Genes and smoking play role in rheumatoid arthritis

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Recent genetic studies have revealed several new sites of genes that are risk factors for developing rheumatoid arthritis (RA). The strongest association with anti-citrullinated protein antibody (ACPA)-positive RA (ACPAs are autoantibodies detected in RA that are used as a major diagnostic tool) has been found for the HLA-DRB1 gene, and this site seems to play a central role in susceptibility to the disease in Caucasian populations. Previous studies have shown a high increase in the risk of ACPA-positive RA associated with smoking in those who have certain variations of the HLA-DRB1 gene. There are several types of such alleles related to a particular amino acid sequence known as shared epitope (SE). ACPAs occur in about 60 percent of RA patients and are closely linked to the presence of SE alleles. In fact, SE alleles are the strongest genetic risk factor for ACPA-positive RA.

Of several environmental factors that predispose people toward developing RA, smoking has been found to be the main risk factor and a strong gene-environment interaction between smoking and SE alleles for ACPA-positive patients has been shown in previous studies in Europe. Results in North America have not been as conclusive, however. A new large population-based study examined the gene-environment interaction between smoking and SE alleles in RA and found that all SE alleles strongly interact with smoking in conferring an increased risk of ACPA-positive RA. The study was published in the June issue of *Arthritis & Rheumatism* .

Led by Emeli Lundström of Karolinska Institutet in Stockholm, the

study consisted of genetic analysis of 1,319 RA cases and 943 controls in Sweden and included Caucasian smokers and non-smokers. Researchers set out to determine whether all HLA-DRB1 SE alleles demonstrated a similar gene-environment interaction or if the interaction was restricted to a particular DRB1 SE group. A total of 972 cases and 488 controls were SE positive.

"Our data illustrate that regardless of the fine specificity of the SE alleles of DRB1, the interaction between these genetic risk factors and smoking is evident," the authors state.

Although the molecular mechanisms underlying the risk and interaction of smoking and SE alleles are incompletely understood, there are several possible explanations. One is that long-term exposure to cigarette smoke may accelerate the modification of arginine into citrulline in autoantigens present in the lungs, enhancing an immune response in individuals carrying the SE alleles. Another possibility is that substances present in smoke may trigger the innate immune system to contribute to the development of arthritis. It may also be that an as yet undetermined genetic factor (factors) plays a role or that there is a genetic interaction between the HLA-DRB1 gene and the gene involved in the behavior that includes smoking.

The authors conclude that while SE alleles do not seem to confer an increased risk of ACPA-negative RA either on their own or in combination with smoking, all SE DRB1 alleles strongly interact with smoking in the development of ACPA-positive RA.

More information: "Gene-Environment Interaction Between the DRB1 Shared Epitope and Smoking Regarding the Risk of Anti-Citrullinated Protein Antibody-Positive Rheumatoid Arthritis," Emeli Lundström, Henrik Källberg, Lars Alfredsson, Lars Klareskog, Leonid Padyukov, Arthritis & Rheumatism, June 2009.

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