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Genome-wide association study of ankylosing spondylitis identifies non-MHC susceptibility loci

John D Reveille[1], **Anne-Marie Sims**[2], **Patrick Danoy**[2], **David M Evans**[3], **Paul Leo**[2], **Jennifer J Pointon**[4], **Rui Jin**[1], **Xiaodong Zhou**[1], **Linda A Bradbury**[2], **Louise H Appleton**[4], **John C Davis**[5], **Laura Diekman**[1], **Tracey Doan**[2], **Alison Dowling**[2], **Ran Duan**[2], **Emma L Duncan**[2], **Claire Farrar**[4], **Johanna Hadler**[2], **David Harvey**[4], **Tugce Karaderi**[4], **Rebecca Mogg**[6], **Emma Pomeroy**[6], **Karena Pryce**[2], **Jacqueline Taylor**[2], **Laurie Savage**[7], **Panos Deloukas**[8], **Vasudev Kumanduri**[8], **Leena Peltonen**[8], **Sue M Ring**[3], **Pamela Whittaker**[8], **Evgeny Glazov**[2], **Gethin P Thomas**[2], **Walter P Maksymowych**[9], **Robert D Inman**[10], **Michael M Ward**[11], **Millicent A Stone**[6,10], **Michael H Weisman**[12], **B Paul Wordsworth**[4], and **Matthew A Brown**[2,4] **for The Australo-Anglo-American Spondyloarthritis Consortium (TASC)**

[1]Rheumatology and Clinical Immunogenetics, University of Texas Health Science Center at Houston, Houston, Texas, USA

[2]Diamantina Institute of Cancer, Immunology and Metabolic Medicine, Princess Alexandra Hospital, University of Queensland, Brisbane, Queensland, Australia

[3]Medical Research Council Centre for Causal Analyses in Translational Epidemiology, Department of Social Medicine, University of Bristol, Bristol, UK

[4]Botnar Research Centre, Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences, University of Oxford, Oxford, UK

[5]University of California, San Francisco, San Francisco, California, USA

[6]Royal National Hospital for Rheumatic Diseases National Health Service Foundation Trust and University of Bath, Bath, UK

[7]The Spondylitis Association of America, Sherman Oaks, California, USA

[8]Wellcome Trust Sanger Institute, Cambridge, UK

[9]Department of Medicine, University of Alberta, Edmonton, Alberta, Canada

[10]University of Toronto, Toronto, Ontario, Canada

[11]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, Maryland, USA

[12]Department of Medicine/Rheumatology, Cedars-Sinai Medical Center, Los Angeles, California, USA

Correspondence should be addressed to M.A.B. (matt.brown@uq.edu.au) or J.D.R. (john.d.reveille@uth.tmc.edu) .

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Abstract

To identify susceptibility loci for ankylosing spondylitis, we undertook a genome-wide association study in 2,053 unrelated ankylosing spondylitis cases among people of European descent and 5,140 ethnically matched controls, with replication in an independent cohort of 898 ankylosing spondylitis cases and 1,518 controls. Cases were genotyped with Illumina HumHap370 genotyping chips. In addition to strong association with the major histocompatibility complex (MHC; $P < 10^{-800}$), we found association with SNPs in two gene deserts at 2p15 (rs10865331; combined $P = 1.9 \times 10^{-19}$) and 21q22 (rs2242944; $P = 8.3 \times 10^{-20}$), as well as in the genes *ANTXR2* (rs4333130; $P = 9.3 \times 10^{-8}$) and *IL1R2* (rs2310173; $P = 4.8 \times 10^{-7}$). We also replicated previously reported associations at *IL23R* (rs11209026; $P = 9.1 \times 10^{-14}$) and *ERAP1* (rs27434; $P = 5.3 \times 10^{-12}$). This study reports four genetic loci associated with ankylosing spondylitis risk and identifies a major role for the interleukin (IL)-23 and IL-1 cytokine pathways in disease susceptibility.

