, and primary SS; opposite association of TNF polymorphism with autoimmunity and TB, suggested that autoimmune diseases are a consequence of natural selection for enhanced TB resistance. Ates et al., (2008), detected TNF-α (-308 G/A, -238 G/A, -376 G/A) and IL10 (-1,082 G/A, -819 C/T, -592 C/A) polymorphisms in patients with TB and healthy controls. A significant association was found between TB and -1,082 G allele. Significant difference was observed in IL10 GCC and ACC haplotypes distribution between TB and controls. No significant association was found between IL-10 -819 C/T, TNF-α, 308 G/A, -238 G/A, -376 G/A polymorphisms and Tuberculosis. Sharma et al. 2010, performed a case control study including TNF-α gene (-1031, -863, -857, -308,-238) and LT-α gene (+252) polymorphisms in North-Indian population. No significant differences of the allele frequencies between the tuberculosis patients and controls have been reported. All the polymorphisms included in this study did not give a significant association with any of the patient sub-groups but a significant difference in the serum TNF-α level in the patients and the controls have been reported.

8.2 ALOX5 polymorphisms

ALOX5 gene encodes 5-lipoxygenase (5-LO) that play a key role in the biosynthesis of LTs and LXs from arachidonic acid. Leukotrienes (LTs) and lipoxins (LXs) are play a role in the generation of appropriate responses to inflammatory disease (Parkinson, 2006) and are involved in the regulation of immune cells and cytokine release. Phagocytosis of microorganisms by alveolar macrophages and polymorphonuclear leukocytes PMN was shown to be dependent on LTB_4, class of LXs (Bailie, 1996; Mancuso et al., 2001). A T-helper cell type 1 immune response is supported by enhanced production of interferon (IFN)- γ and interleukin (IL)-12 (Aliberti et al., 2002). The anti-inflammatory properties of LXs antagonize those of LTs in innate immunity by inhibiting PMN and NK cell functions, suppressing IL-12 release and modulating the immune response by stimulation of IL-4 production (Hachicha et al., 1999), while blocking IL-5 and IL-13 and inhibiting eosinophil effector functions (Bandeira-Melo et al., 2000). A case control study was performed by Herb et al. 2008 including a variable number of tandem repeats (VNTR) in promoter and an exonic non-synonymous variant g.760G>A polymorphisms in TB patients and controls from Ghana. Carriers of one variant and one wild-type VNTR allele (n = 5) or of the exonic allele g.760A had a higher risk of TB. The strongest association with TB was for the 'non-5/760A' haplotype as compared to the 'non-5/760G' haplotype.

8.3 CD209 polymorphism

CD209 on chromosome 19p13.3, encodes dendritic Cell-Specific ICAM3-Grabbing Non-integrin (DC-SIGN), is a C-type lectin, expressed on subsets of dendritic cells (DCs) and alveolar macrophages (Soilleux, 2000; Tailleux, 2003). DC-SIGN has ability to bind a variety of ligands (Gordon, 2002), endogenous ligands include endothelial cells through ICAM-2, T-lymphocytes through ICAM-3, neutrophils through MAC-1 and various endogenous glycosylated structures (Gordon, 2002; Van Kyook et al., 2003), exogenous ligands such as glycosylated moieties on *M. leprae, M. tuberculosis,* Bacillus Calmette-Guérin (BCG), *H. pylori, K. pneumoniae, S. pneumoniae,* HIV-1, HIV-2, SIV-1, Dengue virus, Ebola Virus, Cytomegalovirus, Hepatitis C virus, *S. mansoni, L. pifanoi and C. albicans* (Alvarez et al., 2002;

Tassaneetrithep et al., 2003). The contribution of *CD209* polymorphisms in human susceptibility to infectious diseases including *M. tuberculosis* and *M. leprae*, HIV-1, and Dengue is important (Barreiro et al., 2006). CD209 -336A/G (rs4804803) promoter polymorphism have shown an association with infectious disease susceptibility or protection in *M. leprae* case-control study. Martin et al. (2004) demonstrated that the -336G allele was associated with susceptibility to parenteral but not mucosal HIV-1 infection, although this was not replicated in individuals of recent African descent. Vannberg et al. (2008), investigated the role of the *CD209* -336A/G polymorphism and susceptibility to tuberculosis in sub-Saharan Africans. Significant protection was observed with *CD209* -336G variant allele in individuals from sub-Saharan Africa and, cases with -336GG were significantly less likely to develop tuberculosis-induced lung cavitation. Therefore it has been suggested, that decreased levels of the DC-SIGN receptor may be protective against both clinical tuberculosis and cavitory tuberculosis disease.

