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Study identifies genetic risk factor for rheumatoid arthritis, lupus

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A genetic variation has been identified that increases the risk of two chronic, autoimmune inflammatory diseases: rheumatoid arthritis (RA) and systemic lupus erythematosus (lupus). These research findings result from a long-time collaboration between the Intramural Research Program of the National Institute of Arthritis and Musculoskeletal and Skin Diseases and other organizations.

These results appear in the Sept. 6 issue of the *New England Journal of Medicine*. "Although both diseases are believed to have a strong genetic component, identifying the relevant genes has been extremely difficult," says study coauthor Elaine Remmers, Ph.D., of the Genetics and Genomics Branch of the Intramural Research Program at the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

Dr. Remmers and her colleagues tested variants within 13 candidate genes located in a region of chromosome 2, which they had previously linked with RA, for association with disease in large collections of RA and lupus patients and controls. Among the variants were several disease-associated single nucleotide polymorphisms (SNPs) — small differences in DNA sequence that represent the most common genetic variations between individuals — in a large segment of the STAT4 gene. The STAT4 gene encodes a protein that plays an important role in the regulation and activation of certain cells of the immune system.

"It may be too early to predict the impact of identifying the STAT4 gene as a susceptibility locus for rheumatoid arthritis — whether the presence

of the variant and others will serve as a predictor of disease, disease outcome or response to therapy," says coauthor and NARAC principal investigator Peter K. Gregersen, M.D., of The Feinstein Institute for Medical Research, part of the North Shore Long Island Jewish Health System, in Manhasset, N.Y. "It also remains to be found whether the STAT4 pathway plays such a crucial role in RA and lupus that new therapies targeting this pathway would be effective in these and perhaps other autoimmune diseases."

One variant form of the gene was present at a significantly higher frequency in RA patient samples from the North American Rheumatoid Arthritis Consortium (NARAC)[1] as compared with controls. The scientists replicated that result in two independent collections of RA cases and controls.

The researchers also found that the same variant of the STAT4 gene was even more strongly linked with lupus in three independent collections of patients and controls. Frequency data on the genetic profiles of the patients and controls suggest that individuals who carry two copies of the disease-risk variant form of the STAT4 gene have a 60 percent increased risk for RA and more than double the risk for lupus compared with people who carry no copies of the variant form. The research also suggests a shared disease pathway for RA and lupus.

"For this complex disease, rheumatoid arthritis, this is the first instance of a genetic linkage study leading to a chromosomal location, which then, in a genetic association study, identified a disease susceptibility gene," says Dr. Gregersen.

The study's success, according to NIAMS Director Stephen I. Katz, M.D., Ph.D., can be attributed in part to the uncommon and longstanding collaboration between NIAMS intramural researchers and other scientists the Institute supports around the country. "This work required

the collection and genotyping of thousands of RA and lupus cases and controls, a task that would have been difficult to accomplish without the strong partnerships we forged," he says. NARAC was established 10 years ago by Dr. Gregersen, NIAMS Clinical Director and Genetics and Genomics Branch Chief Daniel Kastner, M.D., Ph.D., and investigators at several academic health centers to facilitate the collection and analysis of RA genetic samples.

Adds Dr. Remmers, "Although we do not yet know precisely how the disease-associated variant of the STAT4 gene increases the risk for developing RA or lupus, it is very exciting to know that this gene plays a fundamental role in these important autoimmune diseases."

Source: National Institute of Arthritis and Musculoskeletal and Skin Diseases

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