Special Article

Human Genetic Influence on Susceptibility of Tuberculosis: From Infection to Disease

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There is substantial evidence from studies on racial variation in susceptibility to tuberculosis (TB) that human genetic variation is an important determinant of the outcome of infection with Mycobacterium tuberculosis (M tb). In only a minority of cases is there an obvious identifiable risk factor such as human immunodeficiency virus (HIV) infection, advanced age, diabetes, corticosteroid usage or alcohol abuse. In the remainder, a complex interaction of genetic and environmental factors causes the development of clinical TB. Assessment of the contribution of genetics of host resistance to human TB is a long-standing challenge of human genetics research. Several studies demonstrated the association of various human leukocyte antigens (HLA) with disease susceptibility in different ethnic populations. There are likely to be many more TB-susceptibility genes to be identified.

Keywords: *Tuberculosis, Influence, Human genetic*

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TB, primarily caused by the *M tb*, continues to be a major public health problem, despite the widespread use of combined-drug therapy, Bacille Calmette-Guerin vaccine and the existence of national and international TB control programs[1]. It is presently estimated that 2.4 billion individuals carry *M tb* and modeling studies show that 70 million individuals will die of TB from 1998 to 2018[1]. Assessment of the contribution of genetics of host resistance to human TB is one of the long-standing challenge of human genetics research, and TB has been considered as a complex disease with strong genetic components. Several large, twin studies revealed a consistent, significant excess of monozygous twins where both siblings had developed TB (disease concordance) when compared with dizygous twins or other pairs of siblings. As monozygous twins are genetically identical these studies provide strong data in support of genetic factors being involved in TB susceptibility[1]. Whilst the contribution of host genetic factors to TB susceptibility is now well established, exposure intensities, malnutrition, poor health or social stress are known to contribute to increased risk of developing TB[1]. The mechanisms of how exposure to these environmental factors is translated into TB disease are not known[1]. It stands to reason that a complex disease like TB is not simply dependent upon the clinical end-point, one could say is not a "function-of-state", but that mechanistic pathways that lead to the same clinical end-point can be different in different epidemiological settings[1].

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Advanced researches and review of literatures

The future TB researches in human genetic aspects of the disease include coordinated studies of human genome scans, genetic epidemiology studies, and new quantitative and bioinformatic approaches to study the interaction between *M tb* and the infected host and how this influences the infection process[2]. Host genetic factors such as 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 the development of the disease[3]. Several studies demonstrated the association of various HLA antigens with disease susceptibility in different ethnic populations[3]. For this type of geographic variation, it seems likely that evolution selection pressures have given rise to frequent polymorphisms in genes involved in resisting infectious pathogens and contributed to marked allele frequency difference at the same loci[3]. The genes involved in defense against infectious pathogens evolve more rapidly than others and excessive polymorphism in the human genome may result from selection pressures exerted by infectious diseases[3]. During evolution, all these polymorphic forms might have evolved due to the host-pathogen interaction[3]. Similarly, *M tb* also has genetic variation[3]. HLA studies carried out in the Asian region, especially in India, demonstrated the association of HLA-DR2 and -DQ1 antigens with susceptibility to pulmonary TB[3]. Molecular study has revealed that the allele DRB1 *1501 of HLA-DR2 was higher compared with DRB1 *1502 in North Indian patients[3]. HLA-DRB1 *0803 and -DQB1 *0601 were associated with TB disease progression in Koreans[4]. HLA-DRB1 *1501, HLA-DQB1 *0601 (a subtype of HLA-DQ1) and -DPB1 *02 were found to be positively associated with pulmonary TB susceptibility, supported by haplotype analysis while a negative association (preventive fractions associated with resistance) has also been identified (DRB1 *11(5), DRB1 *10, DQB1 *0501 and DRB1 *08) among South Indian patients[3]. The frequencies of HLA-DQA1 *0101, -DQB1 *0501, and -DRB1 *1501 were significantly increased in non-immunosupressed patients with pulmonary TB but the frequencies of HLA-DQB1 *0402 and antigens DR4 and DR8 were significantly decreased in patients with pulmonary TB[5]. HLA-DQB1 *0503 and HLA-DQB1 *0502 alleles were reported among Vietnamese and Thai patients, respectively[3,6]. An increased frequency of HLA-B8 in Canada, HLA-B5, -B15, and -DR5 in the North American blacks, HLA-A2 and -B5 in the Egyptians and-B27 in the Greeks were observed[3]. A negative association for HLA-DR6 in the American blacks has been reported[3]. The "Transporter" associated with antigen processing gene 2 (TAP 2) along with HLA-DR2 has been shown to be associated with the pulmonary TB susceptibility in north Indian patients, compared with control subjects[3]. Definite association between the haptoglobin 2-2 phenotype and TB has been shown in Russian patients[3]. Several studies suggested that mannose-binding lectin (MBL) deficiency might have been maintained evolutionarily by a reduced capacity of mycobacteria to invade macrophages in the absence of MBL[3]. A Mexican study of surfactant genes expressing collectins that are functionally and evolutionarily related to MBL genes has been suggested to influence TB susceptibility[3]. Analysis of association of mannose-binding protein (MBP) genes and HLA-DR2 has revealed that these genes are associated with pulmonary TB, independent of each other[3]. A study in south Indian populations demonstrated an increased genotype frequency of MBP functional mutant homozygotes (including codons 52, 54 and 57) in pulmonary TB (10.9%) compared with control subjects (1.8%)[3]. A study conducted in South Africa suggested that MBL-54 heterozygotes may be associated with protection against tuberculous meningitis[3]. In spite of an increased susceptibility to respiratory infections associated with MBL deficiency, mbl-2 deficient alleles would have been selected along different populations as consequence of its selective advantage against intracellular pathogens, such as *M tbc*[7]. 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[3]. Both MBP and VDR genes influence the cell mediated immune response in pulmonary TB patients[8]. In a study conducted in the Gambian (West Africa) pulmonary TB patients, the tt genotype of *Taq*I polymorphism of *VDR* gene was found less frequently in pulmonary TB cases, suggesting that this genotype may be associated with pulmonary TB resistance[3]. Studies in south Indian pulmonary TB patients on *Bsm*I, *Apa*I, *Taq*I and *Fok*I polymorphisms of *VDR* gene demonstrated an increased frequency of the genotype Bb (heterozygote) of *Bsm*I, TT (homozygote) of *Taq*I and FF (homozygote) of *Fok*I polymorphism in males and tt genotype (homozygote) of *Taq*I polymorphism in female patients which suggested the association with TB susceptibility[3], whereas, genotypes BB (homozygotes) of *Bsm*I and AA (homozygotes) of *Apa*I polymorphism are associated with pulmonary TB resistance in male subjects[3]. The human natural resistance associated macrophage protein 1(*NRAMP1*, renamed as *SLC11A1*-solute carrier family 11, member 1) gene has several polymorphisms[3].

