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The *PTPN22* susceptibility risk variant is not associated with the rate of joint destruction in anti-citrullinated protein antibody-positive rheumatoid arthritis

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A missense single-nucleotide polymorphism in the protein tyrosine phosphatase non-receptor 22 (*PTPN22*) gene, which encodes a negative regulator of T-cell activation, is an important genetic risk factor for rheumatoid arthritis (RA) susceptibility.¹ The association of the *PTPN22* susceptibility risk allele and the severity of joint destruction is unclear as a result of contradictory observations.^{2–6} To determine an individual patient's rate of joint destruction accurately, it is required that radiological measurements are collected by means of standard procedures, scored quantitatively and sensitively and are repeated in time. Consequently, differences in used measurements and analysis methods may contribute to the occurrence of contrasting findings. Second, although the effect of *PTPN22* on RA susceptibility is confined to the anti-citrullinated protein antibody (ACPA)-positive group,²⁶ most studies on *PTPN22* and joint destruction did not analyse the ACPA-positive subset.^{2–5} The present study studied the effect of the *PTPN22* susceptibility risk variant on the rate of joint destruction in two large cohorts of ACPA-positive RA patients, using sensitive methods for measurement and analysis.

The first cohort consisted of 593 RA patients from the Leiden Early Arthritis Clinic,⁷ of whom 55% were ACPA-positive. Radiographs were made at baseline and on consecutive years. The radiographs were scored by one experienced scorer. The intraclass observer correlation coefficient was 0.91. The progression in Sharp van der Heijde score (SHS) during 6 years of follow-up was compared between RA patients with and without the risk variant (T allele) of rs6679677, a perfect proxy for rs2476601/C1858T ($r^2=1$), using a repeated measurement analysis. Such analysis takes advantage of the longitudinal, repetitive character of the data and does not exclude patients with incomplete follow-up data, avoiding selection bias. In a linear mixed model with radiological score as response variable, the effect of time was assumed to be linear in the interaction terms. *PTPN22* and its interaction

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with time were entered in the model, to test whether *PTPN22* T/non-T carriers had different radiological scores over time. Age, gender and inclusion period (a proxy for treatment strategy) were entered in the model to correct for possible confounding effects.⁸

The replication cohort consisted of 397 ACPA-positive RA patients from the North American Rheumatoid Arthritis Consortium with cross-sectional radiological measurements (SHS) and genotypic data of rs2476601. Estimated radiological progression rates per year were compared using the Mann–Whitney test. In this cohort, no corrections were made for age, gender or treatment.

In the first cohort, 69.0% of RA patients were women and the mean age was 56.4 ± 15.8 years. The genotype frequencies (GG/GT/TT) were 462/120/11 (77.9%/20.2%/1.9%). The presence of the T allele (TT+TG genotype) was not associated with a higher rate of radiological joint destruction compared with the absence of this allele (GG genotype) ($p=0.10$ and $p=0.93$, respectively, in ACPA-positive and in all RA patients) (figure 1). In the second cohort, 72.8% of the patients were women and the mean age was 40.8 ± 12.0 years. The genotype frequencies (CC/CT/TT) were 282/105/10 (71%/26%/3%). Again, no significant difference in estimated radiological progression per year was found (median 2.11 Sharp units per year in the CC group vs 2.4 Sharp units per year in the TT+TC group, $p=0.22$). The exclusion of 10 genetic outliers did not change these results.

Using the present Early Arthritis Clinic data, this study had a power of 0.986 to detect a difference of 2.14 SHS scores with a SD of 4.07 (difference in increase in SHS over 6 years) and an α of 0.05; indicating that this study was sufficiently powered to prevent false-negative findings.

In conclusion, this study shows that *PTPN22*, although it predisposes to ACPA-positive RA, is not associated with RA severity measured by the radiological rate of joint destruction, proving a further indication that the contribution of *PTPN22* to RA is primarily found in setting the balance involved in the emergence of ACPA.

A total of 315 ACPA-positive patients had radiographs available. The number of radiographs declined from 303 to 267, 251, 212, 185, 169 and 139, respectively, from baseline to the 6-year follow-up. The available radiographs of the total RA population were in total 593, this declined to 577, 488, 442, 365, 309, 263 and 212, respectively, from baseline to the 6-year follow-up.

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Figure 1. Median Sharp van der Heijde score (SHS) during 6 years of follow-up for patients with and without the T allele of protein tyrosine phosphatase non-receptor 22 (PTPN22) (A) in anti-citrullinated protein antibody-positive rheumatoid arthritis (RA); (B) as well as all RA in the Early Arthritis Clinic.