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Scientists unmask genetic markers associated with psoriasis

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Scientists at the University of Michigan Department of Dermatology, the U-M School of Public Health and their collaborators have found DNA "hotspots" that may reveal how genetic differences among individuals result in psoriasis, an autoimmune disease of the skin. Published in *Nature Genetics*, the findings could lead to new drug targets and tailored treatments for the disease.

"This discovery highlights the role of several genes in mediating the immune responses that result in psoriasis," says Goncalo Abecasis, Ph.D., co-principal investigator on the project, and associate professor of biostatistics in the School of Public Health. "Some of the highlighted genes, like those in the IL-23 pathway are already targeted by effective psoriasis therapies. Others, like TNFAIP3 and TNIP1, may become targets for the psoriasis treatments of the future."

Psoriasis affects some 7.5 million people in the United States, causing sore, itchy patches of red, scaly skin. In many cases psoriasis is not only disfiguring; between 10 and 30 percent of patients develop psoriatic arthritis, a painful inflammation of the joints. Current treatments, including different types of immunosuppressive agents, aren't always effective, and they can cause serious side effects.

Psoriasis has a strong genetic component; a child with two affected parents has a 50 percent chance of developing it; siblings have a three- to six-fold risk. But the genes responsible for psoriasis haven't yet been completely understood.

In this large, multi-center study, researchers used cutting-edge genomic technology to identify subtle genetic signals influencing the risk of psoriasis. They scanned millions of DNA variations in the genome to find those that occur significantly more often in psoriasis patients than unaffected people.

The study was led by James Elder, M.D., Ph.D., a professor in the Department of Dermatology, and Abecasis. Among the first authors were Rajan Nair, Ph.D., assistant research professor of dermatology, and Jun Ding of the Biostatistics Department in the School of Public Health.

Within the past 18 months, researchers have increased the number of independent genetic "hotspots," or loci, confidently associated with psoriasis from one—HLA-Cw6, previously identified by Elder, et al., in 2006—to 10. Four of these have been identified for the first time by this study, and two more have since been confirmed by these researchers.

Research details

The team looked for single nucleotide polymorphisms (SNPs), or DNA changes, at 438,670 sites in 1,359 psoriasis cases and 1,400 healthy controls. Initial scans signaled differences in at least three previously identified DNA sites, with HLA-Cw6 producing the strongest genetic signal. They then expanded the study to look at 18 of the most interesting loci in an additional 5,048 cases and 5,051 controls.

In all, seven of the 18 loci showed consistently strong association with psoriasis. As a result, four proteins produced from the altered DNA code now can be targeted for further study.

This study is the first to identify changes in the IL23A gene in psoriasis patients. Notably, two of the previously identified psoriasis genes (IL12B and IL23R) encode proteins that bind to IL23A protein.

Variations in the structure any of these three genes may predispose people to chronic immune responses that ultimately result in psoriasis.

The team also found that genetic signals for proteins activated by TNF-□, a key signaling molecule involved in inflammation, are distinct from the patterns in healthy controls. Two genes activated by TNF-□—TNFAIP3 and TNIP1—show strong association with psoriasis. Together, these genes limit immune responses. Genetic alterations in this "brake" may allow the immune system to work overtime within the skin. Variants of TNFAIP3 also have been associated with rheumatoid arthritis and lupus, two other autoimmune conditions.

The fourth novel hotspot implicates two "next-door neighbor" genes, IL4 and IL13. These genes support development of Th2 cells, a type of immune system T cell. Any condition that leads to too few or too many Th2 cells in relation to other types of T cells may result in disease, including psoriasis.

This new research, together with recent immunology work by Elder and colleagues, links four psoriasis loci (IL12B, IL23A, IL23R and IL4/IL13) together in a common functional pathway.

Implications

The large library of genetic data increases the number of proteins and pathways that can be targeted by emerging therapies to fight psoriasis.

Once the full catalog of psoriasis genes has been identified, it may be possible to generate a "psoriasis gene profile" that can accurately predict one's risk of developing the disease. Such work may one day help assess risk of heart attack and stroke, since psoriasis carries an increased risk of coronary artery disease, and TNFAIP3 has also been shown to influence risk of coronary artery disease in mice.

The number of disease genes that can be identified more than triples if the study size can be increased two to three fold. "We invite participation of psoriasis patients from across the country," says Elder.

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