Association has been found between *NRAMP1* gene and TB susceptibility in populations as diverse as West Africans, Koreans and Japanese[3,9]. Studies on *NRAMP1* gene polymorphism [$(CA)_n$, 823 C/T, TGTG+/del and D543N G/A] in South Indian pulmonary and spinal TB patients demonstrated no association with pulmonary and spinal TB susceptibility[3]. A significant association between pulmonary tuberculosis and a micro satellite marker in the 5′ $(CA)_n$ locus situated in the *SLC11A1* gene was shown[10]. A study conducted in a Taiwanese population showed no association of *NRAMP1* gene variants with TB susceptibility[3]. Linkage between *NRAMP1* locus and TB has been revealed in a large Canadian pedigree, but linkage was not shown in Brazilian, South African or West African populations[3]. A case-control study conducted in The Gambia showed that *NRAMP1* polymorphisms were significantly associated with TB susceptibility, although it was not formally possible to distinguish between TB infection susceptibility and TB disease progression susceptibility[11]. A study conducted in a northern Malawi population showed that genetic variants in *NRAMP1* were associated with protection against TB in both HIV-positive and HIV-negative TB cases, and homozygosity for the CR1 Q1022H polymorphism was associated with TB susceptibility[12]. A study of interleukin-1 receptor antagonist (*IL-1RA*) gene polymorphism in Indian pulmonary TB patients demonstrated no association with any of the genotypes[3]. Association of the haplotype IL-1 Ra $A2^-$/IL-1-beta (+ 3953) $A1^+$ with tuberculous pleuritis susceptibility has been reported[3]. The associations of TB susceptibility with the homozygosity for R214-T365-R378 allele (genotype 2/2) of the *IL-12R* gene and the heterozygosity for the -1082 polymorphism of the *IL-10* promoter have been reported in Japanese and Cambodian patients, respectively[3]. IL-10 108 2G/A alleles or haplotypes containing these alleles may influence the Th1/Th2 balance and hence may play a role in TB susceptibility and increased risk of developing disease[13]. Evidence of TB linkage loci on both chromosomes 15q and Xq was supported by an independent analysis designated common ancestry using micro satellite mapping[11,14]. IL12RB1 polymorphisms might influence the risk of development of adult pulmonary TB[15].

Variation in IL12RB1 could contribute to TB susceptibility in the Japanese population[16]. A study in a Turkish population revealed association between interferon (IFN)-gamma+874T > A polymorphism and TB disease and it effects the magnitude of IFN-gamma responses to mycobacterial antigens[17,18]. A study conducted in The Gambian population showed no association between the IFNGR1 variants and TB[19]. A study conducted in West Africa demonstrated that C allele of rs2114592, A allele of sp110int10, and C allele of rs3948464 which are variants of the *SP110* gene were associated with TB disease in The Gambia, the Republic of Guinea and Guinea-Bissau; The Gambia and the Republic of Guinea, and The Gambia and the Republic of Guinea, respectively[20]. A study conducted in African families by a genome-wide linkage analysis showed the association between TB and a 7 base-paired deletion in *UBE3A* gene in chromosome 15q11-13 region[21]. TNF (Tumor Necrosis Factor)-alpha gene expression may increase power to detect disease-predisposing loci[22]. Some studies in Colombia showed an opposition association of TNF polymorphism with autoimmunity and TB, association of TNF-alpha-1 allele and TB, a protective factor of TNF-alpha-1/TNF-alpha-2 genotype for TB, and TB protection of TNF-alpha-2 allele[23,24]. A strong association of toll-like receptor 2 (TLR2) single nucleotide polymorphisms T597C with the development of TB meningitis and miliary TB was found which indicated that TLR2 influences the dissemination of *M tb*[25] as well as influence of the Arg753Gln TLR2 polymorphism on the risk of developing TB[26]. A study conducted in Tanzania revealed that Asp299Gly TLR4 polymorphism increased risk of developing active TB[27] while another study conducted in The Gambia showed no influence on TB susceptibility[28].

