Host Genetic Factors in Resistance and Susceptibility to Tuberculosis Infection and Disease

Mary J. Maliarik, Ph.D.[1] and Michael C. Iannuzzi, M.D.[2]

ABSTRACT

The worldwide public health threat of tuberculosis and the search for novel strategies for preventing and treating disease have focused attention on the interaction between host and pathogen. Despite widespread presence of *Mycobacterium tuberculosis*, only a relatively small percentage of people exposed to the organism progress to clinical disease. Increasing evidence indicates that host genetic factors influence the outcome of exposure to *M. tuberculosis*. This evidence is presented here, along with strategies used to identify host genes responsible for resistance/susceptibility in MTB infection. Studies on host genes involved in response to infection by MTB and the relationships between infection and polymorphisms in immune response genes are reviewed. Research on how host genes can influence vaccine responses and the efficacy of drugs or other interventions as well as studies into the relationship of host genes to tuberculosis outcomes may lead to new strategies for prevention and control.

KEYWORDS: Tuberculosis, genetics, infection, disease-resistance

Objectives: Upon completion of this article, the reader should be able to summarize approaches to studying genetic factors in tuberculosis; understand the model of host–pathogen interactions; and list candidate genes for host susceptibility to infection with *Mycobacterium tuberculosis.*

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With one third of the world's population infected with *Mycobacterium tuberculosis*, tuberculosis is the number one cause of death from infectious disease. Exposure to *M. tuberculosis* (MTB) generally has one of three outcomes: a person may resist infection, become infected but show no clinical signs of disease, or progress from mild to severe disease. Which outcome occurs is determined by the interaction of environmental factors and the genetic makeup of both host and pathogen. The significance of host genetic makeup is emphasized by the fact that, in similar environmental conditions, only about 25% of those exposed to MTB become infected, and only one in 10 of those infected develop clinical disease.[1,2] This means that most of us are resistant to infection.

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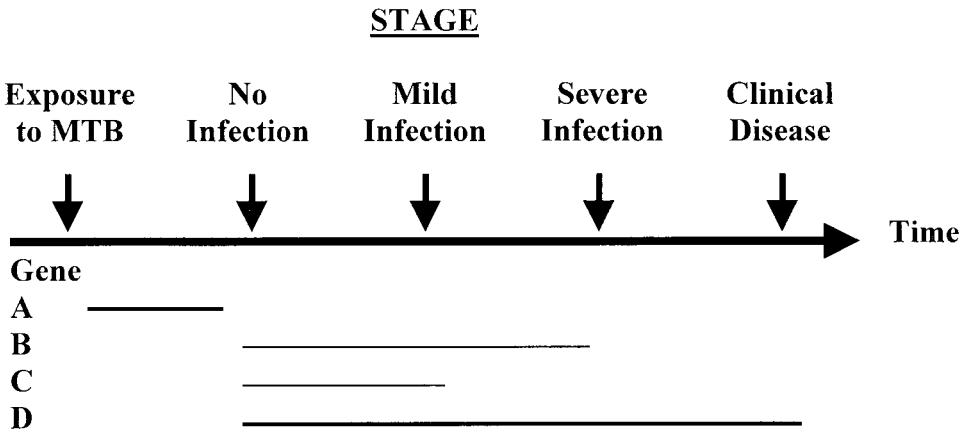

Figure 1 Simplified model of stepwise pathogenesis of tuberculosis from exposure to infection to clinical disease indicating multigenic involvement. (Adapted from McNicholl et al.[3a])

Qureshi et al[3] proposed that host genes involved in the complex host–pathogen interactions leading to infection and development of disease may be considered along a continuum of pathogenesis. This model consists of several stages, from exposure, to illness, to disease (Fig. 1[3a]). Host genes likley influence every stage of the process. Two important points can be made with respect to this model: (1) resistance/susceptibility to infection and disease outcome is often the result of multiple genes; (2) genes involved in risk for infection are likely different from those affecting clinical disease developmnet.

We next review the evidence for host gene involvement in risk for MTB infection and development of tuberculosis, discuss approaches to dissecting the role of host genes, and describe genetic polymorphisms currently identified as contributing to infection and disease risk.

