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U-M scientists identify major psoriasis susceptibility gene

Found with genes that control human immune response, discovery could lead to safer and more effective psoriasis treatments

ANN ARBOR, MI – University of Michigan scientists have found a common genetic variation in an immune system gene that makes people much more likely to develop [psoriasis](#) – a disfiguring inflammatory skin disease.



Named *PSORS1* (SORE-ESS-1), for psoriasis susceptibility 1, the gene is the first genetic determinant of psoriasis to be definitively identified in a large clinical study. Its discovery could lead to new, more effective treatments for psoriasis without the risks and side-effects of current therapies.

The gene's causative role in psoriasis was demonstrated in a [University of Michigan Medical School](#) study of 2,723 people from 678 families in which at least one family member had the disease.

Results of the [U-M study](#) – the most comprehensive analysis of a psoriasis gene to date – will be published in the May 2006 issue of the [American Journal of Human Genetics](#).

Psoriasis is a chronic disease that affects about 2 percent of the U.S. population. People with psoriasis develop thick, flaky white patches on their skin and scalp. The disease is disfiguring and can have a negative effect on quality of life. About 25 percent of people with psoriasis eventually develop psoriatic arthritis, which can be severe.

Unlike diseases caused by a mutation in just one gene, psoriasis is what scientists call a multi-factorial disease. This means that people must inherit several disease-



Typical skin and nail lesions seen in patients with moderate to severe psoriasis. Photo credit: Harrold Carter, U-M Medical School.

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related genes, plus be exposed to one or more environmental triggers, in order to get psoriasis.

“For every individual with psoriasis who carries the *PSORS1* gene, there are 10 other people with the gene who don’t get psoriasis,” says study director James T. Elder, M.D., Ph.D., a professor of dermatology and of radiation oncology in the U-M Medical School and the [Ann Arbor VA Healthcare System](#).

“It’s as if you are pushing a shopping cart down the aisle at the grocery store and putting genes in your cart,” Elder adds. “There are several different brands of each gene on the shelf and one of them is bad for you. If you pull down enough bad ones, then you can get sick.

“But even if you get all the bad genes, you still need a trigger from the environment to develop the disease,” explains Elder. “In psoriasis, strep throat is a very common initial trigger. It activates the immune system to attack the strep bacteria. But once the strep infection is cleared, the immune system starts attacking the patient’s own skin cells.

About half the time, strep-induced psoriasis goes away and never comes back. But for the other 50 percent of young people who get it, psoriasis progresses to become a chronic life-long disease.”

The *PSORS1* gene is actually one of over 20 different varieties (scientists call them alleles) of a gene called *HLA-C*. “In terms of our grocery store analogy, think of *PSORS1* as one of 20 ‘brands’ of *HLA-C* on the shelf,” Elder says.

Located on human chromosome 6, *HLA-C* is one of several genes in the major histocompatibility complex (MHC) that regulate how the immune system fights off infection. MHC genes carry DNA-coded instructions for proteins whose job it is to distinguish between what belongs in the body and what doesn’t.

“There is a great deal of genetic variation in the MHC, because it’s on the front lines of dealing with pathogens and cancer,” Elder explains. “It’s an area where it’s good to be different. If everybody were the same, we’d be like hybrid corn. A plague could come along and wipe us all out.”

Scientists have been searching for genes associated with psoriasis for more than 30 years, but until now studies have been inconclusive, according to Rajan P. Nair, Ph.D., the study’s first author and a U-M assistant research professor in dermatology.

“Researchers have identified 19 candidate loci, or areas on chromosomes, that may be genetically linked to psoriasis,” Nair says. “Many studies confirmed a strong association with the MHC, but no one could determine which gene in the MHC was involved in psoriasis.”

In a previous study, Nair and his U-M colleagues narrowed the search for the *PSORS1* gene down to a 300,000-base-pair segment of chromosome 6 that included *HLA-C* and at least 10 other genes.

To determine which of the 11 genes was linked to psoriasis, U-M scientists used a technique called haplotype mapping. Haplotypes are clusters of alleles that tend to be inherited together as a group, because they are located close to each other on the same chromosome. This means that small individual variations in DNA, which originated in a distant ancestor, are often passed intact from generation to generation. If a haplotype contains genetic changes that make people more

susceptible to a disease, scientists can find it by comparing DNA sequences in haplotypes from people with the disease to those of people who don't have the disease.

U-M researchers first sequenced and compared all DNA within the 300,000 base-pair target segment from 10 MHC chromosomes carried by five people enrolled in the study. Detailed analysis of these 10 DNA sequences revealed differences that were only present on psoriasis chromosomes, but never on normal chromosomes. Further analysis by U-M scientists narrowed the search down to one gene, *HLA-C*, and one specific disease-causing allele, *HLA-Cw6*.

Drugs used to treat psoriasis are also used for other autoimmune diseases, such as lupus and rheumatoid arthritis. These drugs turn off the immune response, which leaves the body vulnerable to infection. Now that U-M scientists have identified *HLA-Cw6* as being the *PSORS1* gene, Elder says scientists can concentrate on finding ways to block its ability to bind to cell surface antigens, which could lead to the development of safer treatments for psoriasis.

"What we're all shooting for is trying to find out which branches of the immune system are triggering psoriasis, so you don't have to shut down the whole immune system – only the parts that are important," Elder says.

While Elder believes that *PSORS1* is the major gene involved in susceptibility to psoriasis, he cautions that it's not the only one. He says much additional research will be required to find the other genes involved and to understand all the secrets of this complex and puzzling disease.

"Access to a large, diverse pool of study subjects is vital to the success of this type of clinical research," Elder says. "We are grateful to the 5,000 people who have participated in our psoriasis study so far. It has been a collaborative effort involving physicians, scientists and patients from dermatology departments at many institutions – including the U-M, the University of Kiel in Germany, Detroit's Henry Ford Hospital, and the Ann Arbor VA Healthcare System."

The study was funded by the National Institute of Arthritis, Musculoskeletal, and Skin Diseases, the Dudley and Dawn Holmes Fund, the National Psoriasis Foundation, and the National Center for Research Resources.

Additional U-M collaborators in the study include Philip E. Stuart, senior research associate; research fellows Ioana Nistor, M.D., Ravi Hiremagalore, M.D., and Nicholas Chia, M.D.; Goncalo R. Abecasis, D. Phil., associate professor of biostatistics and John J. Voorhees, M.D., the Duncan O. and Ella M. Poth Distinguished Professor of Dermatology.

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NOTE: The paper is posted on the journal's preprint Web site at www.journals.uchicago.edu/AJHG/journal/preprints.epi. The site is available to journal subscribers only. If you do not have a subscription, contact Sally Pobjewski to receive a copy of the paper.

Written by Sally Pobjewski



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