Researchers uncover new genetic links to psoriasis

April 4 2008

In the first comprehensive study of the genetic basis of psoriasis, researchers at Washington University School of Medicine in St. Louis have discovered seven new sites of common DNA variation that increase the risk of the troublesome skin condition. They also found that variations in one genetic region link psoriasis and a related joint disorder, psoriatic arthritis, to four autoimmune diseases: type 1 diabetes, Grave's disease, celiac disease and rheumatoid arthritis. The study's results appear April 4 in the open-access journal *PLoS Genetics*.

"Common diseases like psoriasis are incredibly complex at the genetic level," says lead investigator Anne Bowcock, Ph.D., professor of genetics at the School of Medicine. "Our research shows that small but common DNA differences are important in the development of psoriasis. Although each variation makes only a small contribution to the disease, patients usually have a number of different genetic variations that increases their risk of psoriasis and psoriatic arthritis."

The DNA variations uncovered by the researchers point to different biological pathways that underlie psoriasis and may eventually lead to new targeted drugs and treatments that hit specific pathways, Bowcock says.

An estimated 7 million Americans have psoriasis, an autoimmune disease that occurs when the body's immune cells mistakenly attack the skin. The condition is characterized by red, scaly patches that can be itchy, painful or both. Some 10 to 30 percent of patients with psoriasis

develop psoriatic arthritis, a condition that is often excruciatingly painful and debilitating.

The Washington University researchers focused on points of common variation in the genome called single nucleotide polymorphisms, or SNPs. While most of the 3 billion nucleotides that comprise DNA are thought to be identical from one person to the next, some 10 million SNPs build variation into the genome and make each individual unique. Some of these SNPs play a crucial role in a person's predisposition to disease or good health.

Using an approach known as whole genome association, the investigators scanned more than 300,000 SNPs in the genomes of 223 psoriasis patients, including 91 who had psoriatic arthritis. They compared the DNA variations in people with psoriasis to those found in 519 healthy control patients, looking for specific differences that may be linked to the disease. They then replicated their findings in a larger set of patients -- 577 with psoriasis and 576 with psoriatic arthritis -- and more than 1,200 healthy controls.

Bowcock and her team found seven novel DNA variations linked to psoriasis. Four other variations associated with the disease that had been identified previously by other researchers also were confirmed by the current study.

Whole genome association studies have recently been used to identify common genetic variations that increase the risk of diseases such as breast cancer, heart disease and type 2 diabetes. They typically involve more than 1,000 patients with a particular disease to help ensure that the genetic variations identified in the study do not occur by chance. While the current study included fewer patients, nearly half of them had a sibling and, in some cases, a parent with psoriasis, which increases the odds of finding genetic variations that contribute to the disease.

The researchers found the strongest genetic risk for psoriasis lies in a region of the genome that contains the major histocompatibility complex, a collection of genes involved in distinguishing the body's own cells from foreign invaders. "Although this region has been known to play a major role in psoriasis, DNA variations in the MHC alone have been known to not be enough to trigger disease," Bowcock says. "Only 10 percent of patients with variations in the major histocompatibility complex developed psoriasis. This tells us that other genetic or environmental factors also contribute to the disease."

One MHC variation linked to psoriasis and psoriatic arthritis occurs in the gene HCP5, the scientists noted. That variation was recently reported to delay the onset of AIDS in people infected with HIV. This is particularly interesting, Bowcock says, because psoriasis can be triggered by infection with HIV or other viruses. It may be that in people with this SNP variant, viral infection triggers a larger immune response that slows the development of AIDS but also leads to excessive inflammation in the skin and bone joints in genetically susceptible individuals, leading to the onset of psoriasis and psoriatic arthritis.

Notably, DNA variations on chromosome 4 were strongly linked to psoriatic arthritis. These same variations were also associated with psoriasis and had been previously linked to type 1 diabetes, rheumatoid arthritis, Grave's disease (caused by an overproductive thyroid gland) and celiac disease (caused by the inability to digest gluten). "Doctors have noticed that some psoriasis patients have autoimmune diseases such as celiac disease, Grave's disease, and type 1 diabetes," Bowcock says. "But we didn't know whether this was a coincidence. Now we know there is a genetic component underlying all of these diseases."

The same region of chromosome 4 contains genes that code for the signaling molecules IL2 and IL21. This opens the door to investigating whether existing drugs that block either molecule may be effective in

some psoriasis patients, especially those with psoriatic arthritis.

The researchers also uncovered significant DNA variations on chromosome 13 in a genetic region involved in modifying proteins, and on chromosome 15, in a region responsible for producing a protein that activates TNF alpha (tumor necrosis factor-alpha) in a specialized immune cell known as a dendritic cell. While TNF alpha normally helps fight infections, it is thought to be a major player in psoriasis and psoriatic arthritis. Several FDA-approved psoriasis medications work by binding to TNF-alpha, thereby preventing it from communicating with cells.

Bowcock is now involved in a larger genome-wide association study of psoriasis patients and says she expects it will uncover additional genetic variations that are associated with psoriasis.

Eventually, she predicts, such studies will lead to more effective, better-targeted therapies.

"The goal of this study and other genome-association studies is to get to personalized medicine, where you can diagnose a disease and ask what genetic risk factors this person has that points to altered pathways," she says. "Then, we can target those pathways for specific therapeutic interventions."

Source: Washington University