EVIDENCE FOR THE CONTRIBUTION OF HOST GENES TO TUBERCULOSIS

Despite the global spread of tuberculosis, wide variation in geographic disease incidence exists. In modern times, the lowest incidence of tuberculosis is in western Europe, the highest is in South Africa. These rates led Bates and Stead[4] to observe that resistance to tuberculosis correlated with region of ancestry and that ancestors of more susceptible people come from regions once free of the disease. The incidence of clinical tuberculosis was also particularly high in outbreaks in populations with no ancestral experience of the pathogen, such as Native Americans.[4] In Canada, where the incidence of tuberculosis is low, 15% of cases occur in Aboriginal Canadians, where the annual rate is 10 times higher than the national average.[5]

Although some incidence variation may be explained by environmental and socioeconomic factors, ethnic differences in the incidence and severity of tuberculosis[6] have been observed. For instance, Stead et al[7] studied MTB infection among Arkansas nursing home residents and observed that African Americans were nearly twice as likely to become infected, as measured by tuberculin skin testing (TST), as were Caucasians. Interestingly, there was no racial difference in the percentage of residents who, once infected with MTB, developed clinical disease.

Familial clustering,[8] twin studies,[9–11] and segregation analyses[12] support the hypothesis that susceptibility to mycobacterial disease is genetically regulated. Kallman and Reissner's[9] analysis of tuberculosis among twins revealed that if one of a pair of identical twins had the disease, the other had an 87% chance of also having the disease. The risk to an affected individual's spouse was only 7.1%. Segregation analyses of several multicase families in Brazil suggested that one or two loci control susceptibility to tuberculosis in this population.[12]

Animal models provide the strongest evidence that genetic host factors play a significant role in susceptibility to mycobacterial infection. Fifty years ago, Lurie[13] used selective breeding of rabbits to demonstrate hereditary susceptibility to MTB. More recently, using segregation and linkage analysis in mice, investigators identified five candidate gene regions controlling infection by intracellular pathogens.[14,12] These regions include mouse chromosomes 1, 4, 17, and distal and proximal chromosome 11. Proximal mouse chromosome 1 (corresponding to human 2q35) carries the Ity/Lsh/Bcg (Nramp1) gene. This locus controls innate resistance to *Salmonella typhimurium*, *Leishmania donovani,* and mycobacterial species.[14] Mouse chromosome 4 (human chromosome 9p) carries the Scl 2 gene that controls a "no lesion growth" phenotype in DBA mice infected with *Leishmania mexicana*. Mouse chromosome 17 (human chromosome 6p) contains the major histocompatibility complex (MHC). Distal mouse chromosome 11 (human chromosome 17q11.2-q12) contains the Scl1 gene that controls cutaneous *Leishmania major* infection. Proximal murine chromosome 11 (human 5q23-q32), contains a T helper 2 cytokine gene cluster involved in later phases of *L. major* infection.

Studies in knockout mice further support host factors in susceptibility to MTB. Increased mycobacter-

ial lethality has been observed in mice rendered genetically deficient in T cell subsets, T cell receptor, and genes[15–17] or in those cytokines and receptors responsible for macrophage activation (interferon gamma, interferon gamma receptor, tumor necrosis factor receptor 1).[18–21] Disruption of the inducible nitric oxide synthetase (NOS2) gene also results in a highly susceptible mouse, and using N6- (1-iminoethyl-L- lysine) to inhibit NOS2 accelerates chronic tuberculosis in wild-type mice.[22]

APPROACHES TO STUDYING HOST GENETIC FACTORS

Association Studies

The most common approach to studying candidate genes in tuberculosis has been the use of case control design. Frequencies of specific alleles at a polymorphic candidate locus are compared between groups of affected individuals and unaffected, unrelated controls (Fig. 2A). This study design suffers from confounding by population stratification.

A second study design is the family-based association study, in which parents and/or unaffected siblings of a case with tuberculosis are genotyped (Fig. 2B). This design utilizes the transmission disequilibrium test to determine whether a specific allele is transmitted from parent to affected offspring more often than expected by chance. The strength of the family-based study design is that it provides a perfectly matched control to the affected offspring. That is, the nontransmitted parental alleles are controls for the alleles transmitted to the case (offspring). This removes the problem of population stratification due to ethnic admixture. However, this design is often more difficult to carry out than case control.

Linkage Studies

This study design involves genotyping multiple individuals from families with more than one affected family member. Either relatives from multigenerational families (Fig. 2C) or pairs of affected siblings (Fig. 2D) may be used. "Scanning" the genome with anonymous markers is often performed on families and is the most likely method of finding genes linked to disease resistance/susceptibility because no a priori judgment is made regarding candidate genes. Statistically relevant chromosomal regions are identified, which then may be more closely investigated using high-resolution mapping, association studies, or sequencing of candidate regions.

