GENETICS

New genetic link to disease severity in RA

Single nucleotide polymorphisms (SNPs) in *CD40* have been identified as the first non-HLA-related genetic risk factor for severity of rheumatoid arthritis (RA), according to the results of a study published in *Arthritis & Rheumatism*.

> "...genetic analyses ... showed a significant link between the *CD40* polymorphism and disease severity..."

"The recent discovery of six new genetic risk factors for developing RA by Raychaudhuri and colleagues, together with the availability of a large database with yearly radiographic data, enabled us to perform an up-to-date study of the relation of the same six SNPs to the rate of joint destruction," says Michael van der Linden, the lead researcher on this paper.

Genotype analysis and yearly radiographs to assess joint damage were performed on patients with RA from the Leiden Early Arthritis Clinic longitudinal cohort ($n = 563$; median follow-up 5 years). A replication study was also performed using radiographic data from anti-citrullinated protein antibody (ACPA)-positive patients who were included in the North American Rheumatoid Arthritis Consortium ($n = 393$). Of the six polymorphisms examined, rs4810485 in the *CD40* locus and rs42041 in the *CDK6* locus were found to be associated with a higher rate of joint destruction in ACPA-positive patients than that seen in patients of other genotypes in the Leiden cohort ($P = 0.003$ and $P = 0.012$, respectively); after correction for multiple testing, only the association with the *CD40* polymorphism was significant. In the replication study, genetic analyses again showed a significant link between the *CD40* polymorphism and disease severity in ACPA-positive patients from the North American cohort ($P = 0.021$).

"The main reason for doing this research was that, although numerous risk factors for developing RA have been identified, our knowledge of risk factors for severity of RA is relatively limited," explains van der Linden. "It will be interesting to further investigate the discrepancy between risk factors for development and disease course of RA, and to try to identify underlying pathophysiological mechanisms. The identification of risk profiles that can be used for disease severity prediction in individual patients might, in the future, lead to personalized medicine for this disease."

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Original article van der Linden, M. P. *et al.* Association of a single-nucleotide polymorphism in *CD40* with the rate of joint destruction in rheumatoid arthritis. *Arthritis Rheum.* **60**, 2242–2247 (2009).