8.4 SP110 polymorphisms

Ipr1 gene is attributed to tuberculosis susceptibility gene in mice. Polymorphisms in the human homologue, SP110, have been investigated in various populations and only one study reports an association with TB susceptibility. Eight SP110 polymorphisms in a South African population, including two novel polymorphisms had been investigated. No significant association was found with any of the polymorphisms investigated, including two polymorphisms that were previously found to be associated with TB susceptibility in West African populations (Babb et al., 2007).

8.5 CARD15 polymorphisms

Caspase recruitment domain-containing protein 15 genes (*CARD15*) encodes the nucleotide-binding oligomerization domain 2 proteins (NOD2) and is considered as a susceptibility gene for Crohn's disease (CD). *CARD15* gene was investigated as a candidate gene in Tuberculosis and its product (NOD2) have been recognized as a non-redundant recognition mechanism of *M. tuberculosis*. Moller et al. 2007, genotyped the R702W, G908R and 1007fs variants, in TB cases and controls from the admixed South African Coloured population. No statistically significant differences between cases and controls were observed for these variants. Previously these polymorphisms have been reported to be associated with CD. The CD-associated mutations occur at very low frequencies in this population. The *CARD15* is not a major susceptibility gene for TB in the South African Coloureds.

8.6 BTNL2 polymorphisms

Butyrophilin-like2 gene (*BTNL2)* gene, a MHC class II gene-linked butyrophilin family member, has been recently associated with the inflammatory autoimmune diseases, such as tuberculosis, sarcoidosis, and leprosy. *BTNL2* was investigated as a candidate gene for tuberculosis in the South African Coloured population. Moller et al. (2007) genotyped 18 SNPs in *BTNL2* gene in pulmonary tuberculosis cases and controls. No significant association was detected between the truncating rs2076530 SNP, previously associated with sarcoidosis, and tuberculosis. No other studied SNPs have shown an association with disease and none of the predicted haplotypes showed any association with TB. Comparative

analyses of the data from South African, German and American populations revealed that, for a segment of *BTNL2*, the admixed, but not stratified, South African population resembles the African-Americans more than white populations. Six SNPs of *BTNL2* gene in tuberculosis cases and controls in Chinese Han population was investigated by Lian et al. 2010. No significant association was detected between any of the polymorphisms investigated and TB, including rs2076530 SNP that was previously found to be associated with sarcoidosis. Genetic study revealed a significant association between the rs3763313, rs9268494, rs9268492 SNPs in the *BTNL2* gene and tuberculosis. Haplotypes 1–5, and 8 (C/A/G/T/G/A, C/A/G/T/G/G, C/A/T/G/C/A, C/A/T/G/C/G, and C/G/T/G/C/G, T/A/T/G/C/A) presented a significant association with susceptibility to tuberculosis.

8.7 IL1 B, IL4, IL10, IL12B, IL12RB, IL12RB2, IL18, IFN-γ WNT5A, FZD5 gene polymorphisms

Genes involved in the regulation of inflammatory cytokine, interferon gamma, may influence tuberculosis susceptibility, as interferon gamma is a major macrophage-activating cytokine, during *M. tuberculosis* infection. Cytokine gene polymorphisms and cytokine levels in pulmonary tuberculosis were detected (Selvaraj et al., 2008). Moller et al. (2010), investigated fifty-four polymorphisms in eight candidate genes [Interleukin 4 (*IL4*), interleukin 10 (*IL10*), interleukin 12B (*IL12B*), interleukin 12 receptor beta 1 (*IL12RB1*), interleukin 12 receptor beta 2 (*IL12RB2*), interleukin 18 (*IL18*), wingless-type MMTV integration site family, member 5A (*WNT5A*) and frizzled homolog 5 (*FZD5*)] in tuberculosis cases and healthy controls in South African population. A functional SNP (rs2243250, IL-4 -C590T), has been associated with increased promoter strength, stronger binding of transcription factors and with different levels of IL-4 activity (Luoni et al., 2001; Rosenwasser et al., 1995) but was not associated with TB in study population. The CC genotype of this polymorphism was previously associated with protection against pulmonary TB in south India and Russia (Naslednikova et al., 2009; Vidyarani et al., 2006) but not in Gambia (Bellamy et al., 1998). Two polymorphisms -511 and +3953 in *IL1B* and one in the *IL1RN*, 86 bp VNTR in smear positive TB patients, and control in Gambian individuals (all HIV negative) was investigated. Decreased risk of pulmonary TB was associated with both heterozygosity and homozygosity for the *IL1B* -511-C allele. There was no association between the *IL1B*+3953-T/C polymorphism or the 86 bp *IL1RN* pentallelic repeat and TB in this population. Using an *ex-vivo* whole blood assay, healthy Gambian individuals who are homozygous for the *IL1B* -511-T allele failed to exhibit a significant increase in IL-1β production in response to LPS after IFN-γ priming.