The most comprehensive way to identify host genes is to combine all three approaches. Recently Bennet et al[23] and Lienhardt et al[24] proposed such a study in three West African countries.

CANDIDATE GENE ASSOCIATIONS

Class II human lymphocyte antigens (II) have been a major target of study due to their importance in antigen presentation. Associations with tuberculosis susceptibility have been reported for the HLA-DR2 antigen in Indian,[25] Indonesian,[26] and Soviet populations.[27] HLA-DRB1 1501 allele has been identified with pulmonary tuberculosis in two Indian populations.[28] HLA-DQB 503 was significantly associated with tuberculosis progression in Cambodian patients,[29] and DQB1 *0601 was associated with pulmonary tuberculosis in a case control study of Indian patients.[25,28,30] Interestingly, no association of the cytokine tumor necrosis factor alpha (TNF-α), located near the HLA genes, has been observed.[29] The MHC is a complex region with many immunoregulatory genes, and the diversity of results suggests that further clarification of its relationship to tuberculosis is needed.

Finding that Nramp1 results in MTB susceptibility in mice led to studies aimed at defining the role of the human homologue, NRAMP1. Bellamy and coworkers investigated four NRAMP1 polymorphisms in a large case-control study comparing Gambians with smear-positive tuberculosis and those without active disease.[31] All four polymorphisms were associated with tuberculosis. A single base change in intron 4 and a 5′ deletion were particularly overrepresented in tuberculosis cases (OR = 4.07, 95% CI 1.86–9.12). Whether this

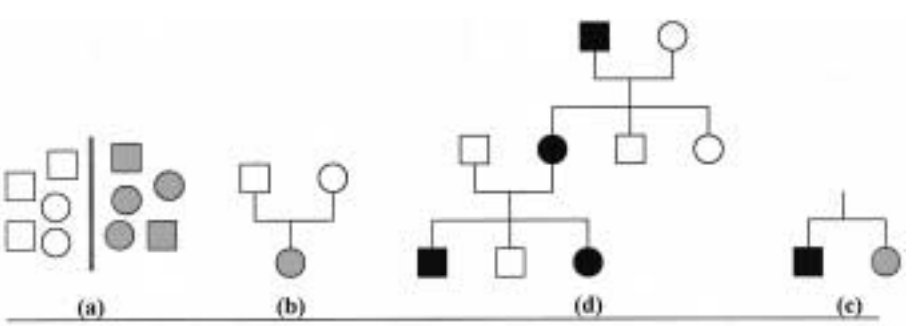

Figure 2 Structure of samples and families collected in different study designs: (A) case control association, (B) family-based association, (C) linkage, (D) affected sibling pairs. Squares indicate males, circles indicate females. White is unaffected status, black indicates affected status.

association holds true in other populations remains to be determined because several smaller case-control studies in other populations have found no association.[32] Results from segregation and linkage studies have also had conflicting results: 36 multicase families and 33 affected sib pairs from Brazil have provided no evidence of linkage between NRAMP1 and tuberculosis or leishmaniasis[14]; whereas a second similar study in Brazilian patients suggests a weak linkage.[33]

The importance of cytokine genes in host defense has led to several studies on proinflammatory and antiinflammatory chemokines. For TNF-α, a key cytokine in this process, no associations with tuberculosis have been established. Polymorphisms in interleukin-1beta (IL-1β) and its receptor antagonist IL-1R beta were associated with tuberculosis in Gujarati Indians living in London.[34]

Several immunologically relevant receptors have also been targeted. One example is the vitamin D receptor. Among its many effects, dihydroxy vitamin D is an important immunomodulator. In vitro studies have reported that vitamin D inhibits the growth of *M. tuberculosis* in human macrophages. A polymorphism in the 3′ end of the vitamin D receptor identified by Taq I was associated with susceptibility along with 25 hydroxy cholecalciferol deficiency in Gujarati Indians.[35]

Candidate genes are selected for study based upon (1) known features of innate and adaptive immunity, (2) animal studies, and (3) pathophysiology of the disease. This approach is very sensitive in detecting gene effects but is highly dependent on first identifying key steps in disease development.

