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Statistical analysis could yield new drug target for MS

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(PhysOrg.com) -- An elaborate statistical analysis of genes from more than 7,000 individuals has identified an amino acid that appears to be a major risk factor for multiple sclerosis, a devastating autoimmune disorder that afflicts 2.5 million people worldwide. In research published this month in BMC Medical Genetics, scientists from The Rockefeller University and colleagues from the University of Oxford in England and the University of British Columbia in Canada report a binding pocket in a previously implicated gene that may be an attractive research prospect as a potential drug target.

The analysis by biostatistician Knut M. Wittkowski, of Rockefeller's Center for Clinical and Translational Science, is the most sweeping to date of a database containing disease-relevant genes of 13,000 individuals who either have multiple sclerosis or are closely related to someone who does. Wittkowski and colleagues focused on a gene identified about a year ago in the New England Journal of Medicine as the single most important genetic risk factor for multiple sclerosis. The gene, HLA-DRB1, is part of the major histocompatibility complex, a large cluster of particularly complex genes evolved to help the immune system adaptively respond to foreign invaders that it has never before encountered. How it contributes to the disease remains a mystery, however.

Unlike most human genes, which have only two alleles per locus, HLA-DRB1 has up to four, making traditional statistical analyses problematic. Wittkowski extended a variant of a commonly used method he

developed in 2002 with a postdoc from Rockefeller's Laboratory of Statistical Genetics to deal with multi-allelic loci so that it could handle the complexity of HLA-DRB1. He analyzed 93 locations with genetic variations and found that a single amino acid in the protein that the gene encodes, number 13, is the telltale indicator of susceptibility to multiple sclerosis. Amino acid 13 is at the center of a pocket in the HLA-DRB1 molecule that helps present an invading pathogen to the immune cells that can kill it. The researchers speculate that a mutation in this amino acid could cause the molecule to present healthy tissue for execution, one of the possible ways multiple sclerosis attacks the body.

"We have identified the most important part of the gene for MS risk," says Sreeram Ramagopalan, a postdoctoral research fellow at Oxford's Wellcome Trust Center for Human Genetics, who collaborated with Wittkowski. "And it looks plausible. Amino acid 13 is part of a piece of the molecule that presents peptides to trigger the immune reaction."

Although multiple sclerosis is a complicated disease that likely has other genetic as well as environmental risk factors, the collaboration between Wittkowski and clinical and translational colleagues has provided researchers a specific hypothesis to explore. "It is rare to find investigators who are open to developing new statistical methods to address the data at hand," Wittkowski says. "This is the type of transformative result a real collaboration can produce beyond the more common consultation about off-the-shelf methods."

Ramagopalan says his researchers at Oxford will be following up on the statistical analysis with wet-lab experiments using animal models to detail the role amino acid 13 plays. "Now we want to know exactly how it works and what happens without it or when it is changed," he says.

More information: *BMC Medical Genetics* online: February 4, 2009, www.biomedcentral.com/1471-2350/10/10/abstract