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# 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 population [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 socio-economic conditions and is from ethnically homogenous population. 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+874TT 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, halpotype 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

1. Dye C (2006) Global epidemiology of tuberculosis. Lancet 367: 938-940.
2. Crofton J (1990) Crofton and Douglas Respiratory Diseases. In: Clinical features of tuberculosis. London: Blackwell Scientific. pp. 395-421.
3. Altmuller J, Palmer LJ, Fischer G, Scherb H, Wjst M (2001) Genomewide scans of complex human diseases: true linkage is hard to find. Am J Hum Genet 69: 936-950.
4. Kruglyak L, Nickerson DA (2001) Variation is the spice of life. Nat Genet 27: 234-236.
5. Moller M, Hoal EG (2010) Current findings, challenges and novel approaches in human genetic susceptibility to tuberculosis. Tuberculosis (Edinb ) 90: 71-83.
6. Flynn JL, Chan J, Triebold KJ, Dalton DK, Stewart TA, et al. (1993) An Essential role for Interferon gamma in resistance to Mycobacterium tuberculosis infection. J Exp Med 178: 2249-2254.
7. Cooper AM, Dalton DK, Stewart TA, Griffin JP, Russell DG, et al. (1993) Disseminated tuberculosis in Interferon gamma gene disrupted Mice. J Exp Med 178: 2243-2247.
8. Altare F, Jouanguy E, Lamhamedi S, Doffinger R, Fischer A, et al. (1998) Mendelian susceptibility to Mycobacterial infection in man. Curr Opinion Immunol 10: 413-417.

***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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9. Al-Muhsen S, Casanova JL (2008) The genetic heterogeneity of mendelian susceptibility to mycobacterial diseases. J Allergy Clin Immunol 122: 1043-1051.

10. Van de, Vosse, Hoeve MA, Ottenhoff TH (2004) Human genetics of intracellular infectious diseases: molecular and cellular immunity against mycobacteria and salmonellae. Lancet Infect Dis 4: 739-749.

11. Kumararatne DS (2006) Mendelian susceptibility to mycobacterial disease 3. Respiration 73: 280-282.

12. Lopez-Maderuelo D, Arnalich F, Serantes R, Gonzalez A, Codoceo R, et al. (2003) Interferon-gamma and interleukin-10 gene polymorphisms in pulmonary tuberculosis. Am J Respir Crit Care Med 167: 970-975.

13. Sallakci N, Coskun M, Berber Z, Gurkan F, Kocamaz H, et al. (2007) Interferon-gamma gene+874T-A polymorphism is associated with tuberculosis and gamma interferon response. Tuberculosis (Edinb ) 87: 225-230.

14. Selvaraj P, Alagarasu K, Harishankar M, Vidyarani M, Nisha RD, et al. (2008) Cytokine gene polymorphisms and cytokine levels in pulmonary tuberculosis. Cytokine 43: 26-33.

15. Ansari A, Talat N, Jamil B, Hasan Z, Razzaki T, et al. (2009) Cytokine gene polymorphisms across tuberculosis clinical spectrum in Pakistani patients. PLoS ONE 4: e4778.

16. Vallinoto AC, Graca ES, Araujo MS, Azevedo VN, Cayres-Vallinoto I, et al. (2010) IFNG +874T/A polymorphism and cytokine plasma levels are associated with susceptibility to Mycobacterium tuberculosis infection and clinical manifestation of tuberculosis. Hum Immunol 71: 692-696.

17. Pacheco AG, Cardoso CC, Moraes MO (2008) IFNG +874T/A, IL10 -1082G/A and TNF -308G/A polymorphisms in association with tuberculosis susceptibility: a meta-analysis study. Hum Genet 123: 477-484.

18. Moran A, Ma X, Reich RA, Graviss EA (2007) No association between the +874T/A single nucleotide polymorphism in the IFN-gamma gene and susceptibility to TB. Int J Tuberc Lung Dis 11: 113-115.

19. Delgado JC, Baena A, Thim S, Goldfeld AE (2002) Ethnic-specific genetic associations with pulmonary tuberculosis. J Infect Dis 186: 1463-1468.

20. Bagheri M, Abdi-Rad I, Omrani D, Khalkhali HR (2006) Heterogeneity of cytokine single-nucleotide polymorphisms among the Iranian and in the other East-South Asian populations. Transfus Med 16: 192-199.

21. Larcombe LA, Orr PH, Lodge AM, Brown JS, Dembinski IJ, et al. (2008) Functional gene polymorphisms in canadian aboriginal populations with high rates of tuberculosis. J Infect Dis 198: 1175-1179.

22. Anuradha B, Rakh SS, Ishaq M, Murthy KJ, Valluri VL (2008) Interferon-gamma Low producer genotype +874 overrepresented in Bacillus Calmette-Guerin nonresponding children. Pediatr Infect Dis J 27: 325-329.

23. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC (1999) Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. JAMA 282: 677-686.

24. Comstock G (1982) Epidemiology of Tuberculosis. Am J Respir Dis 125: 8-15.

25. Hussain R, Talat N, Ansari A, Shahid F, Hasan Z, et al. (2011) Endogenously Activated Interleukin-4 Differentiates Disease Progressors and Non-Progressors in Tuberculosis Susceptible Families: A 2-Year Biomarkers Follow-Up Study. J Clin Immunol DOI 10.1007/s10875-011-9566-y

26. Moller M, Nebel A, van Helden PD, Schreiber S, Hoal EG (2010) Analysis of eight genes modulating interferon gamma and human genetic susceptibility to tuberculosis: a case-control association study. BMC Infect Dis 10: 154.

27. Henao MI, Montes C, Paris SC, Garcia LF (2006) Cytokine gene polymorphisms in Colombian patients with different clinical presentations of tuberculosis. Tuberculosis (Edinb ) 86: 11-19.