IFN-γ play a central role in the modulation of Tuberculosis disease severity as it is involved in host immune response against *M. tuberculosis* infection. The 12 CA repeat microsatellite allele in the non coding region of the first intron is associated with a high level of *in vitro* cytokine production (Pravica et al., 1999). Recently, it has been reported that, polymorphism at position +874 is associated with risk of tuberculosis in different populations (Rossouw et al., 2003; Lopez-Maderuelo et al., 2003). Ansari et al. (2009) have reported that the ratio of two key cytokines (IFN-γ and IL10) show significant correlation with the severity spectrum of tuberculosis in Pakistani population. In this study frequency of cytokine gene polymorphisms linked to high and low responder phenotypes (IFNγ +874 T/A and IL10 -

1082 G/A) in tuberculosis patients was analyzed. These findings are consistent with the role of IL10 in reducing collateral tissue damage and the protective role of IFNγ in limiting disease in the lung.

A+874T polymorphism on the intron 1 of IFNγ gene, which is associated with the secretory capacity of IFNγ, was reported to be associated with the development of TB among Sicilians, South Africans, Hong Kong Chinese and Spanish, although this association was not found in Malawians54 and in other populations from Houston, West Africa, South India and China. A recent study of 77 TB patients from Japan revealed that the *IFNG + 874 AA* genotype were strongly and independently predictive of a lower likelihood of sputum conversion. Indeed, IL-12, a heterodimeric pro-inflammatory cytokine produced by monocytes, macrophages, DCs and B lymphocytes and SNP in the gene responsible in the expression of this subunit was first described by Hall et al. (2000). Several polymorphisms in promoter, introns and 3'UTR in the IL-12B gene have been reported to be associated with TB in various populations, with inconsistent results. Polymorphisms in the coding sequence of the IL-12 receptor b1 gene have been reported to be associated with TB in Moroccan and Japanese populations, but, again, not in Koreans. Reports indicate that, the *IL-12B* polymorphism is not correlated with susceptibility to tuberculosis in black and white North American populations. Four SNPs, 641 A-G, 684 C-T, 1094 T-C, and 1132 G-C causing three mis-sense variants (Q214R, M365T and G378R) and one synonymous substitution in the extracellular domain of the *IL-12Rβ1* genes have been detected. Investigators have reported that the association of R214-T365-R378 allele (allele 2) is over-expressed in Japanese tuberculosis patients with the homozygosis for R214 - T365 - R378 (the 2/2 allele) being significantly associated with tuberculosis.

8.8 IFNγR1 polymorphisms

Interferon-γ Receptor-1 plays a role in host immune response. Several SNPs in IFNγR1 have been studied in falciparum malaria cases and controls. The frequencies of interferon-γ (IFN-γ) receptor-1 (IFNγR1) promoter polymorphisms (G-611A, T-56C) in tuberculosis patients and controls were not significantly different. Because of these studied SNP affect transcription, the expression of the IFNγR1 gene does not confer susceptibility to disease in patients from Croatia (Bulat-Kardum et al., 2006). A significant association between the protective (CA) n polymorphism (22 repeats, 192 FA1), located in intron five of the IFNγR1 gene and GT promoter haplotype (-611; -56) that showed the strongest expression capacity have been reported. In addition to this cis relationship, the (CA) 22 allele was correlated in trans with an IFN-γ SNP (IFNγ Gþ2109A), which might affect the transcription of the IFNγ gene. These results suggest that a particular combination of IFNγ and IFNγR1 SNP (gene-gene) interaction might provide a better protection against tuberculosis in this population. Several families with Mendelian susceptibility to mycobacterial disease that has mutations in one of two subunits of the *IFN-γ* receptor gene (*IFN-γR1* and *IFN-γR2*) (Ottenhoff et al., 2002) have been discovered.

8.9 NOS2A polymorphisms

Nitric oxide (NO) act as is a free radical and second messenger and has been shown to be important in the development of several diseases, including tuberculosis. NO, produced by NOS2A, plays a major role in the pulmonary host-defense mechanism in response to

