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Common threads seen in autoimmune diseases

As genes conferring risk for autoimmunity are revealed, the shared pathways underlying seemingly different illnesses are coming to light

Researchers studying what goes wrong in autoimmune diseases now have a road map to guide future work, thanks to two ambitious international studies published in August in which School of Medicine researchers played key roles. One, reported in *Nature*, doubles the number of known genetic culprits in multiple sclerosis (MS). The other, in *PLoS Genetics*, finds that the genetic basis of autoimmunity is largely shared among autoimmune disorders.

Chris Cotsapas

Autoimmune diseases, which occur when the immune system attacks the body's healthy tissue, are three times more common among women than men, and rank among the top 10 causes of death for women under age 65 in the United States, according to Chris Cotsapas, Ph.D., assistant professor of neurology and genetics and lead author of the *PLoS* paper.

"All autoimmune diseases have a substantial heritability," Cotsapas says, much of which is due to variants in the major histocompatibility complex, a section of chromosome 6 that is well populated with immune-related genes.

Other genes also play a role. For example, recent genome-wide association studies (GWAS) have implicated over 20 additional genomic regions in MS, a condition in which the immune system targets myelin, a fatty sheath around nerve cell extensions that is crucial for efficient neural transmission. But these studies left much of the heritability of the disease unexplained, leaving researchers wanting a bigger and better study.

David Hafler

"Everyone realized that no one could do it individually," says MS expert David Hafler, M.D., the Gilbert H. Glaser Professor and chair of neurology, part of the team that published the study in *Nature*. That paper, authored by the International MS Genetics Consortium and the Wellcome Trust Case Control Consortium 2, involved 11 years of work by nearly 250 researchers in 15 countries.

In genome-wide comparisons of DNA from about 10,000 people with MS and from 20,000 unaffected people, Hafler and colleagues confirmed 23 out of 26 previously reported genetic associations with MS, and they identified an additional 29 gene regions that had never before been tied to the illness.

The vast majority of genes in the implicated regions play a role in the immune system. Many affect white blood cells, particularly helper T cells, which prime their B cell cousins to fight perceived threats. In addition, the researchers noted that over a third of the genes associated with MS had been previously flagged as possible culprits in at least one other autoimmune disorder, findings that should "put to rest" any doubts that MS is primarily an autoimmune disease, says Hafler.

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The *PLoS Genetics* study, on which Hafler, Cotsapas, and others joined a group organized by the Federation of Clinical Immunology Societies (FOCIS), investigated whether seven common autoimmune disorders share genetic influences, as would be expected from the way these disorders co-occur within individuals and families. "People often get more than one," says Hafler.

Cotsapas, Hafler, and colleagues on the FOCIS team analyzed data from previous GWAS of celiac disease, lupus, type 1 diabetes, Crohn's disease, MS, rheumatoid arthritis, and psoriasis, focusing on 107 genetic variants that had been tied to autoimmune disease. They found that nearly half the genes were associated with increased risk of multiple autoimmune disorders. "I was really surprised that the degree of sharing was that high," says Cotsapas.

Next, the researchers grouped the variants by their associated diseases and found that many affected genes code for proteins that closely interact in networks. "They talk to each other, and that suggests that there are entire pathways that underlie risk to multiple diseases," Cotsapas says. Crohn's disease, MS, and psoriasis have symptoms that are "about as different as you can get," but these conditions share a pathway involving helper T cells. Other autoimmune conditions might converge on a different protein network, says Hafler. "If you look at a certain pathway, certain diseases share that pathway, and others do not."

The new findings, Hafler says, are examples of the "brave new world" of autoimmune disease research in the post-genomic era, a world in which we will find treatments for these diseases by seeing them in completely new ways. ■

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