Ankylosing spondylitis is a common cause of inflammatory arthritis, with a prevalence of ~5 per 1,000 in European populations[1]. It is characterized by inflammation of the spine and sacroiliac joints causing pain and stiffness and ultimately new bone formation and progressive joint ankylosis. Hip and peripheral joint arthritis is common, and inflammation may also involve extra-articular sites such as the uveal tract, tendon insertions, proximal aorta and, rarely, the lungs and kidneys. The disease is strongly associated with the gene *HLA-B27*; however, only 1%–5% of HLA-B27-positive individuals develop ankylosing spondylitis, and there is increasing evidence to suggest that other genes must also be involved[2–5]. Association has previously been confirmed between ankylosing spondylitis and SNPs in *IL23R* at chromosome 1p23 and *ERAP1* (previously known as *ARTS-1*) at chromosome 5p15 (ref. 6), and linkage has been demonstrated at genome-wide significance to chromosome 6p (where HLA-B is encoded) and chromosome 16q (lod score 4.7)[7]. We report here the first genome-wide association study (GWAS) for ankylosing spondylitis.

To identify ankylosing spondylitis susceptibility genes, we performed a GWAS in a sample of ankylosing spondylitis cases among Australian, British and North American individuals of European descent ($n = 2,053$ in the final data set), using data from previously genotyped, ethnically matched British and North American individuals as controls ($n = 5,140$). Cases were genotyped with Illumina HumHap370 genotyping chips; 288,662 SNPs were available for study that were common to case and all control data sets after quality-control filtering (see Online Methods). After data cleaning, a modest overall inflation of test statistics remained, with a genomic inflation factor (λ) of 1.06 (ref. 8), excluding SNPs in the MHC (Supplementary Fig. 1). We then genotyped a total of 163 SNPs in a replication cohort of 898 British ankylosing spondylitis cases and 1,518 unselected British controls. The SNPs genotyped included 49 ancestry-informative SNPs and 114 SNPs in 105 chromosomal regions selected from the discovery sample on the basis of their strength of association in that sample and because of close proximity to genes of biologically plausible involvement in ankylosing spondylitis (Supplementary Table 1). Of the confirmation SNPs, 102 markers from 95 regions passed quality control filters and are reported here.

As expected, SNPs in the MHC on chromosome 6p were strongly associated with ankylosing spondylitis (rs7743761 $P = 5.0 \times 10^{-304}$). Association was evident across a very broad region surrounding the MHC, including five SNPs lying in a 153-kb region at 26.0–26.1 Mb from the p-telomere (5.4 Mb from HLA-B), which achieved $P < 10^{-5}$. The most associated SNP in this region was rs3734523 ($P = 1.6 \times 10^{-6}$). However, conditional logistic regression analysis suggested that this was unlikely to represent a separate independent association because conditioning on five of the most significant SNPs from the MHC

(rs7743761, rs2596501, rs3915971, rs2516509, rs1265112) caused the association to disappear ($P = 0.27$).

Excluding the MHC and surrounding regions, 25 SNPs from six independent loci were significantly associated with ankylosing spondylitis, including the known ankylosing spondylitis–associated genes *ERAP1* and *IL23R*, and two new loci, chromosomes 2p15 and 21q22 (Table 1 and Supplementary Fig. 2). We also observed strong association within two more genes, *ANTXR2* and *IL1R2*, with support in both the discovery and confirmation data sets.

Both non-MHC genes previously associated with ankylosing spondylitis, *ERAP1* and *IL23R,* were significantly associated in this data set. The most strongly associated SNPs were rs30187 ($P = 2.6 \times 10^{-11}$) and rs11209026 ($P = 9.1 \times 10^{-14}$), confirming the strong association observed for these SNPs in the initial discovery set[6].

We used SNP imputation to investigate association strength at untyped markers of the six non-MHC loci associated with ankylosing spondylitis. Considering *IL23R,* only marginally stronger association was observed with one imputed SNP (rs11465817, $P = 1.2 \times 10^{-10}$) than with the strongest associated genotyped SNP, rs11209026 ($P = 2.3 \times 10^{-9}$) (Fig. 1a). *IL23R* has ten exons, with marker rs11209026 encoding a Q381R substitution in exon 9, and rs11465817 falling in intron 9, suggesting that this is the critical region involved in the association of *IL23R* with ankylosing spondylitis.