infections, and is implicated in bacteriostatic as well as bactericidal processes. The cytokines like, TNF-α, IL-1β along with IFN-γ produced by T-cells can induce NO via action of NOS2A. It has been proposed that NO produced by tuberculosis-infected human macrophages and by epithelial cells is anti mycobacterial against *M. tuberculosis* (Liu et al., 2006). A report indicates that the alveolar macrophages from the lungs of patients with tuberculosis express NOS2A in potentially mycobactericidal amounts and this NOS2A can kill mycobacterium *in vitro* (Qidwai & Jamal, 2010). We have review the role of three SNPs (-954G/C, -1173C/T, -1659 A/T), one microsatellite repeat in promoter and one SNP in exon 16 of gene in several case control studies (Qidwai & Jamal, 2010). The promoter polymorphisms (-954G/C, -1173C/T, -1659 A/T) have been shown to increase NO synthesis (Hobbs et al., 2002). This region in the human gene is situated from -0.7 to -2.6 kb upstream of the transcription start and contains important DNA motifs for binding of NF-κB, activator protein 1, signal transducer, and activator of transcription protein 1, and NF-κB repressing factor (Coia et al., 2005). The -954G/C variant is believed to have originated as a consequence of selective pressure of *Plasmodium* in endemic area of Africa. The G allele has been shown to be absent from Caucasian populations (Kun et al., 1998) as well as from the Peruvian population (Martin et al., 1999). In Mexicans, the G allele was not associated with tuberculosis (Flores-Villanueva et al., 2005). Two chromosome 17 genes NOS2A and CCL2 plays a role in susceptibility to tuberculosis in South African population (Moller et al., 2009). Haplotype of two functional (rs9282799 and rs8078340) SNPs in the NOS2A promoter have been significantly associated with tuberculosis. Presence of T allele decreases the DNA-protein complex formation and decreases the duration of DNA-protein interaction, which leads to decrease NO production. The T allele of SNP rs8078340 is over represented in the patients. As NO possess potent antimicrobial effects, having ability to inhibit the growth of many infectious organisms *in vitro*, polymorphism in the promoter alters the level of NOS2A, decreasing the level of NO and thereby increases the susceptibility to tuberculosis.

A case-control association study of TB, patients and controls was performed in African-Americans and Caucasians by Velez et al. (2009). Thirty-nine SNPs were selected from the NOS2A gene, for single SNP, haplotype, and multilocus interaction analyses with other typed candidate genes. In African-Americans, ten NOS2A SNPs were associated with TB. The strongest associations were observed at rs2274894 and rs7215373. The strongest gene–gene interactions were observed between NOS2A rs2248814 and IFNGR1 rs1327474 and NOS2A rs944722 and IFNGR1 rs1327474. Three other SNPs in NOS2A interacted with TLR4 rs5030729 and five other NOS2A SNPs interacted with IFNGR1 rs1327474. No significant associations were observed in Caucasians. These results suggest that NOS2A variants may contribute to TB susceptibility, particularly in individuals of African descent, and may act synergistically with SNPs in TLR4 and IFNGR1.

9. Vitamin D receptor (VDR) polymorphisms

The investigation of the genetic polymorphisms of vitamin D, VDBP, TLR, NOS2A and IFN-γ genes and resistance or susceptibility to *M. tuberculosis* infection was summarized by (Preto, 2009). The vitamin D receptor (VDR) gene is one of the most important candidate genes that play role in susceptibility to tuberculosis. Polymorphisms that affects the activity of the receptor have profound impact. Genetic variants of the natural resistance-associated macrophage protein (*NRAMP1*) and vitamin D receptor (*VDR*) genes are associated with smear-positive pulmonary tuberculosis in Gambian populations (Bellamy et al., 1998a,b;

1999). Vitamin D receptor (VDR) genotypes have been shown to be associated with differential susceptibility or resistance to tuberculosis. The influence of FokI, BsmI, ApaI and TaqI variants of VDR gene on 1, 25(OH)(2) D(3) modulated granzyme A expression of cytotoxic lymphocytes induced by culture filtrate antigen (CFA) of Mycobacterium tuberculosis (Vidyarani et al., 2009). The ApaI aa genotype and bbaaTT extended genotype were associated with a significantly decreased percentage of granzyme A positive cells in normal healthy controls. The study suggest that 1, 25(OH)(2) D(3) suppresses granzyme A probably by down-regulating Th1 cytokine response. Gao et al. (2010), has reviewed published studies on VDR polymorphisms and TB susceptibility and quantitatively summarized associations of the polymorphisms (*Fok*I, *Taq*I, *Apa*I and *Bsm*I). Among Asians, the *Fok*I ff genotype showed a pronounced positive association, a significant inverse association was observed for the *Bsm*I bb genotype, and marginal significant associations were found for *Taq*I and *Apa*I polymorphisms. None of the studied polymorphisms have shown a significant association to TB among Africans or South Americans.