The association of important candidate-gene variants of HLA and non-HLA genes among the Indian population is shown in Table 1.

Conclusion

The development of TB 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. Genome-wide linkage studies on sib-pairs of families affected with TB enable the identification of several candidate genes that are associated with the susceptibility to TB. Advances in single nucleotide polymorphism typing, micro array technology and bioinformatics will be helpful in the study of infectious diseases. However, only a small part of the total familiar clustering observed in TB can be explained by the host genes identified to date. There is much work still to be done as there are likely

Table 1. Association of important candidate gene variants of HLA and non-HLA genes with the susceptibility or resistance to pulmonary tuberculosis in Indian population

Candidate gene	Effect	Ref.
1) HLA		
1.1) HLA-DR2	Susceptibility	29, 30, 31
Sub-type		
- DRB1 *1501, *1502	Susceptibility	32
- DRB1 *1501	Susceptibility	33, 34
1.2) HLA-DQ1	Susceptibility	31, 33
- DQB1 *0601	Susceptibility	33
1.3) HLA-DP		
- DPB1 *02	Susceptibility	33
1.4) Haplotype:		
- DRB1 and 1501-DQB1 *0601	Susceptibility	33
- DRB1 *11(5)	Resistance	33
- DRB1 *10	Resistance	33
- DQB1 *0501	Resistance	33
2) Non-classical HLA		
2.1) Transporter associated with antigen processing (TAP) gene TAP2 and DR2	Susceptibility	35
3) Non-HLA		
3.1) Functional Mutant		
- Homozygotes of mannose-binding lectin (MBL) gene (codon 52, 54 and 57)	Susceptibility	36
- Heterozygotes of MBL codon 57	Resistance to bacteriological relapse	36
3.2) Vitamin D Receptor (VDR) gene variants (*Bsm*I, *Apa*I, *Taq*I and *Fok*I)	Differential susceptibility and resistance in males and females	37, 38
3.3) NRAMP1 [(CA)n, 823 C/T, TGTG+/del and D543N G/A]	No association with susceptibility or resistance	39
4) Cytokine gene		
4.1) TNF-alpha-238, -308	No association	40
4.2) TNF-beta	No association	40
5) Haplotypes		
5.1) HLA-B17-TNF-alpha-238/A	Associated with bacteriological relapse	40
5.2) HLA-B17-TNF-alpha-308/2		40
5.3) HLA-B17-TNF-beta-2		40

to be many more TB-susceptibility genes to be identified.

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อิทธิพลของพันธุกรรมมนุษย์ต่อความไวในการติดเชื้อและการป่วยเป็นวัณโรค

อรรถพล ชีพสัตยากร, เรืองรอง ชีพสัตยากร

มีหลักฐานอย่างหนักแน่นจากการศึกษาการผันแปรของเชื้อชาติต่อความไวในการติดเชื้อและการป่วยเป็นวัณโรคว่าความผันแปรของพันธุกรรมมนุษย์เป็นตัวกำหนดที่สำคัญอย่างหนึ่งต่อผลลัพธ์ของการติดเชื้อวัณโรค มีผู้ป่วยเพียงส่วนน้อยที่มีปัจจัยเสี่ยงอย่างเด่นชัดเช่น การติดเชื้อ HIV อยู่ในวัยสูงอายุ เบาหวาน การดื่มสุราอย่างหนัก หรือ การใช้ยาที่เข้าคอร์ทิโคสตีรอยด์เป็นเวลานาน ส่วนกลุ่มผู้ป่วยที่เหลือจะป่วยเป็นวัณโรคจากปฏิสัมพันธ์ที่ซับซ้อนของปัจจัยทางพันธุกรรมมนุษย์และสิ่งแวดล้อม การวิจัยเพื่อประเมินปัจจัยทางพันธุกรรมมนุษย์เป็นความท้าทายที่มีมานานแล้ว การศึกษาที่หลากหลายต่าง ๆ แสดงให้เห็น ถึงความสัมพันธ์ของที่หลากหลายของ HLA ต่อความไวในการเกิดวัณโรคในกลุ่มประชากรหลากหลายเชื้อชาติ ดูเหมือนว่ายังจะมีจีนที่สัมพันธ์กับการติดเชื้อ หรือ ป่วยเป็นวัณโรคอยู่อีกจำนวนมากที่จะต้องค้นหาต่อไป