LINKAGE STUDIES

The most extensive linkage study to date is a two-stage genome scan performed on 92 African sib pairs, mainly from Gambia. This screen indicated nominal linkage of tuberculosis to several chromosomes (3, 5, 6, 8, 9, 15, and X).[36] These regions were reassessed in a scan on a second group of 81 affected sibling pairs from South Africa. Two chromosomal regions from the first scan, 15p11 and Xq27, showed moderate evidence of linkage in the second. Of interest is the lack of significant linkage to the MHC and NRAMP1. The MHC has been found associated with tuberculosis in several studies. The evidence for NRAMP1 is less clear but remains an attractive candidate based on animal models and human association studies. A major gene effect was indicated in a family of Aboriginal Canadians.[5] Linkage analysis indicated a major susceptibility locus at chromosome 2q35, which includes NRAMP1. A second family was studied in another tuberculosis outbreak among the same population. Unfortunately, the original result was neither confirmed nor negated.

Differing results in both association and linkage studies may be explained by the complexity of the host–pathogen interaction (Table 1). The continuum model presented earlier suggests that different genes are involved at different steps in the pathogenesis of tuberculosis. When studying family members who have clinical disease, one is really measuring the effects of genes involved in the process of infection, as well as those contributing to progression from infection to clinical disease. For linkage studies, the greater the number of genes that contribute to disease, the less distinct the observed *statistical* contribution of any single gene. Therefore, it is advantageous to attempt to separate affected individuals into distinct phenotypes whenever possible. This limits the probable number of genes in a particular phenotype and increases the observed contribution of a particular gene or locus. For example, comparing clinically distinct forms of tuberculosis, such as exposed individuals with positive skin test but without clinical disease, and patients with equal exposure but without positive skin test would likely define genes involved in infection. However, such comparisons are complicated by the difficulty in measuring exposure time, intensity, and virulence of the pathogen, among other factors.

Table 1 Host Genes with Associations or Linkage to Risk of Tuberculosis

Gene	Study Type	Population (References)
Tuberculosis		
MHC Class II		
HLA-DRB1	Association	Indian[28,30]
HLA-DQB1	Association	Soviet[27]
		Cambodian[29]
NRAMP1	Association	West African[31]
		Aboriginal Canadians[5]
	Linkage	
Vitamin D receptor	Association	Gujarati Asians[35]
IL-1β	Association	Indian[34]
Chromosome 15	Linkage	West African[36]
Chromosome X	Linkage	West African[36]
Rare mycobacterial susceptibility		
IFNGR1	Linkage	Maltese[38]
IFNGR2	Linkage	Maltese[40]
IL-12	Linkage	Pakistani[41]
IL-12 receptor	Linkage	Pakistani[42]
		Japanese[43]

MENDELIAN SUSCEPTIBILITY TO MYCOBACTERIAL INFECTIONS

A clear relationship is observed between mycobacterial disease and genetic defects in host defense in a rare syndrome described as Mendelian susceptibility to mycobacterial infections (MIM 209950). These patients are vulnerable not only to infection by *M. tuberculosis,* but to other, less virulent, mycobacterial species as well.

Numerous studies have been performed in families with this particular susceptibility syndrome. Levin et al[37] investigated a Maltese family with four children that had severe disseminated infection with several atypical mycobacteria. Homozygosity mapping in these children revealed nonsense[38] and frameshift[39] mutations within the interferon gamma receptor ligand-binding chain (IFNGR1) gene. These mutations led to the absence of expression of the cell surface receptor. Subsequently, mutations in the interferon signaling chain (IFNGR2) were identified in another kindred.[40] In vitro studies have established the causative relationship between the presence of two mutated alleles and impaired response to IFN gamma.

Other mutations were found in patients infected with bacille Calmette-Guérin and *Salmonella enteritidis* infections. These mutations were found in the IL-12[41] and IL-12 receptor beta chain genes,[42] resulting in IL-12 and IL-12RB1 deficiency, respectively. These patients had impaired IFN gamma secretion, underscoring the key role of IFN gamma in controlling mycobacteria. Interestingly, a separate mutation in IL-12RB1 has recently been found in a Japanese patient infected with *Mycobacterium avium* complex.[43]

Susceptibility to tuberculosis in these families is due to a defect in one gene. Unfortunately these rare causal mutations do not account for the majority of cases worldwide. These patients most likely represent one extreme of the continuum of susceptibility to disease, whereas a complex polygenic situation exists in the more common predisposition to disease.

CONCLUSION

Strong evidence exists that host genes play a major role in resistance/susceptibility to tuberculosis infection or disease. Several host genes have been implicated in this process, but to date no confirmed, universal "susceptibility" gene(s) are known. This is likely due to the complexity of the host–pathogen interaction and the process by which exposure to tuberculosis travels from infection to clinical disease. Understanding the host genes involved in these processes is key to developing new prevention and treatment strategies.

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