

Risk genes for multiple sclerosis uncovered

A large-scale genomic study has uncovered new genetic variations associated with multiple sclerosis (MS), findings that suggest a possible link between MS and other autoimmune diseases. The study, led by an international consortium of clinical scientists and genomics experts, is the first comprehensive study investigating the genetic basis of MS. Findings appears in the July 29 in the online edition of the New England Journal of Medicine.

MS, a disease of the central nervous system whose symptoms range from mild muscle weakness to partial or complete paralysis, is widely considered an autoimmune disease, one that arises from a combination of genetic and environmental factors. This collusion of events leads the body to attack and destroy the insulation along nerve fibers. This study, which analyzed genomic information from 12,360 people, confirmed that immune system genes are altered in people diagnosed with MS, and pointed to potential mechanisms of the disease.

The researchers gathered 931 sets of DNA samples from MS patients and their parents. They analyzed single nucleotide polymorphisms (SNPs), that is, small differences in DNA sequence that represent the most common genetic variations between individuals, and looked for variations that were more commonly inherited by people with MS compared to samples from people without the disease. To double-check the findings, they performed a second analysis of other sets of families, individual cases of MS, and a control group. In the end, all the samples were combined for a final analysis of more than 12,000 subjects.

The only genetic link for MS previously identified using other techniques is in the major histocompatibility complex (MHC), a large cluster of genes responsible for many immune functions, including preventing the body's immune cells from attacking its own tissues. This analysis confirmed that link but went further to find other variants in genetic regions that are more common in people with MS.

One of the regions contains a gene called the IL-2 receptor, which has also been linked to two other autoimmune diseases; type 1 diabetes and autoimmune thyroid disease.

“Scientists are increasingly finding genetic links between autoimmune diseases that affect different tissues in the body, including type one diabetes and rheumatoid arthritis,” says David Hafler, the Jack, Sadie and David Breakstone professor neurology at Harvard Medical School and Brigham and Women's Hospital, one of the study's authors. “This study will likely spur further research into the connection between these seemingly separate conditions.”

Another region harbors a gene called the IL-7 receptor, which helps to control the activity of a class of immune cells called regulatory T cells. Two papers appearing

simultaneously in *Nature Genetics* confirm this finding, and explore how the change in the IL-7 receptor affects the immune system. “I believe that this receptor and its interaction with regulatory T cells will now become a major focus of research on MS,” says Stephen Hauser, professor of neurology at University of California San Francisco, and another author on the paper.

“The whole genome screen provides valuable replication of our IL-7 receptor finding but, importantly, places the gene in the context of others that may contribute to MS,” said Simon Gregory PhD, Assistant Professor at the Duke University Center for Human Genetics, first author of the *Nature Genetics* paper that explores the function of IL-7 receptor, and co-author of this study. “The next step will be to identify how these genes act together to cause the complex pathology of MS.”

This latest paper is among a series of recent whole-genome association studies that have begun to uncover the genetic basis of complex diseases like diabetes, schizophrenia, and coronary artery disease. Unlike diseases caused by a mutation in a single gene, these conditions seem to arise from a combination of genetic, behavioral, and environmental factors. Scientists believe that a host of genetic variations may contribute to a person’s susceptibility. For instance, Hafler points out that in MS, “each gene contributes only a small amount of risk. The big question is, how do they interact with each other, and are they in common pathways?” If so, this can point scientists to the underlying cause of the disease, which may guide future treatments.

Genomic technologies have now made it possible to uncover these subtle genetic associations. “People have been looking for genes involved in MS for 30 years,” Hafler says. “Why weren’t they found? The answer is you couldn’t do it without the sequence of the human genome.” Collaboration with Eric Lander at the Broad Institute, who led the effort to sequence the human genome, was critical. The next step, Hafler said, is to begin to collect larger numbers of samples and examine more DNA sequences, which will allow scientists to identify subtler variations that contribute to the disease.

One of the most encouraging outcomes of this current genomic study,” say Dr. John Richert, Executive Vice President, Research & Clinical Programs, National MS Society, “is that it is helping us to pin point genes that may elevate the risk of developing MS and other autoimmune diseases pointing the way to new areas of research and therapeutic targets to both treat and eventually prevent these diseases.”

“This study illustrates the power of collaboration”, added author Adrian Ivinson, Director of the Harvard Center for Neurodegeneration and Repair. “Individually, none of us could have completed a study of this scale and complexity. But using a Collaborative Research Award from the National MS Society we formed a truly effective international consortium that was able to deliver the most exhaustive search for MS risk factors ever published. In an effort to see the work extended, we are now committed to making the entire data set available to MS researchers worldwide.”

“This is just the beginning,” says Hauser. “This international collaboration is currently planning even larger and more detailed explorations of the genetic landscape of MS.”

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Lead investigators at each institution:

David A. Hafler, M.D. Brigham and Women’s Hospital, and Harvard Medical School, Boston MA; Alastair Compston, FMedSci, FRCP, Ph.D. University of Cambridge School of Clinical Medicine, Cambridge, United Kingdom; Eric S. Lander, Ph.D. Broad Institute of Harvard University and Massachusetts Institute of Technology, Cambridge, MA; Simon G Gregory, Ph.D. Duke University Center for Human Genetics, Durham, NC; Margaret A. Pericak-Vance, Ph.D. University of Miami School of Medicine, Miami, FL; Jonathan L. Haines, Ph.D. Vanderbilt University Medical Center, Nashville, TN; Stephen L. Hauser, M.D. University of California at San Francisco, San Francisco, CA