HIGHLIGHTS

HUMAN GENETICS

An unlikely association?

The first successful identification, by positional cloning, of genetic variants with an important function in a common human infectious disease has just been reported. The disease in question is leprosy, and Mira and Alcaïs *et al.* found that susceptibility to *Mycobacterium leprae* infection, the causative agent of the disease, is associated with polymorphisms in the upstream regulatory regions of the Parkinson disease gene *PARK2* and the co-regulated gene *PACRG*.

The authors previously mapped susceptibility to leprosy to a 6.4-Mb region on the short arm of chromosome 6. They used comparative sequencing and database searches to identify 64 SNPs in the region, such that at least one of them was associated with each of the 31 genes that reside in this region. Using these markers, they conducted an association scan among 197 Vietnamese families with two parents and one leprosy-affected child to find that the most significantly associated SNPs clustered in the regulatory region that is shared by *PARK2* and *PACRG*.

Comparative sequencing of the exons, 5′ and 3′ non-coding regions of both genes identified no coding SNP variants. Moreover, when the authors looked for more densely distributed markers in the regions of high association, all markers that were highly associated with susceptibility to leprosy clustered in that same 5′ regulatory region.

A look at the linkage-disequilibrium map of this 500-bp 5′ region showed that the variants that control susceptibility to leprosy lie in an 80-kb block. Multivariate statistical analysis showed that two SNPs in particular captured all of that association. Importantly, the authors subsequently confirmed these findings in an independent sample of almost 1,000 unrelated individuals from Rio de Janeiro, Brazil.

What might this unlikely association mean in biological terms? Although the function of *PACRG* is unknown, it has been implicated in the delivery of polyubiquitylated proteins to the proteasome, and *PARK2* itself encodes a ubiquitin E3 ligase. Both genes are expressed in immune tissues, in particular, to varying degrees, in Schwann cells and macrophages. Because both of these cell types are the primary host cells for *M. leprae*, these results highlight an exciting possibility that ubiquitin-mediated proteolysis might be important in the control of this infection, as well as neurodegeneration.

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References and links

ORIGINAL RESEARCH PAPER Mira, M. T. & Alcaïs, A. *et al.* Susceptibility to leprosy is associated with *PARK2* and *PACRG*. *Nature* 25 Jan 2004 (doi:10.1038/nature02326)

FURTHER READING Casanova, J.-L. & Abel, L. The human model: a genetic dissection of immunity to infection in natural conditions. *Nature Rev. Immunol.* **4**, 55–66 (2004)