Gene Association Studies in Tuberculosis: A Question of Case-Control Definitions?

Rabia Hussain*

Department of Pathology and Microbiology, Aga Khan University, Karachi, Pakistan

One third of the world population is infected with Mycobacterium tuberculosis. However, only 10% of infected individuals will progress to disease during their lifetime [1]. Furthermore, tuberculosis (TB) is a spectral disease with a wide spectrum of severity outcomes [2]. A central question remains if there are inherent genetic factors which play a role in determining disease susceptibility and severity in TB and to what extent? During the 1990's Genome Wide Linkage analysis for genetic susceptibility traits in TB were largely uninformative [3]. The discovery of a large number of single nucleotide polymorphisms (SNPs) in the human genome [4] has revived interest in TB genetic association studies [5]. IFN-γ gene knockout studies in the experimental mouse model [6-7] and the identification of extreme phenotypes in TB patients (Mendelian Susceptibility to Mycobacterial Diseases) associated with mutations in the IFN-γ/IL-12/IL-23 pathway [8-10] indicated IFN-γ to be a key player in immunity to TB [11]. However, studies with functional SNPs in the IFN-γ gene [12-16] have shown highly variable and sometimes opposing effects of the same SNPs in different ethnic populations [17-19]. The reasons for such highly variable results when studying complex traits can be attributed to variable frequencies of target SNPs amongst different populations [20,21]. In this context, the frequency IFN-γ SNP (+874) TT genotype, (a high IFN-γ producer phenotype) varies from 0 to 36% in different populations [21-22]. A further complexity is introduced by healthy population controls used as reference in these studies. The rate of asymptomatic latent tuberculosis infection as tested by PPD Skin Tests is also highly variable in different populations [23]. A study in Spain showed significant differences in IFN-γ SNP +874 T/A between PPD- and PPD+ controls and significant associations with tuberculosis disease were observed when compared to PPD- controls but not to PPD+ as controls [12]. In Pakistan we reported a strong association of IFN-γ SNP +874 TT genotype with pulmonary TB of moderate severity but not with pulmonary advanced TB compared to healthy controls while PPD+ donors in controls had only a modest effect on the strength of association [15]. The differences in results in the two populations may be due to the rate of latent infection. However, most of the association studies do not stratify the control population in terms of latency. The question as to what constitutes a true negative control in association studies remains unclear. The gold test for genetically resistant background (true negative) is the absence of disease after infection. In acutely exposed household contacts of TB patients, the incidence of secondary disease occurs within 1-2 years [24] and is between 5-10% in different populations. Therefore, acutely exposed individuals who remain disease-free over a period of 2 years post acute exposure may fulfill the criteria of having genetically resistant background particularly if the cohort was matched for socioeconomic conditions and is from ethnically homogenous population.

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In a recent report, when such genetically resistant individuals fulfilling most of the above criteria were used as controls for comparison, significant associations of IFN-γ SNP +874 TT genotype (p = 0.000146; \( \chi^2 = 14.42 \) and T allele (p = 0.0003; \( \chi^2 = 12.98 \); OR = 3.18) were observed with susceptibility to TB [25]. The strength of association in this study was modest and similar to other gene association studies [17,26]. This is not surprising as several IFN-γ modulating cytokine can have an additive effect on the final outcome of disease. Recently Moller et al [26] have reported haplotype analysis of eight genes which modulate IFN-γ in South African populations of mixed ethnic background and reported very modest association with only IL-12 B. Although this study had a large sample size, the admixture of several ethnic groups and high latency in the control population may have affected the analysis [26]. This study also does not take into account cytokine genes on other loci that may contribute to the eventual outcome of TB. Only one study has addressed the issue of multi-loci cytokine gene interaction [27], where they showed that only a limited number of gene combinations were associated with TB disease susceptibility. Although single gene, haplotype and multi-loci gene combination studies have been informative, the question still remains as to what genetic factors determine TB disease progression, disease susceptibility, disease severity in different sites. Is there a unifying inheritability component which determines TB disease susceptibility and severity within and among populations? Multi-loci analysis of functional cytokine gene SNPs with better defined controls and cases may provide insights into this complex issue.

References


*Corresponding author: Dr. Rabia Hussain, PhD, Professor of Microbiology, Department of Pathology and Microbiology, The Aga Khan University, Pakistan, E-mail: rabia.hussain@aku.edu

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