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COMMENTARY

Linkage of Leprosy Susceptibility to Parkinson's Disease Genes

ABSTRACT

In early 2003, an international team of scientists conducted a genome scan in Vietnamese multiplex leprosy families and found that susceptibility to leprosy was significantly linked to region q25 on the long arm of chromosome 6. Further confirmation of the chromosome 6 locus was provided by high-resolution linkage mapping in simplex leprosy families. Now, in a continuation of these findings, the team has pinpointed the chromosome 6 susceptibility locus to the 5′ regulatory promoter region shared by both the Parkinson's disease gene *PARK2* and its co-regulated gene *PACRG*. The surprising discovery has important implications for the understanding of leprosy pathogenesis and for the strategy of genetic analysis of infectious diseases.

Genomic strategy to identify the chromosome 6 leprosy susceptibility gene. Although the localization of the leprosy susceptibility locus to chromosome 6q25 was an enormous breakthrough, the task of identifying the responsible gene still presented major difficulties, since the target region delineated by the two markers *D6S4155* and *D6S1277* covered approximately 6.4 million nucleotides that encoded 31 known genes ([2]). Since the region was too large to attempt straightforward comparative DNA sequencing, another strategy was needed to dissect out the gene. Thus a panel of 64 single nucleotide polymorphisms (SNPs) was selected that tagged each of the 31 genes in the core interval by at least one SNP marker ([3]). The SNP markers used for the Mira, *et al.* study were selected either directly from the human SNP database or obtained by comparative sequencing of unrelated Vietnamese individuals. Next, DNA samples were isolated from all members of 197 Vietnamese families composed of two healthy parents and one leprosy-affected child, so called "simplex" families. These DNAs were genotyped for the 64 SNPs, and systematic analysis of association with leprosy disease was performed for each SNP marker ("association scan"). Importantly, the phenotype employed was leprosy disease independent of specific clinical paucibacillary or multibacillary forms (PB or MB) of the disease. The association scan showed that SNPs with strongest association were located in an 80 kilobase fragment that overlapped the promoter (regulatory region) of the *PARK2* (parkin) and *PACRG* (parkin co-regulated gene) genes. A higher density screening with a further 81 SNPs in the 80 kilobase segment further confirmed the regulatory promoter region and a total of 17 SNP markers were found associated with leprosy disease. By conducting a multivariate analysis, it could be shown that only 2 of the 17 SNPs captured the entire association between the 80 kilobase fragment and leprosy disease. Most importantly, the findings in the Vietnamese families were confirmed in patients from a second leprosy endemic country ([3]). A subsequent analysis found that the SNP markers associated with leprosy in Vietnam were also associated with leprosy susceptibility in 975 unrelated individuals from Brazil. In both populations, the risk alleles are associated with leprosy *per se,* meaning that persons carrying the risk alleles would be equally likely to develop PB as MB. Therefore, the cause of susceptibility is likely to involve an early, common cellular pathway used by the *M. leprae* bacillus. While the study conclusively implicates *PARK2* and/or *PACRG* in leprosy pathogenesis, the question if any of the leprosy-associated SNPs is directly and causally involved in leprosy susceptibility remains unanswered.

***PARK2* and *PACRG* genes reveal the function of a novel cellular pathway in susceptibility to leprosy infection.** The possible identity of a "leprosy *per se*" pathway was revealed through knowledge of the function of the *PARK2* and *PACRG* genes ([1, 5]). Mutations in *PARK2* are responsible for familial early-onset Parkinson disease (PD), which represents approximately 3% of all PD cases. The mutations in *PARK2* in PD are not found in leprosy patients. The

PARK2 (parkin) gene product is an ubiquitin-protein ligase, which activates deposition of certain proteins such as alpha-synuclein in so-called intracellular Lewy bodies. The lack of ubiquitin ligase activity in patients with *PARK2* mutations causes protein accumulation and neurodegeneration. *PACRG* appears to be involved in the transport of polyubiquitylated proteins to the proteasome. Overall, PD is a complex disease with both genetic and environmental factors, and it has been suggested that infections may trigger its onset. However, neither *PARK2* or *PACRG* genes have yet been associated with susceptibility to any infectious disease other than leprosy. One important aspect to determine then is whether the *PARK2* or *PACRG* associations are found only in leprosy, or are associated with other mycobacterial diseases, such as tuberculosis, and, if the polymorphisms associated with leprosy also predict risk of PD.

***In vitro* experiments to determine the function of the leprosy susceptibility gene.** The primary focus now should be to establish a connection between the risk alleles for leprosy susceptibility, the ubiquitin proteolysis pathway and the course of *M. leprae* infection and growth. There are many unknowns to this next phase of experimentation. For example, it is not known whether the leprosy susceptibility alleles would up or down regulate the *PARK2* or *PACRG* encoded proteins, or affect the cellular ubiquitin pathway. In the context of further functional studies, it is revealing that both *PARK2* and *PACRG* are expressed by Schwann cells and monocyte-derived macrophages ([3]). Nevertheless, testing of the risk alleles in patients will have to await a reliable functional assay for biological activity of *M. leprae*. In parallel, it is also hoped that the analysis of *M. leprae* and the parkin genes will yield information relevant to the neurological aspects of Parkinson's disease.

CONCLUSION

The clinical spectrum of leprosy has long been recognized as an immunological model in which various aspects of human T cell subset and cytokine function can be characterized ([4]). It is fitting that leprosy has proven once again to be a model for molecular genomics, by providing the first infectious disease locus isolated by positional cloning. Since this success is largely rooted in the framework provided by the Human Genome Project, the identification of this novel and entirely unexpected leprosy susceptibility locus also provides a good example that recent advances in genomics can be used for the study of diseases primarily prevalent in resource-poor countries. Taken together, the papers by Mira, *et al.* provide a general framework for the genetic analysis of complex infectious diseases. Above all, it is hoped that the novel link of leprosy susceptibility to the ubiquitin proteolysis pathway will yield some insight to the transmission of leprosy, a disease which has so far evaded eradication despite many years of effective drugs and case finding ([6]).

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