9.1 Vitamin D-binding protein

VDBP is a multifunctional, highly expressed, polymorphic serum protein encoded by Gc gene and is the major plasma carrier of vitamin D_3 and its metabolites and ensures that vitamin D is transported to the liver, $25(OH)_2D_3$ to the kidney, and 1, $25(OH)_2D_3$ to target cells and organs. A multi gene cluster at chromosome 4q11-q13 includes albumin, α-fetoprotein and *Gc* gene. Variations in exon 11 of the *Gc* gene at codons 416 and 420 give rise to electrophoretic variants of VDBP, called Gc1 fast (Gc1F), Gc1 slow (Gc1S) and Gc2 differing by amino-acid sequence, as well as by attached polysaccharides. Combinations of the three VDBP or Gc variants result in six common circulating phenotypes: Gc1F/Gc1F, Gc1F/Gc1S, Gc1S/Gc1S, Gc1F/Gc2, Gc1S/Gc2, and Gc2/Gc2 (23). *DBP* polymorphism (Gc phenotype) is related to the VDBP concentration and vitamin D status (Lauridsen et al., 2005). The authors showed a strong correlation between higher, intermediate and lower circulating levels of $25(OH)_2D_3$ and $1,25(OH)_2D_3$ with Gc1-1, Gc1-2 and Gc2-2 phenotypes, respectively, in Danish Caucasian postmenopausal women population. Variations in this property could affect the functioning of the immune system, as *DBP* knockout mice exhibited an impaired immune response to bacterial infections (White & Cook, 2000). A role of *DBP* polymorphism in autoimmune diabetes mellitus and infectious disease in Polynesia and Japan (Hirai et al., 2000) has been suggested. No differences in *DBP* phenotype were seen among patients and the control group. In that study, frequency of Gc2 in tuberculosis patients was slightly but not significantly higher than in the control group and this elevation was at the expense of both Gc1F and Gc1S alleles.

9.2 The Toll-like receptors

The TLRs represent a group of single-pass transmembrane receptors, are expressed on innate immune cells and works as sensors for pathogen-derived molecules, and play a role in host-pathogen interaction (Aderem et al., 2000). TNF-α and NO is induced mostly by macrophages soon after innate recognition of mycobacteria through TLRs (Underhill et al., 1999). The role of TLR in resistance to *M. tuberculosis* was suggested initially by the fact that MyD88-deficient mice are more susceptible to *M. tuberculosis* infection and by the observation that TRL2/TLR1 reduced the viability of intracellular *M. tuberculosis* in human

monocytes and macrophages, but not in monocyte-derived DCs (Liu et al., 2006). They have also reported that TLR induces up-regulation of the *VDR*, 1α-vitamin D hydroxylase (enzyme that converts inactive to active vitamin D), and *CYP27B1* gene expression in monocytes and macrophages.

The human TLR2 gene is located on chromosome 4q32 and is composed of 2 non-coding exons and 1coding exon (Haehnel et al., 2002). In TLR2 gene, 89 SNPs have been reported, (26 in the 5'-untranslated region, 17 in the 3'-untranslated region, 29 located in intronic parts of the gene, and 17 modify bases of the third exon of TLR2). Six non-synonymous SNPs of the *TLR2* gene change amino acids in the cytosolic part of this receptor. Out of which, only two have been linked to reducing NF-κB activation and increasing risk of infection. The first SNP changes of C to T replacing arginine (Arg; R) with tryptophan (Trp, W) at position 677, abolishing the binding with MyD88 with TLR2. This specific polymorphism located within the *bb* loop of *TLR2* (Arg677Trp) abolishes activation of NF-κB in response to *M. tuberculosis*, resulting in decreased IL-12 serum level production by 677W carriers. The second *TLR2* SNP changes G to A, which substitutes an arginine for glutamine at position 753. The *TLR2* 753Q seems to be associated with an increased risk of developing tuberculosis for carriers the AA and AG genotypes (Ogus et al., 2004). Thuong et al. (2007) described a strong association of SNP T597C *TLR2* with susceptibility to military tuberculosis patients from Vietnam. Further association was described among Koreans regarding the microsatellite polymorphisms in intron II or *TLR2* (Yim et al., 2006). In addition, *TLR1* polymorphism in a non-synonymous region (I602S) could be associated with TLR1/2 heterodimer binding sites to mycobacterial lipopeptide, since individuals with 602II genotype produced substantially more IL-6 than those with the 602SS variant. Currently, the polymorphism in *TLR2* might be an important risk factor for disease progression. The G to A (Arg753Gln) polymorphism at position 2258 in exon 3 and the guanine-thymine (GT) microsatellite repeat polymorphism (100 bp upstream of the translational start site) in intron 2, have been associated with susceptibility to clinical tuberculosis (TB) disease in Turkish and Korean patients, respectively (Ogus et al., 2004; Yim et al., 2006). TLR2 promoter region, namely, -16934 A>T and -196 to -174 insertion (Ins) >deletion (Del), polymorphisms have been associated with asthma and gastric cancer, respectively (Eder et al., 2004; Tahara et al., 2007).

