INVITED EDITORIAL
Genetic Predisposition to Clinical Tuberculosis: Bridging the Gap between Simple and Complex Inheritance

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Tuberculosis, a chronic infectious disease caused by *Mycobacterium tuberculosis,* has reemerged as a leading public health problem. Approximately one-third of the world's population is infected with *M. tuberculosis*, and a recent World Health Organization report estimated that, in 1998, there were 8 million new cases of clinical tuberculosis and 1.9 million deaths from the disease. Interestingly, not all individuals exposed to *M. tuberculosis* become infected. Moreover, progression toward clinical tuberculosis is far from an inevitable consequence of infection with *M. tuberculosis,* since only ~10% of the vast number of infected individuals actually develop clinical disease (Bloom and Small 1998). Both *M. tuberculosis* infection and clinical tuberculosis result from complex interactions between the infectious agent, environmental factors, and the host.

The involvement of human genes in tuberculosis has been suggested by numerous epidemiological observations. Several studies have shown that a person's resistance level to *M. tuberculosis* infection correlates with the region of his or her ancestry and that the ancestors of more-susceptible persons tend to come from areas once free of tuberculosis (Stead 1992). Similarly, the incidence of clinical tuberculosis has been found to be particularly high during outbreaks in populations, such as that of Native Americans, with no ancestral experience of the infection (Stead 1997). Twin studies have also demonstrated the importance of host genes, by showing higher concordance rates for clinical tuberculosis among MZ than among DZ pairs (Comstock 1978).

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Recent population-based studies have reported associations between some candidate genes and clinical tuberculosis. Genes were selected on the basis of their known or suspected role in innate or adaptive antimycobacterial immunity. Association of tuberculosis with some HLA class II alleles has been reported in populations from Cambodia (Goldfeld et al. 1998) and India (Ravikumar et al. 1999). Certain mannose-binding–protein alleles have been shown to influence tuberculosis in a population from India (Selvaraj et al. 1999). Four polymorphic mutations of natural resistance–associated macrophage protein 1 (*NRAMP1*) were shown to predispose individuals to tuberculosis in Gambia (Bellamy et al. 1998). In the same Gambian population, an association was also reported with polymorphisms in the vitamin D–receptor gene (Bellamy et al. 1999). Finally, polymorphisms in the genes encoding the cytokine interleukin (IL)-1beta and its receptor antagonist IL-1Ra were found to be associated with tuberculosis in patients of Gujarati origin who were living in England (Wilkinson et al. 1999). The predisposing alleles reported in these studies have only moderate effects, and their functional relevance needs to be established before their role can be validated. Thus, the molecular basis of the genetic control of clinical tuberculosis in large populations remains largely elusive.

In contrast, there is clearly a causal relationship between certain rare Mendelian immunodeficiencies affecting T cells or phagocytes and severe tuberculosis (World Health Organization 1997). These rare patients are vulnerable not only to *M. tuberculosis* but also to a variety of other microorganisms. Recently, a genetic syndrome described as Mendelian susceptibility to mycobacterial infections (MIM 209950) has been extensively investigated. Children and adults with this syndrome are highly and specifically vulnerable to weakly virulent mycobacterial species, such as environmental nontuberculous mycobacteria and live-attenuated bacille Calmette-Guérin (BCG) vaccines. Different types of causal mutations in four genes involved in IL-12–dependent interferon (IFN)γ–mediated immunity have been identified

(Altare et al. 1998; Picard et al. 2000). The most-severe genetic defects are invariably fatal in early childhood, whereas other defects have a better prognosis and may be revealed in adults. Remarkably, one child with a mild defect who was not vaccinated with BCG had symptomatic tuberculosis (Jouanguy et al. 1997), which represents the first case of a specific Mendelian predisposition to tuberculosis. However, these rare mutations cannot account for the millions of tuberculosis cases reported annually worldwide. There is, therefore, a gap between causal susceptibility in rare individuals and uncertain predisposition in general populations. In our opinion, these two aspects of genetic predisposition to tuberculosis do not conflict but, rather, are likely to represent the two ends of a continuous spectrum.

In this context, the article by Greenwood et al. (2000 [in this issue]) provides a unique opportunity to reconcile these two extreme poles of tuberculosis genetics. That article analyzes an extended pedigree rather than a single patient or a large population. Predisposition to tuberculosis in that study is associated with a major gene effect and is neither fully monogenic nor polygenic. More specifically, the authors analyzed a large aboriginal Canadian pedigree after an epidemic of tuberculosis and found, for the first time, convincing evidence of the existence of a major locus of susceptibility to clinical tuberculosis. This locus maps to chromosome 2q35 (two-point LOD score 3.8; three-point LOD score 4.2), which includes the *NRAMP1* gene. The authors used a model-based linkage method (classical LOD score) with both a recessive and a dominant mode of inheritance assumed, and, to model gene-environment interactions, they assigned individuals to risk (liability) classes on the basis of age, BCG vaccination, tuberculin skin-test results, and previous disease information. The specification of these liability classes was crucial to obtaining evidence for linkage, which stresses the importance of properly accounting for the epidemiological context in this type of analysis. Maximum LOD scores were obtained with a dominant susceptibility allele having a major effect, since carriers of at least one copy of this allele have a risk of tuberculosis 10 times higher than that for wild-type homozygotes.

