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Association of IL2RA and IL2RB with rheumatoid arthritis: a replication study in a Dutch population


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INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease with a worldwide prevalence of approximately 1%. The aetiology of RA is largely unknown, but it is thought that both genetic and environmental factors play a role in the pathogenesis of the disease. Genome-wide association studies (GWAS) and candidate gene approaches have led to the association of a number of genetic susceptibility loci\(^1-7\). The Wellcome Trust case-control consortium (WTCCC), the first GWAS in RA, identified a number of loci reaching genome-wide significance including the HLA region and the PTPN22 gene\(^5\). To identify new genetic risk factors, Thomson et al investigated whether tier 2 single nucleotide polymorphisms (SNPs) \((p = 1 \times 10^{-5} \text{ to } 1 \times 10^{-7})\) in the WTCCC-GWAS showed an association with RA in an independent validation study of 5063 patients and 3849 healthy controls\(^8\). Of the nine loci investigated, a significant association was identified with rs6920220 in the TNFAIP3-OLIG3 region (odds ratio \((\text{OR}) 1.23, 95\% \text{ confidence interval (CI) 1.15 to 1.33, } p=1.1\times10^{-8})\). The association of RA with this region was independently identified by Plenge and co-workers\(^2\), and a recent meta-analysis of GWAS data from three independent case-control populations of European descent confirmed these results\(^3\).

To further investigate these tier 2 SNPs, the control group of the validation study was enlarged from 3849 to 11 487 individuals by including non-RA disease groups consisting of bipolar disorder, type 2 diabetes, hypertension and coronary artery disease\(^9\). In addition to an association with rs6920220, other statistically significant SNPs surfaced, located in MMEL1, IL2RA and IL2RB. Furthermore, investigation of 49 tier 3 loci \((p = 1 \times 10^{-4} \text{ to } 1 \times 10^{-5})\) from the original WTCCC-GWAS identified significant RA-associated SNPs located in PRKCQ and KIF5A.\(^8\) Three of these regions, encoding MMEL1, KIF5A and PRKCQ, were also identified in a large independent study of RA samples of European descent\(^1\), suggesting that these regions harbour true RA susceptibility loci.

In the present study we addressed the contribution of the two interleukin 2 (IL2) pathway SNPs - specifically, rs743777 located in IL2RB and rs2104286 in IL2RA - to the risk of RA in an independent Dutch case-control study. This is of relevance not only because additional replication would strengthen the putative contribution of IL2 receptor-positive cells to RA, but also because only a trend towards association for the IL2RA SNP was observed after correction for multiple testing using the Bonferroni method \((p<0.005)\).

METHODS

A total of 616 Dutch patients and 545 healthy ethnically- and geographically-matched controls were genotyped by allele-specific kinetic PCR as previously described.\(^10\)
RESULTS

In this study a significant association with RA was observed for both rs743777 and rs2104286 (OR 1.26, 95% CI 1.06 to 1.50, \(p = 0.009\) and OR 0.81, 95% CI 0.67 to 0.98, \(p = 0.026\) respectively; table 1). Combining the data from our study with the UK data strengthened the evidence for an association (rs743444: OR 1.12, 95% CI 1.06 to 1.18, \(p = 8.6 \times 10^{-6}\); rs2104286: OR 0.92, 95% CI 0.87 to 0.97, \(p = 1.2 \times 10^{-3}\); table 1). To bypass the phenomenon of the “winner’s curse”, in which effect sizes are often overestimated in the original study,\(^{13}\) we opted to analyse the data without the original WTCCC data to provide an estimate of the most likely effect size.

Table 1. Analysis of rs743777 and rs2104286 with rheumatoid arthritis (RA) in two populations of northern European descent

<table>
<thead>
<tr>
<th>Allele</th>
<th>Cases (MAF)</th>
<th>Controls (MAF)</th>
<th>OR (95% CI)</th>
<th>(p) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs743777</td>
<td>This study</td>
<td>616 (0.12)</td>
<td>288 (0.47)</td>
<td>544 (0.41)</td>
</tr>
<tr>
<td></td>
<td>Validation study UK</td>
<td>4680 (0.11)</td>
<td>2031 (0.43)</td>
<td>11200 (0.45)</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>1.12 (1.06 to 1.18)</td>
<td>8.6 \times 10^{-6}</td>
<td></td>
</tr>
<tr>
<td>rs2104286</td>
<td>This study</td>
<td>616 (0.06)</td>
<td>226 (0.37)</td>
<td>545 (0.57)</td>
</tr>
<tr>
<td></td>
<td>Validation study UK</td>
<td>4660 (0.07)</td>
<td>1740 (0.37)</td>
<td>11260 (0.56)</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>0.92 (0.87 to 0.97)</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

Allele frequency data of RA cases versus controls was compared using a fixed effects (Mantel-Haenszel) meta-analysis. No significant heterogeneity or deviation from Hardy-Weinberg (HW) equilibrium was observed among the studies.

CONCLUSION

In conclusion, this study provides additional evidence for the association of IL2RB and IL2RA with RA by independent replication in a Dutch population, underlining the importance of the IL2 pathway in RA. Recently, the IL2RA region was also found to be associated with other autoimmune diseases\(^{11,12}\) - specifically, multiple sclerosis and type 1 diabetes - which suggests a possible common functional pathway.
REFERENCES

5. The Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 2007;447:661-78.
Replication study of IL2RA and IL2RB