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RESEARCH/CLINICAL UPDATE

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International Collaborators Identify New Genetic Risk Factors for MS

National MS Society Supported the Largest Whole Genome Scan for MS

The International Multiple Sclerosis Genetics Consortium (IMSGC) has identified two new genetic variations associated with MS, completing the largest replicated whole genome scan (scan of all the genes in the body) for multiple sclerosis to date. In addition, two independent collaborating groups published papers in *Nature Genetics* confirming one of these gene variations. The findings point to potential mechanisms underlying the disease and present possible new targets for designing better therapies to stop the immune attack in MS. The IMSGC, a group of international MS genetic experts created with funding from the National MS Society, report their results in *The New England Journal of Medicine* (published early online July 29, 2007). The Society and Harvard united to jointly raise a total of $3.63 million to fund this genome scan study.

"By pinpointing genes that elevate the risk of developing MS and other autoimmune diseases," stated Dr. John R. Richert, Executive Vice President, Research & Clinical Programs at the National MS Society, " these studies lead us in new directions for both treating and eventually preventing these diseases." All of the data from the gene scan is being made publicly available to aid future research.

Background: A major effort has been under way for over a decade to search for the genetic underpinnings of MS – the inherited set of genes that make people susceptible to developing the disease. If successful, it would give scientists a roadmap to the cause of MS, as well as to concrete targets for new therapies and possibly even ways to prevent the disease. But this painstaking search, involving analysis of the genome and the banking of thousands of DNA samples from patients and family members, has not yet borne fruit beyond several possible "hot spots" on areas of the 23 pairs of ribbon-like chromosomes which require further exploration.

In 2003, Drs. David A. Hafler (Harvard Medical School and Brigham and Women's Hospital) Stephen Hauser (University of California, San Francisco) and Eric Lander (Broad Institute of MIT and Harvard) jointly received the Palmer Collaborative MS Research Center Award: MS Targeted Haplotype Project from the National MS Society to pool expertise and resources in attempts to speed work toward discovering MS genes. This award propelled the formation of the IMSGC, a collaborating group of investigators with expertise in genetics, database design/construction, and clinical assessment and immunology of MS. This group includes Drs. Alistair Compston and Stephen Sawcer (University of Cambridge), Drs. Jonathan Haines (Vanderbilt University) and Margaret Pericak-Vance (University of Miami) and Dr. Jorge Oksenberg (UCSF). They have established a shared DNA repository, which enables them to gather the large amounts of data necessary to conduct genetics studies.

The Genome Scan Study: Using a new technological advance, a DNA chip that enabled the collaborators to test 500,000 individual genetic locations (sites within genes) at one time for possible involvement in MS, they scanned blocks of the genome – all the genes in the human body – for variations that were more commonly inherited by people with MS compared to those without the disease. They screened the genome in 931 "trio families," which comprised people with different types of MS and their unaffected parents.

To double-check their findings, they performed a second analysis of other sets of families, individual cases of MS and a control group. Ultimately, all samples were combined for a final analysis of more than 12,000 people. This is the first genome scan in MS in which the results were replicated, which is a crucial step in establishing the validity of results.

The IMSGC's high-powered analysis yielded two novel genetic variations showing a highly significant association with MS. These variations are in the genes that control the function of messenger proteins, or cytokines, that regulate immune cells including T cells, major players in the immune attack that is launched on the brain and spinal cord in MS. The variations are in the genes for interleukin-2 receptor-alpha and interleukin-7 receptor-alpha. Interleukin-2 and Interleukin-7 have been associated with certain T cells (called regulatory T cells) that have the power to turn off the immune attack and there is evidence of dysfunction of these cells in MS. Interleukin-2-alpha has previously been implicated in other autoimmune diseases, including type 1 diabetes.

Two Confirming Studies: Two papers published online July 29 in *Nature Genetics* also report on the association of interleukin-7 receptor-alpha with MS, and how the change in this protein affects the immune system. One is by Drs. Jonathan Haines (Vanderbuilt University Medical Center), Margaret Preicak-Vance (University of Miami Miller School of Medicine) and an international group of collaborators and was funded in part by the National MS Society. This team explored three possible candidate MS genes that had been pinpointed by previous studies, but was only able to confirm that the gene for interleukin-7 receptor alpha was

associated with MS. They also found evidence that the gene variation may alter the amount of interleukin-7 receptor alpha that is available, possibly leading to impaired suppression of autoimmunity.

The second *Nature Genetics* paper is by Drs. Frida Lundmark and Jan Hillert (Karolinska Institute, Stockholm, Sweden) and collaborators from Sweden, Denmark, Finland, and Norway. To follow up their previous study identifying interleukin-7 receptor alpha as a possible susceptibility gene in MS, the group conducted a series of studies in people with MS and people without MS, all of which confirmed the association of this gene with susceptibility to MS.

Implications: Taken together, the findings of all three studies point to potential mechanisms underlying the disease and present possible new targets for designing better therapies to stop the immune attack in MS. Already under testing in people with MS is the monoclonal antibody "daclizumab" (PDL BioPharma and Biogen Idec), which targets interleukin-2 receptor-alpha.

Investigators agree that the identification of these two new genetic risk factors is unlikely to change current clinical practice, and that there are likely many more genes that contribute to disease susceptibility. "This study also uncovered a number of other genes that approached statistical significance, some of which may relate to the risk of developing MS," added Dr. Richert. "As these additional genes are probed further for their role in MS, not only will we understand a great deal more about the cause of MS, but a number of important new therapeutic targets will emerge."

-- Research and Clinical Programs Department