Whether these results reflect the role of *NRAMP1* itself or that of a closely linked gene remains to be established. It is clear that *NRAMP1* is an excellent candidate gene, since it is the human orthologue (Cellier et al. 1994) of the murine *Nramp1* gene (Vidal et al. 1993), which regulates the early phase of mouse mycobacterial infection. Functional studies have shown that *Nramp1* has pleiotropic effects on macrophage function (Canonne-Hergaux et al. 1999). A single homozygous null mutation in *Nramp1* is associated with susceptibility to several mycobacteria (Govoni et al. 1996; Vidal et al. 1996), including *M. bovis* BCG and *M. lepraemurium,* the latter being the rodent-tropic equivalent of *M. leprae,* which causes leprosy in humans. The *Nramp1* gene does not appear to affect the susceptibility of mice to *M. tuberculosis* (North et al. 1999), but *M. tuberculosis* is not a natural pathogen of rodents.

The major gene identified in the Canadian pedigree studied by Greenwood et al. (2000) appears to control the progression from infected status (individuals with positive tuberculin skin test) to affected status (individuals with tuberculosis) in a dominant manner. This mode of inheritance is consistent with the results observed in a Gambian case-control study (Bellamy et al. 1998) in which the risks associated with one copy of one *NRAMP1* predisposing mutation were, however, much smaller (odds ratio <2) than those observed for the major susceptibility allele in the study by Greenwood et al. (relative risks 10). The risks were larger (odds ratio ~4) for Gambian individuals heterozygous for two specific mutations. Weak evidence for linkage between the *NRAMP1* region and tuberculosis was also reported in multicase Brazilian families (Shaw et al. 1997). Further supporting its role in mycobacterial diseases, *NRAMP1* was found to be linked to susceptibility to leprosy per se in Vietnam (Abel et al. 1998). In the same population, *NRAMP1* was shown to be linked to the in vivo Mitsuda reaction, which assesses the delayed immune response against intradermally injected lepromin (Alcais et al. 2000), indicating that *NRAMP1* may also influence the risk of *M. leprae* infection. Whether *NRAMP1* can be involved in the control of tuberculin skin-test reaction and of *M. tuberculosis* infection is an important question that deserves further study.

In any case, the results of Greenwood et al. (2000) strongly support the view that, in certain genetic epidemiology contexts, predisposition to tuberculosis results mostly from major gene control. This kind of control for infectious diseases had already been suggested by segregation studies for leprosy (Abel and Demenais 1988) and by schistosomiasis caused by the parasite *Schistosoma mansoni* (Abel et al. 1991). In the latter disease, linkage studies identified two distinct loci—one controlling infection levels by *S. mansoni* (Marquet et al. 1996) and the other determining progression from infection to severe clinical disease (Dessein et al. 1999). Overall, these results indicate that, as in some other complex diseases (e.g., breast cancer and Alzheimer disease), and at least in certain contexts, Mendelian-like subentities can be involved in the genetic control of common infectious diseases.

For tuberculosis, this may be the case for populations that have not been extensively exposed to *M. tuberculosis* for a long time, such as the aboriginal Canadian population studied by Greenwood et al. (2000). In such populations and before antibiotics were available, the incidence of tuberculosis during epidemics rapidly in-

creased as the infection spread, slowing as the number of uninfected susceptible subjects was reduced and decreasing to baseline as the pool of susceptible individuals was depleted by death (Stead 1997). It is tempting to speculate that highly susceptible individuals who died early from the disease carried high-risk genotypes. Under this hypothesis, the relatively rare susceptibility allele identified by Greenwood et al. (2000) or any mutations having similar effects (especially dominant ones) have probably disappeared rapidly from populations with an ancestral history of extensive exposure to *M. tuberculosis*. In such populations, however, other alleles, with milder effects, may predispose to tuberculosis in a less-pronounced manner.

The major-gene control reported by Greenwood et al. (2000) supports the hypothesis of a continuous spectrum in the genetic control of clinical tuberculosis, since it bridges the gap between simple Mendelian susceptibility and complex polygenic predisposition to clinical tuberculosis. This view of tuberculosis genetics has major implications for future studies, which should benefit from concepts and techniques developed in the fields corresponding to the two poles of this spectrum. Progress in the molecular genetic dissection of clinical tuberculosis will likely come from complementary approaches searching for rare Mendelian immune defects in particular patients with severe/uncommon clinical features, major-gene effects in certain specific kindreds and populations with no ancestral history of tuberculosis exposure, and more-common polymorphisms with less-pronounced effect in other populations with a longer history of exposure to *M. tuberculosis*. An intriguing question is whether a single gene could be involved in the three levels of genetic control, with rare mutation(s) being responsible for Mendelian susceptibility, relatively rare variants having a major-gene effect, and more-common polymorphisms having a milder effect on the risk of clinical tuberculosis.

This research has major biological implications for an understanding of the genetic control of antimycobacterial immunity. It is now urgent that we find new ways to combat tuberculosis, one of the most fatal infectious diseases worldwide (Murray and Salomon 1998; Dye et al. 1999). The identification of host genes with their functional alleles controlling the response to mycobacterial infection is fundamental to the definition of new prevention (e.g., early detection and prolonged follow-up of high-risk individuals) and treatment (e.g., aimed at restoring partially deficient immune responses) strategies for tuberculosis.

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