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 (SNP) in the protein tyrosine phosphatase non-receptor 22 (PTPN22) gene, that encodes a negative regulator of T-cell activation, is an important genetic risk factor for rheumatoid arthritis (RA) susceptibility. The association of PTPN22 susceptibility risk allele and severity of joint destruction is unclear due to contradictory observations. To determine an individual patient’s rate of joint destruction accurately, it is required that radiological measurements are collected via standard procedures, scored quantitatively and sensitively and are repeated in time. Consequently, differences in used measurement and analysis methods may contribute to the occurrence of contrasting findings. Second, although the effect of PTPN22 on RA susceptibility is confined to the ACPA-positive group, most studies on PTPN22 and joint destruction did not analyze the ACPA+ subset. The present study studied the effect of the PTPN22 susceptibility risk variant on the rate of joint destruction in two large cohorts of ACPA+ patients, using sensitive methods for measurement and analysis.

The first cohort consisted of 593 RA patients from the Leiden Early Arthritis Clinic (EAC), 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 (r²=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 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.

The replication cohort consisted of 397 ACPA+ patients North American Rheumatoid Arthritis Consortium (NARAC) 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 patients were female 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 to the absence of this allele (GG-genotype) (p=0.10 and p=0.93 respectively in ACPA-positive and in all patients) (Figure 1). In the second cohort, 72.8% of the patients were female 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 radiologic progression per year was found (median 2.11 Sharp units per year in the CC group versus 2.4 Sharp units per year in the TT+TC-group, p=0.22). Exclusion of ten genetic outliers did not change these results.
Using the present EAC data, this study had a power of 0.986 to detect a difference of 2.14 SH-scores with a SD of 4.07 (difference in increase in SHS over 6-years) and an alpha of 0.05; indicating 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.

![Figure 1](image-url)

**Figure 1.** Median Sharp van der Heijde scores during 6 years of follow-up for patients with and without the T-allele of PTPN22 in ACPA+ RA (A) as well as all RA (B) in the EAC. Three hundred fifteen 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 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 till 6 year follow-up.
REFERENCES


