Confirmation of association of the REL locus with rheumatoid arthritis susceptibility in the UK population

Genome-wide association studies (GWAS) have contributed to the identification of at least 14 rheumatoid arthritis (RA) susceptibility loci. One of the first RA GWAS included 1522 cases and 1850 controls from the USA/Sweden and identified TRAF1/C5 as a novel RA locus. This GWAS was recently repeated after including an additional 1550 cases and 3310 controls from the USA and restricting analysis to US subjects. In the expanded sample, two novel single nucleotide polymorphisms (SNP) mapping to the REL locus showed association with RA. REL encodes c-Rel, a member of the nuclear factor kappa B family of transcription factors and one of the associated SNP (rs13031237) maps to an intron of this gene. The association was validated in an independent sample of 2604 RA cases and 2882 controls from the USA/Canada, with strong evidence for association in the combined samples (rs13031237, p=3.1×10^{-14}). We aimed to test the association of the same variants with RA in a large UK case-control sample.

White patients with RA were recruited from six centres across the UK, with ethical committee approval (MREC 99/8/84) and after providing informed consent. Genotyping was performed using Sequenom, and only samples and SNP exceeding 90% success rate were included in the subsequent analysis. Genotype frequencies were compared between cases and controls using the trend test implemented in PLINK. DNA samples from 3962 RA cases and 3531 controls were available for testing, and the clinical characteristics have been described previously. The two SNP, rs13031237 and rs13017599, strongly associated with RA in the previous US/Canadian study were genotyped in the UK samples and both SNP showed strong evidence for association, with no deviation from Hardy-Weinberg expectations (table 1). In the previous study, the subjects investigated were overwhelmingly positive for autoantibodies. Anti-CCP− (n=433) vs controls (n=2758)

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Table 1 Genotype counts and frequencies for SNP mapping to chromosome 2p in UK RA cases and controls and association of SNP in subgroups stratified by autoantibody status

The two SNP, rs13031237 and rs13017599, strongly associated with RA in the previous US/Canadian study were genotyped in the UK samples and both SNP showed strong evidence for association, with no deviation from Hardy-Weinberg expectations (table 1). In the previous study, the subjects investigated were overwhelmingly positive for autoantibodies. Anti-CCP− (n=433) vs controls (n=2758)

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1, major allele; 2, minor allele; Anti-CCP+, anti-cyclic citrullinated peptide antibody positive; Anti-CCP−, anti-cyclic citrullinated peptide antibody negative; Auto-antibody +, positive for either rheumatoid factor or anti-cyclic citrullinated peptide antibodies; OR, odds ratio; RA, rheumatoid arthritis; RF+, rheumatoid factor positive; RF−, rheumatoid factor negative; SNP, single nucleotide polymorphism.

Interestingly, many of the RA loci identified, like the one confirmed here, show stronger effects in autoantibody-positive subgroups, suggesting that autoantibody positive RA may have different underlying pathogenic mechanisms underpinned by genes within the linkage disequilibrium block defined by SNP with r²>0.5 with either of the SNP tested.

Figure 1 Meta-analysis of current UK data with previous data. US and US/Canadian allele counts from Gregersen et al. Combined p value=1.53×10^{-17}. OR, odds ratio.
different genetic loci compared with autoantibody-negative disease. However, it should be noted that the number of autoantibody-negative samples included in studies is often quite small.

In summary, we provide confirmatory support for the association of the REL locus with RA. Fine mapping and functional studies will be required to identify the causal variant(s) and inform our understanding of how these variants influence the pathogenesis of RA.

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REFERENCES
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