Patients with pulmonary TB and healthy controls, were examined for TLR2 polymorphisms over locus -100 (microsatellite guanine-thymine repeats), -16934 (T>A), -15607 (A>G), -196 to -174 (insertion>deletion), and 1350 (T>C) (Chen et al., 2010). An association exists between the haplotype [A-G-(insertion)-T] and susceptibility to pulmonary tuberculosis. Patients with systemic symptoms of tuberculosis had a lower -196 to -174 deletion/deletion genotype frequency than those without systemic symptoms. TB patients with the deletion/deletion genotype had higher blood NK cell counts than those carrying the insertion allele whereas patients with pleuritis had a higher 1350 CC genotype frequency than those without pleuritis. Patients of tuberculosis with the 1350 CC genotype had higher blood NK cell counts than those carrying the T allele. TB patients carrying homozygous short alleles for GT repeats had higher blood NK cell counts than those carrying one or no short allele. Thus, an association between the specific TLR2 haplotype and susceptibility to pulmonary TB have been reported. In patients with pulmonary TB, both the -196 to -174 Del/ Del and 1350 CC genotypes were associated with an increased blood absolute NK cell counts.

9.3 TLR4 polymorphism

Toll-like receptor (TLR) 4 has been described to play a main role in the innate immunity against TB. The association between two particular SNPs in human TLR4 (Asp299Gly and Thr399Ile) and active TB has been studied in non-HIV Africans with contradictory results. However, studies focusing on the effect of these TLR4 SNPs in active TB within a Caucasian HIV population are lacking. The association between TLR4 Asp299Gly and Thr399Ile SNPs and active TB, in Caucasian Mediterranean HIV-infected individuals were analyzed by Ildefonso et al. (2010). Asp299Gly were independently associated with active TB and inversely with latent TB prophylaxis. An independent association between TLR4 Asp299Gly SNP and active TB in Caucasian Mediterranean HIV-infected patients was detected.

9.4 Toll-like receptor 8 polymorphisms

Davila et al. (2008) studied TB association and expression of 18 genes involved in the Toll-like receptor (TLR) pathways. The polymorphisms in pulmonary TB patients and controls from Indonesia was genotyped. The four polymorphisms in the TLR8 gene on chromosome X showed evidence of association with TB susceptibility in males, including a non-synonymous polymorphism rs3764880 (Met1Val).They have also genotyped these four TLR8 polymorphisms in an independent collection of pulmonary TB patients and controls from Russia and again found evidence of association in males (for rs3764880). A marked increase in TLR8 protein expression was also observed directly in differentiated macrophages upon infection with *M. bovis*, bacille Calmette-Gue´rin (BCG). A role for the TLR8 gene in susceptibility to pulmonary TB across different populations have been reported. Polymorphisms (1805 G/T in TLR1, 2258 A/G in TLR2, -857 C/T and -863 A/C in TNF-α and -819 C/T in IL-10) was genotyped in tuberculosis patients and controls by Mai Juan et al. 2010. Multivariate logistic regression analysis revealed that the TT genotype of -857 C/T in TNF-α gene was significantly associated with lower risk of PTB, in comparison with other genotypes. The genetic variant of -863 A/C in TNF-α gene was associated with susceptibility to PTB and clinical severity of disease. The results of the study suggest that the variants in TNF-α gene were associated with susceptibility to PTB and clinical severity of disease, while no significant association have been reported for TLRs and IL-10 genes polymorphisms and tuberculosis.

9.5 PTPN22 gene polymorphism

The PTPN22 gene encodes the lymphoid tyrosine phosphatase that has an important regulatory effect on T- and B-cell activation in immune response. Lamsyah et al. (2009) reported an association of PTPN22 gene functional variants with development of pulmonary tuberculosis in Moroccan population. The two missense polymorphisms of the PTPN22 gene (R620W and R263Q) and susceptibility to TB in the Moroccan population was investigated. A statistically significant difference exists in the distribution of the PTPN22 1885T allele between pulmonary TB patients and healthy controls. In case of PTPN22 R263Q (G788A) SNP, there is an increase of 788A allele frequencies in TB patients compared with those in healthy individuals. These results suggest that PTPN22 gene variants may affect susceptibility to TB in the Moroccan population.

9.6 Human V-ATPase polymorphism

Capparelli et al. (2009) tested for polymorphisms in the intron 15 and the 5'-untranslated region of the gene coding for the a3 isoform of the human ATPase gene in pulmonary tuberculosis patients and controls. Alleles (two at each site) segregated in the form of four haplotype pairs. The double heterozygous patients were protected against tuberculosis and the double homozygous patients were susceptible to the disease.

