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**Title:** Genes and environmental factors associated with the severity of progression of rheumatoid arthritis  
**Issue Date:** 2014-01-23
Chapter 7

Studying associations between variants in TRAF1-C5 and TNFAIP3-OLIG3 and the progression of joint destruction in rheumatoid arthritis in multiple cohorts

LETTER TO THE EDITOR


The severity of joint destruction in Rheumatoid Arthritis (RA) is highly variable between patients. Recent twin and population studies indicated that the severity of joint destruction is influenced by genetic factors.\textsuperscript{1,2} Previously we reported associations of rs10818488 (\textit{TRAF1-C5}) and rs675520 (\textit{TNFAIP3-OLIG3}) with progression of joint destruction.\textsuperscript{3,4} The genes near these loci encode for tumor necrosis factor receptor-associated factor-1 (\textit{TRAF1}), complement component-5 (\textit{C5}) and tumor necroses factor alpha-induced protein-3 (\textit{TNFAIP3}); a protein that inhibits NF-kappa B-activation. A basic principle in genetic association studies is to evaluate multiple cohorts to validate observed findings. We therefore studied both SNPs in several RA-cohorts with radiological follow-up data.

6,282 X-rays of 2,666 RA-patients were studied: 147 patients from Lund (Sweden), 385 patients from Sheffield (UK), 285 patients from Iceland, 384 patients from the North American Rheumatoid Arthritis Consortium (NARAC), 756 patients from the National Databank of Rheumatic Diseases (NDB), 113 patients from Wichita and 596 patients from the Leiden-EAC (Table 1). Detailed information on these datasets is provided elsewhere.\textsuperscript{2,5-10} Genotyping of Lund and Sheffield DNA was performed using Sequenom analysis, genotyping results of the Icelandic and NARAC patients were retrieved from genome-wide-association studies\textsuperscript{2,7} and those of the Wichita and Leiden cohorts were done with the Illumina Immunochip.\textsuperscript{11} Radiographs were scored according to the Sharp-van der Heijde method (Iceland, Wichita, NDB, Leiden-EAC) or Larsen method (Lund, Sheffield). Per dataset the relative increase in progression rate per year of follow-up in comparison to the reference genotype was estimated, using multivariate normal regression (cohorts with repeated radiological measures – Leiden-EAC, Lund, Groningen and Wichita) or linear regression (datasets with single measurements per patient – Sheffield, NARAC, NDB and Iceland), adjusting for age and gender. The RA-patients studied were treated in era when treatment strategies were not as intensive as nowadays. In the Groningen and

<table>
<thead>
<tr>
<th>Cohort</th>
<th>N patients</th>
<th>Total no. of X-ray sets</th>
<th>Year of diagnosis</th>
<th>Year of X-ray</th>
<th>Anti-CCP+ n (%)</th>
<th>Tested SNP Traf1-C5 (r\textsuperscript{2*})</th>
<th>Tested SNP TNFAIP3-OLIG3 (r\textsuperscript{2*})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lund</td>
<td>147</td>
<td>781</td>
<td>1985-1990</td>
<td>1985-1995</td>
<td>114 (78)</td>
<td>rs10818488</td>
<td>rs525977 (1)</td>
</tr>
<tr>
<td>Sheffield</td>
<td>385</td>
<td>385</td>
<td>1938-2003</td>
<td>1999-2006</td>
<td>302 (79)</td>
<td>rs10818488</td>
<td>rs525997</td>
</tr>
<tr>
<td>Iceland</td>
<td>285</td>
<td>285</td>
<td>1942-2008</td>
<td>1989-2010</td>
<td>148 (52)</td>
<td>rs3761847 (0.97)</td>
<td>rs525997</td>
</tr>
<tr>
<td>NARAC</td>
<td>384</td>
<td>384</td>
<td>1953-2002</td>
<td>1985-2002</td>
<td>385 (100)</td>
<td>rs3761847</td>
<td>rs666619 (1)</td>
</tr>
<tr>
<td>Wichita</td>
<td>113</td>
<td>555</td>
<td>1963-1999</td>
<td>1976-2006</td>
<td>110 (97)</td>
<td>rs10818488</td>
<td>rs525977</td>
</tr>
<tr>
<td>NBD</td>
<td>756</td>
<td>756</td>
<td>1980-1999</td>
<td>1989-2006</td>
<td>490 (72)</td>
<td>rs10818488</td>
<td>rs525977</td>
</tr>
<tr>
<td>Leiden-EAC</td>
<td>596</td>
<td>3,136</td>
<td>1993-2006</td>
<td>1993-2006</td>
<td>302 (51)</td>
<td>rs10818488</td>
<td>rs525977</td>
</tr>
</tbody>
</table>

Total 2666 6282

\* r\textsuperscript{2} = correlation of the tested SNP with the originally published SNP: for \textit{Traf1-C5} rs10818488 and for \textit{TNFAIP3-OLIG3} rs675520
Leiden-cohorts adjustment for treatment strategies were applied\textsuperscript{12}; in the other datasets no treatment effects on the radiological progression rates were observed.

Considering the number of patients and X-rays studied, it was not expected to obtain statistical significance in individual datasets. Therefore the estimates of the individual datasets, reflecting the relative increase in rate of joint destruction per year, were summarized in a meta-analysis with inverse variance weighting. Rs10818488 was previously associated with joint destruction in a dominant analysis performed on all RA-patients and rs675520 in a recessive analysis on anti-CCP-positive RA-patients. In line with this, analyses were primarily performed using a dominant model on all patients (rs10818488) and recessive model on anti-CCP positive patients (rs675520). SPSS version 17.0 and Stata version 10.1 were used.

Figure 1 summarizes the results. The effect estimates of rs10818488 were not consistent in their direction. Statistical significance was not obtained in the meta-analysis. Analysing the subgroup of anti-CCP-positive patients did also not result in significant findings (data not shown). Similarly, rs675520 was not associated with progression in joint destruction in anti-CCP-positive RA (figure 1) or in all patients (data not shown).

In the Leiden-cohort, rs10818488 was previously found associated with joint destruction over the first 2-years in 278 RA-patients and rs675520 on 181 anti-CCP-positive patients with progression over 5 years. Extending the Leiden dataset to 596 RA-patients and yearly follow-up over 7 years resulted in a different finding for rs10818488 but not for rs675520 (Figure 1).\textsuperscript{3,4} Rs2900180 in TRAF1/C5 is observed to associate with erosiveness in a UK study, this variant is in low LD (R\textsuperscript{2}=0.67) with rs10818488.\textsuperscript{13}
A drawback of the current study is that the studied datasets differed in designs; this heterogeneity may affect findings. Nonetheless, the present data do not support the initial findings that rs10818488 and rs675520 are associated with the severity of joint destruction in RA.

ACKNOWLEDGEMENTS

The authors acknowledge deCODE Genetics for providing the genetic and genealogic data. Specifically we want to thank Ari Kárason and Stacy Steinberg for their assistance in the logistics.

The work of R. Knevel is supported by the Dutch Arthritis Association. The work of AHM van der Helm-van Mil is supported by The Netherlands Organization for Health Research and Development. The research has been funded by The European Community Seventh Framework Program FP7 Health-F2-2008-223404 (Masterswitch)
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