Human Genetic Susceptibility to Tuberculosis: Time for a Bottom-Up Approach?

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(See the article by Horne et al, on pages 586-94.)

Tuberculosis is a leading infectious cause of death; 1.7 million people died from this disease in 2009. Gaps in basic knowledge, such as why most infected persons remain disease free or why if disease occurs it may affect different organs, continue to hamper the development of new prevention and treatment modalities.

A reanalysis of twin studies indicated moderate human genetic susceptibility to tuberculosis [1]. In experimental models, there is clear evidence of genetic influence acting at the level of the innate immune response [2, 3], findings partially supported by studies in humans [4, 5]. The advent of polymerase chain reaction typing and the realization of the extent of single-nucleotide polymorphism (SNP) within the human genome have encouraged a large number of candidate association studies (reviewed in [6]). Of these polymorphisms, association between HLA DR15 and pulmonary disease has frequently been described, and a relationship between polymorphisms within the human SLC11A1 (formerly NRAMP) gene and tuberculosis has been reported in several populations. Association between polymorphism in the interferon γ pathway and disease has been found in several populations. Further insight into immune protection has come from studies on DC-SIGN, MCP-1, SP100, and NOD2 [6]. Homozygotes for a non-coding polymorphism at codon 352 (genotype tt) of the vitamin D receptor gene were significantly underrepresented among Gambians with tuberculosis, an association that was supported by analysis of a separate population of Asians in West London [7, 8]. The study from London made an attempt to analyze gene–environment interactions by concurrent determination of serum vitamin D levels, and more recent work indicates tuberculosis patients of this genotype more rapidly clear Mycobacterium tuberculosis from sputum when prescribed adjunctive vitamin D therapy [9]. Genome-wide scans on affected sibling pairs have detected moderate linkage of tuberculosis to different chromosomal regions. In Africa, linkage was found to chromosomes 15q, Xq, and 20q13 [10], with the linkage on chromosome 20 replicated [11], and in Brazil to chromosome 17q11.2 [12, 13]. More recently, a massive 2-center, genome-wide association scan reported association with an SNP in the gene-poor region on chromosome 18q11.2 [14]. Overall, the lack of a clear major genetic susceptibility locus for tuberculosis is consistent with the possibility that most of the genetic components of susceptibility to tuberculosis are dispersed among many loci.

In this issue of the journal, Horne and colleagues (insert ref.) report a previously unreported association. Drawing on the group’s previous work reporting an association between tuberculosis and polymorphism in the innate Toll-like receptor (TLR) recognition system [15, 16], they hypothesized that polymorphism in the gene encoding a negative regulator (single immunoglobulin interleukin 1 receptor [SIGIRR]) of TLR pathways might associate with tuberculosis. Association was found in a discovery cohort with both pulmonary and microbiologically confirmed meningitic forms of tuberculosis, and 3 of 5 SNPs replicated the association in a second cohort consisting of pulmonary and probable tuberculosis meningitis (TBM). Interestingly, all 3 confirmed SNPs were not within the SIGIRR gene itself but in adjacent genes (2 in Plakophilin-3 [PKP3] and 1 in TMEM16F), both genes having no apparent function consistent with the association. As these polymorphisms were in linkage disequilibrium with polymorphisms in SIGIRR, the authors conclude a likely explanation for the findings is that there is as yet undetected...
polymorphism in the SIGIRR gene itself that may account for association. When analyzed with previously published data on TIRAP and TLR2 SNPs, the SNP in TMEM16J conferred additional susceptibility in those with “at-risk” genotypes. Further work on gene expression patterns in appropriate tissues/cells, for example, may show differential expression of SIGIRR in relation to the associated polymorphisms.

Because most tuberculosis infection in adults is inapparent, the phenotyping of control subjects for association studies presents difficulties. Should controls be tuberculin skin test positive and thus likely to be infected and assumed resistant, or should they be negative? Few, if any, studies have addressed this issue in detail, and most case-control studies to date have compared individuals with disease to those without disease (regardless of exposure). This was the case in the study by Horne and colleagues that employed cord blood samples as controls. The authors argue this may underestimate the size of the genetic effect because some of the controls might ultimately develop tuberculosis. A related phenotyping issue presents difficulties. Should controls be the genes that are targeted for sequence analysis in precisely characterized extreme cases? To do so would require not only a conceptual shift in thinking but also a practical shift toward greater support of clinical science in those developing countries most afflicted. It is notable that the collection Horne and colleagues were able to analyze arose because of the long-term support of the funding agency (Wellcome Trust) of an infectious diseases research unit in a developing country setting (Vietnam).

Notes

**Financial support.** This work was supported by the Wellcome Trust (088316); Medical Research Council (United Kingdom) (U.1175.02.002.00014.01); and the European Union, European And Developing Countries Clinical Trials Partnership.

**Potential conflicts of interest.** Author certifies no potential conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

### References


