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## **Genetics, autoantibodies and clinical features in understanding and predicting rheumatoid arthritis**

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## Chapter 13

# **Variation in radiological joint destruction in rheumatoid arthritis differs between monozygotic and dizygotic twins and pairs of unrelated patients**

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Currently, the research on genetic factors associated with rheumatoid arthritis (RA) flourishes and the number of genetic factors found to associate with RA susceptibility has expanded in the latest years. Besides the long-known HLA class II alleles, a R620W SNP in the PTPN22 gene has been identified and replicated in several different populations (1). A number of other SNPs also confer risk to RA; some of them await replication or gave distinct results in different populations (2). The total genetic contribution to RA susceptibility is estimated by comparing monozygotic and dizygotic twins and is reported to account for 50-60% of the population liability to the disease (3). As the HLA-Class II alleles account for about one third of the genetic contribution, it is expected that in the nearby future more genetic factors will be identified. Currently most attention is paid on the role of genetics in RA susceptibility. So far the contribution of genetics to RA severity is not known. The recognition of genetic factors associating with RA severity might be helpful in predicting the disease course and may lead to the identification of pathways involved in joint destruction. To get more insight in the role of genetics in RA severity, the present report investigates the variability in radiological joint destruction between monozygotic and dizygotic twins and random pairs of unrelated RA patients.

This study includes the monozygotic (n=20) and dizygotic (n=8) twins with RA that were enrolled in the North American RA Consortium (NARAC). The unrelated RA patients were included in the Leiden Early Arthritis Cohort (EAC) (4). The median disease duration at the time of the radiograph was 9 years in dizygotic twins and 10 years in monozygotic twins. The monozygotic twins were all rheumatoid factor positive (see Table 1). To match for differences in era of disease onset and autoantibody status, the unrelated RA patients selected from the EAC cohort were rheumatoid factor positive and included in the cohort in the early or mid '90 years. This resulted in 40 persons with available radiographs made after 8 years of disease; these patients were by the computer assigned in 20 random pairs. All subjects were Caucasian and had radiographs of the hands scored according to the Sharp-Van der Heijde method (5) by a rheumatologist that was unaware of the clinical data (intraclass correlation coefficient for repeated readings 0.96, 95% confidence interval 0.83-0.99). To correct for differences in disease duration, for every subject the Sharp score was divided by the disease duration at the time of the radiograph, yielding the estimated radiological progression per year (6). To determine the variation in joint destruction, for every pair of RA patients, the difference in radiological progression per year was calculated. Subsequently, to evaluate the variation in joint destruction in the different groups of patients, the mean difference and variance in radiological progression per year were compared between monozygotic and dizygotic twins and unrelated patients with RA.

Patient characteristics and results on radiological joint destruction scores are presented in Table 1. Both monozygotic and dizygotic twins were significantly younger than the pairs

**Table 1.** Patient characteristics and radiological joint destruction scores of monozygotic and dizygotic twins with RA and pairs of unrelated RA patients

	Monozygotic twin (n=20)	Dizygotic twin (n=8)	Unrelated RA patients random pairs (n=40)
Gender, % female	70	63	65
Age at diagnosis, mean $\pm$ SD	37.1 $\pm$ 11.4	31.5 $\pm$ 17.3	53.8 $\pm$ 12.3#
Disease duration at radiograph, median	10.5	9.0	8.0
Rheumatoid factor positivity, %	100	63	100
Estimated radiological progression per year ¶, mean $\pm$ SEM	2.8 $\pm$ 0.6	1.7 $\pm$ 0.8	3.3 $\pm$ 0.6
Difference in Sharp scores per year within pairs, mean variance	1.7 3.3	2.4 6.1	4.3 * 16.1

#  $p < 0.001$  unrelated RA patients versus monozygotic as well as dizygotic twins

\*  $p = 0.037$  unrelated pairs of RA patients versus monozygotic twins

¶ Sharp score of the hands divided by the disease duration at the time of the radiograph

of unrelated patients ( $p < 0.001$  Mann Whitney test). The mean estimated radiological progression per year was not significantly different among the groups of monozygotic twins, dizygotic twins and unrelated RA patients. However, the variation in joint destruction was the highest within the pairs of unrelated RA patients (mean difference 4.3 Sharp points per year), followed by the dizygotic twins (mean difference 2.4 Sharp points per year) and the smallest difference was observed within the monozygotic twins (1.7 Sharp points per year), with a significant difference between the monozygotic twins and unrelated RA patients ( $p = 0.037$ , Mann Whitney test). The finding of an increasing variation in degree of joint destruction comparing respectively monozygotic twins, dizygotic twins and unrelated pairs of RA patients supports the notion of a role for genetic factors in RA severity.

The current report indicates that genetic factors are associated with the severity of joint destruction during the disease course of RA. This study has some limitations. First, as the number of dizygotic twins was low, the heritability could not be properly calculated. Classic twin studies compare monozygotic and dizygotic twins and are based on the principle that the environmental factors within twin pairs are (mostly) comparable and that the contribution of genetic factors to covariance within dizygotic twins is half that of monozygotic twins. Unrelated patients are not used for quantifying the genetic contribution, as these patients differ in genetic as well as environmental factors. Nevertheless, as RA starts and progresses at adult age, environmental factors are presumably also different within twin pairs. Therefore, comparison of mono- with dizygotic twins as well as twins with unrelated patients may be relevant. The current report added data on unrelated pairs of

RA patients to dizygotic and monozygotic twin data and observed an increase in variation in joint destruction parallel to a decrease in genetic similarity, indicating that genetics factors are important for the severity of joint destruction in RA.

It might be a concern that twins and unrelated RA patients, although both Caucasian, came from different continents. However, comparison of Sharp scores of American and Dutch early RA patients not treated with disease-modifying antirheumatic drugs (DMARDs) revealed similar scores (7,8).

The most important risk factor for RA severity is the autoantibody status. The unrelated RA patients were matched for rheumatoid factor comparable to the monozygotic twins. Matching on anti-CCP status was not possible as anti-CCP antibodies were determined in only a part of the twins. As the presence of autoantibodies associates with the presence of HLA-shared epitope alleles (9), it is likely that by matching for autoantibodies patients were also partly corrected for differences in shared epitope status. This might have underestimated the difference in variation due to genetic factors.

Given the hypothetical effect of the difference in age of onset between the twins and unrelated RA patients on the rate of joint destruction, the Sharp scores of EAC patients <35 and >60 years were compared, showing no significant difference during 4 years follow-up.

The patients included in this study were diagnosed with RA in the '80 years or beginning of the '90 years. We did not provide detailed descriptions of treatment history of all patients and cannot exclude differences in treatment. Nevertheless, in the mentioned time era's therapy with DMARDs was started in a relatively late stage and medications of choice were among others antimalarials, of which is known that their ability to halt disease progression is limited. Therefore, we suspect that considering the relatively mild medications used in the '80 and begin '90, the natural disease course of the patients is only limited affected.

In conclusion, the present study observed after correction for differences in disease duration and autoantibody status an increase in variation of radiological joint destruction comparing respectively monozygotic twins, dizygotic twins and unrelated pairs of RA patients. This indicates to an important contribution of genetic factors to radiological joint damage in RA. More extensive twin studies are needed to quantify the genetic contribution to disease severity.

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