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Association analysis of the interleukin 17 genes IL17A and IL17F as potential osteoarthritis susceptibility loci

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Primary osteoarthritis (OA) has a major genetic component that is transmitted in a complex, non-mendelian manner. We previously conducted a genome-wide linkage scan on OA affected sibling-pair families and identified several genomic regions potentially harbouring OA risk loci. The strongest evidence was obtained on chromosome 6p12.3–q13, with a multipoint logarithm of the odds score of 4.0.¹ This linkage was restricted to the 146 families in our cohort that contained female sibling-pairs concordant for hip OA. A subsequent high density micro-satellite linkage scan of the interval provided further strong evidence for linkage as well as evidence of association with several markers, including D6S1956.² This marker is located less than 200 kb distal of the interleukin 17 (IL17) genes, IL17A and IL17F.

IL17 was originally identified as a product of CD4+ memory T cells, with subsequent studies demonstrating secretion by CD8+ cells.^{3–4} IL17 is an inducer of several cytokines, including tumour necrosis factor α , IL1, IL6, and RANKL. A number of investigations have demonstrated a role for IL17 in the aetiology and progression of rheumatoid arthritis; the cytokine is expressed by rheumatoid synovium and can induce inflammation and osteoclastic bone resorption.^{5–6} Other studies have shown a widespread pattern of tissue expression of IL17 and its receptors, including expression in articular cartilage.^{3–4} The ability of IL17 to induce catabolic cytokines, nitric oxide, and collagenases in cartilage and in chondrocytes has also been demonstrated, implying a role in cartilage biology.^{7–10}

These biological data, along with our previous genetic results, prompted us to consider IL17A and IL17F as candidates for the strong OA susceptibility that we had mapped to chromosome 6. To maximise our chances of detecting a genetic association we focused on the probands from the 146 female-hip OA families that had provided us with the original linkage. These probands were ascertained through signs and symptoms of OA to have sufficiently severe disease to require hip joint replacement surgery. The radiological stage of the disease was a Kellgren and Lawrence grade of 2 or more. Inflammatory arthritis was excluded as was post-traumatic arthritis, post-septic arthritis, skeletal dysplasia, and developmental dysplasia. Our controls comprised 215 women with no signs or symptoms of arthritis or joint disease. All probands and all controls were white, from the UK, and aged 55 or over.

The exons, the intron-exon boundaries, and the untranslated regions of IL17A and IL17F were screened for common DNA variants by the direct sequencing of 48 women and by searching genome databases. We identified 10 single nucleotide polymorphisms (SNPs), five in IL17A and five in IL17F (table 1). The SNPs were genotyped by polymerase chain reaction restriction enzyme analysis and were in Hardy-Weinberg equilibrium. Two of the IL17A SNPs (rs8193037 and rs3819025) and two of the IL17F SNPs (rs1953325 and rs763780) had low allele frequencies (<0.05) and their genotyping was therefore not completed. Of the six remaining SNPs, two were non-synonymous (rs11465553 and

Table 1 IL17A and IL17F SNPs

Gene	SNP location*	Nucleotide change M→m†	Amino acid substitution	dbSNP accession number‡	Allele frequency§ (number)		
					Probands	Controls	p Value
IL17A	Upstream	G→A	–	rs8193037	Not determined	0.01 (1/91)	–
IL17A	Intron 1	G→A	–	rs3819025	Not determined	0.03 (6/178)	–
IL17A	Exon 3/3'UTR	G→A	–	rs7747909	0.17 (48/230)	0.22 (95/331)	0.14
IL17A	Exon 3/3'UTR	C→T	–	rs1974226	0.19 (53/231)	0.19 (79/337)	0.99
IL17A	Exon 3/3'UTR	C→T	–	rs3748067	0.10 (28/260)	0.08 (35/389)	0.59
IL17F	Exon 3/3'UTR	T→G	–	rs1953325	Not determined	0.03 (6/174)	–
IL17F	Exon 3	A→G	His161Arg	rs763780	Not determined	0.03 (5/175)	–
IL17F	Exon 3	G→A	Val155Ile	rs11465553	0.04 (11/273)	0.06 (27/401)	0.22
IL17F	Exon 3	A→G	Glu126Gly	rs2397084	0.12 (34/252)	0.12 (52/374)	0.99
IL17F	Intron 1	G→A	–	rs11465551	0.07 (19/269)	0.07 (29/389)	0.98

*SNPs are listed in their physical order, from 6p-telomere to centromere; †M=major, common allele in controls; m=minor, less common allele in controls; ‡http://www.ncbi.nlm.nih.gov/SNP, accessed 27 December 2005; §frequency of the minor allele.

Figure 1 The position of the six SNPs genotyped. Black boxes represent exons, continuous lines represent introns and dotted lines represent intergenic regions. Arrows point toward the position of each SNP. The two genes are aligned according to their physical order, from 6p-telomere to centromere. The horizontal arrows demonstrate the transcriptional orientation of each gene. SNPs rs7747909 and rs11465551 are 49.6 kb apart.

rs2397084). Genotyping of the six SNPs in our probands and controls showed that none were associated with OA at $p \leq 0.05$. The SNPs genotyped encompass a genomic distance of 49.6 kb (fig 1; rs7747909 through to rs11465551). None of the pairwise haplotypes or any of the more complex haplotypes, which were constructed from all combinations of 3–6 SNPs, were associated with OA (data not shown).

We focused our analysis on the probands from the families that had provided us with the linkage and the association with chromosome 6. In this way we attempted to maximise our chance of detecting an association with IL17A and/or IL17F, if any such association existed. Our analysis did not provide any evidence of association of either gene. Our investigation does not therefore support IL17A or IL17F as coding for the OA susceptibility that we had previously identified on chromosome 6.

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Rituximab in Churg-Strauss syndrome

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Churg-Strauss Syndrome (CSS) is a small vessel systemic vasculitis, characterised by asthma, peripheral eosinophilia, neuropathy, pulmonary infiltrates, and sinus abnormalities.¹ Conventional treatment with corticosteroids and cyclophosphamide² controls disease activity; however, relapse is frequent and the treatment is toxic. Alternative treatments include plasma exchange,³ interferon alfa,⁴ and intravenous immunoglobulin.⁵ B cell depletion

with rituximab has proved effective in autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, and antineutrophil cytoplasmic antibody (ANCA) associated vasculitis.⁶ We present two cases of patients with refractory CSS who were successfully treated with rituximab.

A 37 year old woman (case 1) presented with an 8 month history of nasal congestion, hearing loss, lymphadenopathy, rash, breast inflammation, peripheral neuropathy, abdominal