9.7 MIF, FCGR2A, and FCGR3A gene polymorphisms

The polymorphisms of macrophage migration inhibitory factor (MIF), Fcg receptors CD16A (FCGR3A) and CD32A (FCGR2A) genes and susceptibility to pulmonary tuberculosis (PTB) in the Moroccan population, was analyzed (Sadki et al., 2010). The genotyping for MIF-173 (G/C) (rs755622), FCGR2A-131 H/R (rs1801274), and FCGR3A-158V/F (rs396991) have been done. A statistically significant increase of the MIF -173CC homozygote genotype and MIF -173*C allele frequencies in PTB patients compared with healthy controls was detected. In contrast, no association was observed between FCGR2A-131H/R and FCGR3A-158V/F polymorphisms and tuberculosis disease. The finding suggests that MIF -173*C variant may play an important role in the development of active tuberculosis.

9.8 CCR2, MCP-1, SDF-1a & DC-SIGN gene polymorphisms

Investigation showed that chemokine, chemokine receptor and DC-SIGN gene polymorphisms were associated with susceptibility/resistance to HIV and HIV-TB in south India (Alagarasu et al., 2009). CCR2 V64I (G/A), monocyte chemoattractant protein-1 (MCP-1) -2518 A/G, stromal cell derived factor-1alpha; (SDF-1alpha) 3'UTR G/A and DC-SIGN gene polymorphisms were studied in HIV-1 infected patients without TB, with pulmonary TB (PTB) and extrapulmonary TB, PTB patients without HIV and healthy controls. No significant difference was detected in the genotype frequencies of CCR2 V64I, MCP-1 -2518 and DC-SIGN polymorphisms between the study groups. A significantly increased frequency of GG genotype of SDF-1alpha polymorphism was observed among positive for HIV and PTB patients compared to healthy controls. The GG genotype of SDF-1alpha 3'UTR polymorphism may be associated with susceptibility to PTB in HIV-1 infected patients. Raghavan et al. (2009) have detected the HLA-DR2 subtypes and the possible HLA-A/-B/-DRB1 haplotype combinations that are associated with susceptibility or resistance to HIV and HIV with pulmonary tuberculosis (HIV+PTB+). Overrepresentation of HLA-DRB1*1501 in HIV+PTB- patients and DRB1*1502 in HIV+PTB+ patients as compared to healthy controls was detected. An increased frequency of HLA-A2-DRB1*1501 haplotype in HIV+PTB- patients and HLA-A2-DRB1*1502 among HIV+PTB+ patients compared to healthy controls have been identified. The study suggests that HLA-A2-DRB1*1501 haplotype may be associated with HIV infection while HLA-A2-DRB1*1502 haplotype might be associated with susceptibility to PTB in HIV patients. HLA-B40-DRB1*1501 and HLA-B40-DRB1*04 haplotypes may be associated with susceptibility to HIV infection and to PTB in HIV patients (Raghvan et al., 2009).

9.9 TIRAP polymorphisms and susceptibility to childhood TB

The adaptor protein TIRAP mediates downstream signaling of TLR2 and TLR 4. TIRAP gene polymorphisms have been associated with susceptibility and resistance to tuberculosis

(TB) in adults in South Africa. Dissanayeke et al. (2009), identified 13 SNPs, and found significant differences in frequency of the variants between the two ethnic groups. The frequency of individual polymorphisms or combinations did not vary between TB cases and controls in either cohort. The 558C→T polymorphism previously associated with TB meningitis (TBM) in a Vietnamese population was found to be associated with TBM in the mixed ancestry group. The study suggests that, polymorphisms in TIRAP do not appear to be involved in childhood TB susceptibility in South Africa.

10. Mannose-binding lectin (MBL) polymorphisms

Mannose-binding lectin (MBL) is considered an important component of innate immunity. Four functional MBL2 alterations in codons 52, 54, 57 and in the promoter at position c.1-290 are correlated with significantly lowered MBL serum levels. These variants have been associated with susceptibility to a variety of infectious agents as well as with various immunologic disorders. The gene encoding MBL is located on chromosome 10 and is designated as MBL2. MBL elicits complement activation by binding to mannose- and N-acetylglucosamine sugar groups on various microorganisms. 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 deficiency is an example of evolutionary selection, as MBL deficiency reduces the capacity of mycobacteria to invade macrophages, thus provide resistance to TB (Garred et al., 1994). Variations at codons 52, 54 and 57 lead to low or near absent serum MBL. A study from South African suggested that hetrozygotes for MBL54 have protection against tuberculosis meningitis (Hoal-Van Helden et al., 1999). TB patients as compared to controls have an increased genotype frequencies for mutant homozygotes at codons 52, 54 and 57in South Indians but no such association have been reported in China, Poland, Turkey, Malawi, Tanzania and Gambia.

