Genetic studies in rheumatoid arthritis

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Chapter 16

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

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Rheumatoid arthritis is an autoimmune-disease with a prevalence of ~1% world wide. The etiology of RA is largely unknown; however it is thought that both genetic as well as environmental factors play a role in the pathogenesis of the disease. Genome wide association studies (GWAS) as well as 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) ($P=1x10^{-5}$-$1x10^{-7}$) in the WTCCC-GWAS showed association with RA in an independent validation study of 5063 patients and 3849 healthy controls(8). Of the nine loci investigated, significant association with rs6920220 in the *TNFAIP3-OLIG3* region was identified (OR 1.23, 95%CI-1.15-1.33, $P=1.1x10^{-8}$). Association of RA with this region was independently identified by Plenge and coworkers (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 11487 individuals by including non-RA disease groups consisting of bipolar disorder, Type 2 Diabetes, hypertension and coronary artery disease(9). In addition to association with rs6920220, other statistically significant SNPs surfaced, located in *MMEL1*, *IL2RA* and *IL2RB*. Furthermore, investigation of forty-nine tier 3 loci ($P=1x10^{-4}$-$1x10^{-5}$) 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 (3), suggesting that these regions harbor true RA susceptibility loci.

In the present study we addressed the contribution of the two IL-2-pathway SNPs, specifically rs743777 located in *IL2RB* and rs2104286 in *IL2RA,* to RA risk in an independent Dutch case-control study. This is of relevance, not only because additional replication would strengthen the putative contribution of IL-2-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 ($P<0.0056$). 616 Dutch patients and 545 healthy, ethnically and geographically matched controls were genotyped by allele specific kinetic PCR as previously described(10). In this study, significant association with RA for both rs743777 and rs2104286 was observed (OR 1.26, 95%CI 1.06-1.50, P=0.009; OR 0.81, 95%CI 0.67-0.98, P=0.026 respectively) (Table1). Combining the data from our study with the UK data strengthened the evidence for association (rs743444: OR 1.12, 95%CI 1.06-1.18, $P=8.6x10^{-6}$; rs2104286: OR 0.92, 95%CI 0.87-0.97, $P=1.2x10^{-3}$) (Table1). To bypass the phenomenon of the 'winners curse', in which effect sizes are often overestimated in the original study(13), we opted to analyze the data without the original WTCCC data to provide an estimate of the most likely effect size. 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 IL-2 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.

		cases					controls						
	N	11	12	22	MAF	N	11	12	22	MAF	OR(95%CI)	P-value	HW-con
IL2RB *rs743777*													
This study	616	76(0.12)	288(0.47)	252(0.41)	0.36	544	58(0.11)	217(0.40)	269(0.49)	0.31	1.26(1.06-1.50)	0.009	0.37
Validation study UK	4660	532(0.11)	2031(0.43)	2117(0.45)	0.33	11200	1040(0.09)	4832(0.43)	5328(0.48)	0.31	1.11(1.05-1.17)	0.0001	0.50
Combined											**1.12(1.06-1.18)**	**8.6*10-6**	
IL2RA *rs2104286*													
This study	616	36(0.06)	226(0.37)	354(0.57)	0.24	545	54(0.10)	200(0.37)	291(0.53)	0.29	0.81(0.67-0.98)	0.026	0.10
Validation study UK	4660	312(0.07)	1740(0.37)	2608(0.56)	0.24	11260	790(0.07)	4464(0.40)	6006(0.53)	0.28	0.93(0.88-0.98)	0.007	0.59
Combined											**0.92(0.87-0.97)**	**0.0012**	

Table 1. Analysis of rs743777 and rs2104286 with RA in two populations of northern-European descent. 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.

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