

The HLA-DRB1 gene and premature death in rheumatoid arthritis

January 31 2008

People with rheumatoid arthritis (RA), an inflammatory autoimmune disease, tend to die younger and, largely from cardiovascular disease (CVD). One explanation for this increasingly recognized fact is that inflammation promotes atherosclerosis. A marker of inflammation, elevation of the C-reactive protein (CRP) level has been shown to predict CVD in the general population. However, other highly inflammatory diseases—Crohn's, for example—do not carry the same high risk of premature death from heart disease.

To identify other possible suspects, researchers in the United Kingdom investigated whether genetic variants linked to the likelihood of developing RA might also make patients more likely to die from CVD. Led by Dr. Tracey M. Farragher at the University of Manchester and funded by the Arthritis Research Campaign (arc), the study focused on two genes—HLA-DRB1 and PTPN22—and their interactions with known RA risk factors.

The evidence, presented in the February 2008 issue of *Arthritis & Rheumatism*, implicates HLA-DRB1 genotypes, already associated with RA susceptibility and severity, as a predictor of premature death from CVD for inflammatory arthritis patients. For RA patients in particular, having the shared epitope (SE)—a group of HLA-DRB1 alleles with kindred amino acid traits—plus anti-cyclic citrullinated peptide (anti-CCP) antibodies and current smoking is an especially deadly combination.

The study focused on 1,022 patients with inflammatory polyarthritis (IP) recruited from a primary-care-based register of adults. The subjects were all white and nearly 65 percent female, with a mean age of 54 at the onset of symptoms. Starting anywhere between 1989 and 1994, data on file for each participant included the results of blood tests for rheumatoid factor (RF), elevation of the C-reactive protein (CRP), and anti-CCP antibodies; evaluations of joint pain and functional disability; smoking habits; and, when applicable, the cause and date of death. DNA samples were also available. 751 of the total patients met the American College of Rheumatology criteria for RA.

HLA-DRB1 and PTPN22 genotyping was performed on every patient's DNA. Using Cox proportional hazards regression models, researchers assessed the association of each gene family with the risk of death from all causes and from cardiovascular disease. They also examined the interactions between SE presence, anti-CCP status, and smoking history, adjusted by patient sex and age at symptom onset.

In the years between the register's inception and the study's completion, 242 (24 percent) of the patients died. CVD was named as the cause of death for 76 (31.4 percent) of the deceased. Based on the researchers' analyses, having two copies of the SE alleles increased the risk of death from all causes and from CVD. For individuals with the HLA-DRB1 combination, the risk of death from CVD was increased more than 3-fold.

The fatal impact was independent of RF and CRP levels. It was aggravated, however, by the interaction of SE, anti-CCP antibodies, and smoking. Current smokers who carried 2 SE alleles and had anti-CCP antibodies had the highest risk of dying from all causes, as well as a substantially higher risk of dying early from CVD. In calculations focusing on RA patients only, this finding remained consistent. Researchers found no evidence of any association between the PTPN22

gene and the risk of death.

This study is the first to link the HLA-DRB1 genotype with premature death, particularly from cardiovascular disease, for those afflicted with any form of inflammatory arthritis, including RA. As Dr. Farragher stresses, the results “raise the possibility of a targeted strategy to prevent CVD in these patients,” while reinforcing the lethal danger of smoking for anyone with a genetic predisposition for arthritis.

Source: Wiley-Blackwell

Citation: The HLA-DRB1 gene and premature death in rheumatoid arthritis (2008, January 31)
retrieved 5 May 2024 from

<https://medicalxpress.com/news/2008-01-hla-drb1-gene-premature-death-rheumatoid.html>

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