10.1 Complement receptor polymorphisms

The complement receptor-1(CR1) present on the surface of the macrophages is associated with phagocytosis of various microorganisms, including *M. tuberculosis*. Homozygotes in one of five CR1polymorphisms (Q1022H) are associated with increased TB risk in Malawi.

10.2 Purinergic P2X7 receptor

Purinergic P2X7 receptors are cationic channels present on the cells in the blood and immune systems. A polymorphism with a 1513 A-C (rs3751143) that replaces the glutamic acid at residue 496 by alanine, was not associated with pulmonary TB in Gambia (Li et al., 2002). No link of 1513 SNP with pulmonary TB was found in Southeast Asian refugees from Australia but a strong association existed between the C polymorphism and extrapulmonary TB (Fernando et al., 2006).

10.3 Association analysis of susceptibility region on chromosome 5q31 for tuberculosis

In the Asian population the chromosome 5q23.2–31.3 has been identified as a region with linkage to tuberculosis (Ridruechai et al., 2010). A putative tuberculosis susceptibility locus was investigated, in a family-based association test between the dense SNP markers within

chromosome 5q31 and tuberculosis in Thai trio families. Seventy-five SNPs located within candidate genes covering SLC22A4, SLC22A5, IRF1, IL5, RAD50, IL13, IL4, KIF3A and SEPT8 were genotyped. Association analysis revealed the most significant association with tuberculosis in haplotypes comprising SNPs rs274559, rs274554, and rs274553 of SLC22A5 gene, which remained significant after multiple testing corrections. The two haplotypes within the SLC22A4 and KIF3A region were associated with tuberculosis. Haplotypes of SLC22A5 were significantly associated with the expression levels of RAD50 and IL13. The variants carried by the haplotypes of SLC22A4, SLC22A5, and KIF3A region potentially contribute to tuberculosis susceptibility among the Thai population.

10.4 Genome-wide analysis of genetic susceptibility to tuberculosis

Bellamy et al. (1998b), performed genome-wide analysis of genetic susceptibility to tuberculosis in Africans. A two-stage genome-wide linkage study to search for regions of the human genome containing tuberculosis-susceptibility genes was carried out. Sibpair families that contain two full siblings, affected by clinical tuberculosis were used. 299 highly informative genetic markers, spanning the entire human genome, were typed in 92 sibpairs ffrom Gambia and South Africa in the first round. To identify whether any of these regions contained a potential tuberculosis-susceptibility gene, 22 markers from these regions were genotyped in a second set of 81 sibpairs from the same countries. Markers on chromosomes 15q and Xq showed suggestive evidence of linkage to tuberculosis. These results indicate that genome-wide linkage analysis can contribute to the mapping and identification of major genes for multifactorial infectious diseases of humans. Thye et al. (2009) have identified a genetic variant, which increases susceptibility to tuberculosis (TB) in African populations using genome-wide association (GWA) study. The studies involve analysing hundreds of thousands of genetic markers across the human genomes in search of variants found in patients but not in healthy controls.

Control of the TB epidemic requires more than developing new drugs. The diagnostic and therapeutic facilities of health care centers in developing countries must be improved, and the socioeconomic status and general welfare of patients (including nutritional and HIV status) should be addressed to help eradicate TB. The development of tuberculosis or other mycobacterial diseases is the result of a complex interaction between the host and pathogen influenced by environmental factors. Numerous host genes are likely to be involved in this process. A variety of study methods, have contributed to substantial progress in advancing our understanding of genetic susceptibility to tuberculosis.

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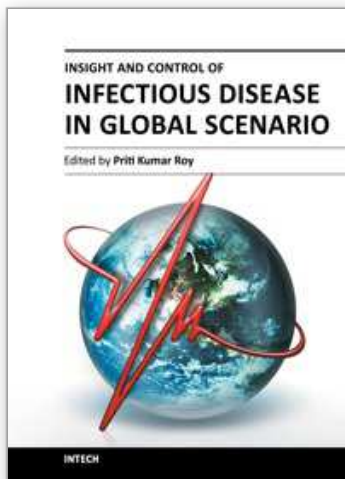
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This book is projected as a preliminary manuscript in Infectious Disease. It is undertaken to cover the foremost basic features of the articles. Infectious Disease and analogous phenomenon have been one of the main imperative postwar accomplishments in the world. The book expects to provide its reader, who does not make believe to be a proficient mathematician, an extensive preamble to the field of infectious disease. It may immeasurably assist the Scientists and Research Scholars for continuing their investigate workings on this discipline. Numerous productive and precise illustrated descriptions with a number of analyses have been included. The book offers a smooth and continuing evolution from the principally disease oriented lessons to a logical advance, providing the researchers with a compact groundwork for upcoming studies in this subject.

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