MedicalXpress

Researchers identify genes that increase rheumatoid arthritis risk

October 5 2007

Researchers in the United States and Sweden have identified a genetic region associated with increased risk of rheumatoid arthritis (RA), a chronic and debilitating inflammatory disease of the joints that affects an estimated 2.1 million Americans. The U.S. arm of the study involved a long-time collaboration between intramural researchers of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and other organizations. NIAMS is one of 27 institutes and centers at the National Institutes of Health. The results appeared in the *New England Journal of Medicine*.

Using the relatively new genome-wide association approach — which makes it possible to analyze between 300,000 and 500,000 single nucleotide polymorphisms (SNPs, or small differences in DNA that are distributed throughout a person's genetic code) — researchers in both countries searched for genetic differences in blood samples from people with RA compared to controls. The U.S. group compared 908 samples from patients provided by the North American Rheumatoid Arthritis Consortium (NARAC) — a group of investigators working together to identify the genetic factors that contribute to RA — with those from 1,282 people without RA (controls). The Swedish group compared 676 samples from the Swedish Epidemiological Investigation of Rheumatoid Arthritis (EIRA) with 673 controls.

Both groups' searches led them to a region of chromosome 9 containing two genes relevant to chronic inflammation: TRAF1 (encoding tumor necrosis factor receptor-associated factor 1) and C5 (encoding

complement component 5).

"The whole-genome screening method lets us identify genes that contribute to disease-susceptibility without imposing our preconceived notions of the disease. We expected to come up with something new," says Elaine F. Remmers, Ph.D., of the Genetics and Genomics Branch of the NIAMS Intramural Research Program and an author of the study. "We were thrilled to find out that TRAF1-C5 showed association not only in the samples that we did with NARAC but also independently in the Swedish group. By combining our information, we were able to make a much stronger case [for a TRAF1-C5 association]. The combined evidence was pretty impressive."

Remmers says the TRAF1-C5 region was the third of three major susceptibility chromosomal regions for RA identified by their whole genome screen. The first two, HLA-DRB1 and PTPN22, had already been well established.

She says that it's not yet known how the genes in the TRAF1-C5 region influence RA risk. Nor can scientists say which of the two genes is causing the disease. "Actually, both genes are very interesting candidates," she says. "They both control inflammatory processes that really are relevant for the disease, so we could easily envision either of them playing a role — or both."

The hope is that by learning more about the genes and their role in the disease, scientists may find clues to influencing treatment of the disease. "We are hoping that we will find variants in either of the genes that will lead us to new targets for therapy. Once we understand how the RA-associated variants work, we may be able interfere with the pathways the variants are influencing and either prevent the disease or block its progression."

According to coauthor Daniel Kastner, M.D., Ph.D., NIAMS clinical director and chief of the NIAMS Genetics and Genomics Branch, "The success of the study can be attributed in part to the productive, longstanding collaboration between NIAMS intramural researchers and other scientists that the Institute supports around the country." NARAC was established 10 years ago by coauthor Peter K. Gregersen, M.D., at the Feinstein Institute for Medical Research, the North Shore Long Island Jewish Health System, in order to facilitate the collection and analysis of RA genetic samples. Kastner was also a key early member of the NARAC, as were many other investigators at several academic health centers across the United States.

Source: National Institute of Arthritis and Musculoskeletal and Skin Diseases