MULTIPLE SCLEROSIS

Surveying the genetic architecture of MS

Two large, collaborative genome-wide association studies (GWAS) have identified several new susceptibility loci for multiple sclerosis (MS), and have highlighted inflammatory immunological mechanisms as the key drivers of MS pathology.

One study, published in *Nature*, involved a collaboration between the International Multiple Sclerosis Genetics Consortium (IMSGC) and the Wellcome Trust Case Control Consortium 2. Previous work had identified 26 genetic loci associated with the risk of developing MS, and highlighted a key involvement of the major histocompatibility complex genes. “The purpose of the current study was to screen on a scale large enough to resolve the status of these risk genes and identify novel susceptibility loci,” explains Alastair Compston from the University of Cambridge, UK, who is a cofounder of the IMSGC and was one of the lead authors of the paper.

The researchers began by genotyping DNA from almost 10,000 patients and over 15,000 controls from populations of European descent in 15 countries. By comparing the data sets, they were able to identify genetic variants, known as single nucleotide polymorphisms (SNPs), that showed an association with MS. Subsequent validation analyses in another, previously reported sample confirmed the status of 23 of the 26 suggested MS-associated loci and identified a further 34. In addition, according to Compston, “the study involved cases and controls drawn from many different populations, which posed a new problem in terms of comparing the data sets. Using a novel analytical approach, we were able to solve that problem, and the methods employed in this paper could be useful for other large multinational studies in the future.”

The pivotal findings of the study emerged from pathway analysis of the GWAS signal to investigate the possible functions of the implicated genes. “Surprisingly, about 80% of the genes were ‘shouting’ T-cell immunology,” says Compston. By contrast, genes related to neurodegeneration were not identified in the GWAS. Previously, the order of events in MS pathology and the relative importance of immune-mediated pathways had been debated. The new findings “highlight the dominance of immunological pathways at the front end of disease in MS,” explains Compston.

In the second study, several groups and consortia, including the IMSGC, performed a genome-wide meta-analysis of seven data sets involving approximately 5,000 MS cases and 12,000 controls of European descent. They identified three new MS susceptibility loci, one of which contains *EOMES*—a gene that encodes a transcription factor involved in the differentiation of certain immune cells.

Next, the researchers compared results from GWAS in other autoimmune diseases, including celiac disease and type 1 diabetes, with their results from the

MS-related GWAS, to investigate whether susceptibility loci were shared between diseases. According to Philip De Jager, who is based at Harvard Medical School, Boston, USA and was one of the authors of the paper, “the overlap among diseases is more extensive than previously appreciated and, importantly, about 50% of the shared loci have opposite effects in MS and other diseases.” Thus, many of the gene variants that confer susceptibility to another autoimmune disease are protective against MS. “This finding illustrates not just extensive sharing of genetic susceptibility among inflammatory diseases, but also an unsuspected complexity in how these loci work together in different contexts,” adds De Jager.

Compston’s group will be looking to mine the data more deeply in the future, with greater emphasis on functional genomics rather than simply mapping genes. They are interested in discovering whether genetic profiles of patients with MS could help us to understand different aspects of disease and enable stratification of patients according to criteria such as disease progression and response to treatment.

De Jager says that, on behalf of the IMSGC, his team is currently working to merge the two studies and add two more data sets to their analysis, “to produce a comprehensive map of common genetic variation in MS.” He concludes that a more complete understanding of the shared genetic architecture of inflammatory diseases could highlight key nodes for drug development efforts and inform the repurposing of existing drugs for new indications.

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Original articles International Multiple Sclerosis Genetics Consortium & Wellcome Trust Case Control Consortium 2. Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. *Nature* **476**, 214–219 (2011) | Patsopoulos, N. A. et al. Genomewide meta-analysis identifies novel multiple sclerosis susceptibility loci. *Ann. Neurol.* doi:10.1002/ana.22609

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