

# Genetic risk factors play role in autoantibody-negative rheumatoid arthritis

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During the past few years, several new genetic risk factors for rheumatoid arthritis (RA) have been identified. The majority of genetic risk factors identified so far have been associated with autoantibody-positive RA, which affects about two-thirds of RA patients, but distinguishing this variant from autoantibody-negative RA, which is less destructive, is considered increasingly important.

A new study led by Diane van der Woude of Leiden University Medical Center in The Netherlands examined 148 twin pairs in which one twin had RA. Participants were tested for antibodies known as anti-citrullinated [protein](#) antibodies (ACPAs), which are used because of their specificity and predictive value and for HLA SE (human leukocyte antigen shared epitope) alleles, the most important genetic risk factor for RA. The study was published in the April issue of [Arthritis & Rheumatism](#).

The findings show that ACPA-positive and ACPA-negative RA are associated with different genetic and environmental risk factors, and may constitute distinct entities with different disease mechanisms. The results also showed that the heritability - the variation in disease susceptibility that can be explained by genetic factors - was about 66 percent for both ACPA-positive and ACPA-negative RA.

The HLA SE alleles contributed 11 percent to the total genetic variance of RA, 18 percent to the genetic variance of ACPA-positive RA, and only about 2 percent to the genetic variance of ACPA-negative RA. In

the past, HLA genes were estimated to contribute 37 percent to the overall inherited risk of RA.

Several new genetic risk factors for RA have recently been identified, but like the HLA SE alleles, they are predominantly associated with ACPA-positive RA. This may be because studies typically include mainly ACPA-positive patients, since most RA patients fall into this group. The authors suggest that new studies that incorporate more ACPA-negative patients will show that these risk factors also predispose individuals to this form of the disease.

The known risk factors for ACPA-negative disease do not confer as high a risk of developing RA as the HLA SE alleles. In light of the finding of the similar heritability of ACPA-positive and ACPA-negative RA, the authors conclude: "This means that genetic predisposition also plays an important role in the pathogenesis of ACPA-negative RA, for which most individual genetic risk factors remain to be identified."

More information: "Quantitative Heritability of Anti-Citrullinated Protein Antibody-Positive and Anti-Citrullinated Protein Antibody-Negative [Rheumatoid Arthritis](#)," Diane van der Woude, Jeanine J. Houwing-Duistermaat, René E.M. Toes, Tom W. J. Huizinga, Wendy Thomson, Jane Worthington, Annette H. M. van der Helm-van Mil, René R. P. de Vries, *Arthritis & Rheumatism*, April 2009.  
[www3.interscience.wiley.com/journal/76509746/home](http://www3.interscience.wiley.com/journal/76509746/home)

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