In *ERAP1*, the imputed data revealed a block of SNPs lying in a 4.6-kb region between rs27529 (in exon 9) and rs469758 (in intron 12) achieving $P < 10^{-11}$, more than 50 times more significant than any other imputed SNP (Fig. 1b). In this region, only marker rs30187 is coding (R528K). It has previously been demonstrated that rs30187 causes a significant reduction in aminopeptidase activity toward a synthetic peptide substrate as well as alterations in substrate affinity[9]. Molecular modeling of the ERAP1 protein suggests that Arg528 lies at the mouth of the putative enzyme substrate pocket, perhaps explaining the lower aminopeptidase activity of this genetic variant. *ERAP1* variants also correlate significantly with expression. Strong *cis*-regulation of ERAP1 expression in lymphoblastoid cell lines was seen from SNPs close to and within *ERAP1*, including the marker rs30187 (C allele reduced expression, $P = 0.00015$)[10]. In our study, we saw no difference in ERAP1 expression in peripheral blood mononuclear cells (PBMCs) from ankylosing spondylitis cases compared with controls (Supplementary Table 2), suggesting that this is a less likely explanation of the mechanism of association of *ERAP1* with ankylosing spondylitis.

Three SNPs at the 2p15 locus achieved genome-wide significance in the discovery set: rs10865331 ($P = 6.1 \times 10^{-15}$), rs10865332 ($P = 3.5 \times 10^{-10}$) and rs4672503 ($P = 9.3 \times 10^{-10}$). No imputed SNP was more significantly associated than rs10865331. In the replication study we genotyped two SNPs in this locus, both of them confirming the discovery set findings: rs4672495 ($P = 8.4 \times 10^{-4}$) and rs10865331 ($P = 5.5 \times 10^{-6}$). The combined level of association of these SNPs was highly significant: rs4672495 ($P = 3.2 \times 10^{-9}$) and rs10865331 ($P = 1.9 \times 10^{-19}$). Combining the imputed and genotyped data, there is a block of SNPs lying between marker rs10865331 and rs4672507 in tight linkage disequilibrium (LD) ($r^2 > 0.8$) with >1,000 times stronger significance than any other SNP at this locus, encompassing a 23-kb region likely to contain the causative variant(s) responsible for the association observed (Fig. 1c). No genes are encoded within this region, the nearest gene to the most strongly associated marker rs10865331 being 100 kb distant (*B3GNT2*). We are not aware of this region being associated previously with any known disease. *B3GNT2* encodes UDP-GlcNAc: betaGal beta-1,3-N-acetylglucosaminyltransferase 2, a protein not as yet known to have any immunological function.

At chromosome 21q22, three SNPs across an 11-kb region achieved genome-wide significance in the discovery cohort: rs2242944 ($P = 2.7 \times 10^{-14}$), rs2836878 ($P = 4.9 \times 10^{-12}$) and rs378108 ($P = 6.1 \times 10^{-11}$) (Fig. 1d). SNP rs2242944 also showed strong association in the confirmation cohort ($P = 5.6 \times 10^{-7}$) and in the combined analysis ($P = 8.3 \times 10^{-20}$). The nearest gene to the most strongly associated SNP, rs2242944, is 82 kb distant (*PSMG1*, proteasome assembly chaperone 1). This region has recently been associated with pediatric-onset inflammatory bowel disease (IBD), in which the most strongly associated SNP was rs2836878; positive association was seen with over-representation of the minor allele, as was the case in our ankylosing spondylitis data set ($P = 4.1 \times 10^{-10}$). This SNP is in strong LD with the strongest ankylosing spondylitis–associated marker, rs2242944 ($r^2 = 0.6$, $D = 1$)[11]. Increased expression of PSMG1 was observed in colonic biopsies from IBD cases, and it was suggested that this may be the gene involved at this locus. Ankylosing spondylitis and IBD are closely related conditions, with ~70% of those with ankylosing spondylitis having microscopic terminal ileitis resembling Crohn's disease[12] and ~10% of those with IBD having ankylosing spondylitis. Crohn's disease and ankylosing spondylitis are each associated with *IL23R* SNPs, and it is likely that further shared genetic susceptibility factors exist. We saw strong association even among those cases with no clinical IBD ($n = 1{,}159$ cases, rs2242944, $P = 1.3 \times 10^{-9}$), indicating that the association was present even in cases of primary ankylosing spondylitis in the absence of clinically manifest IBD.

PSMG1 was not differentially expressed in PBMCs from cases with active ankylosing spondylitis compared with healthy controls (Supplementary Fig. 3), nor in relationship to ankylosing spondylitis–associated chromosome 21q22 SNPs. A large recombination hotspot lying between *PSMG1* and the ankylosing spondylitis–associated SNPs makes it unlikely that the association signal observed is due to effects from SNPs located in or close to *PSMG1*. We feel that its remoteness to the associated locus, absence of differential expression with disease, and lack of evidence of a relevant biological function make it an unlikely candidate to be directly involved in ankylosing spondylitis susceptibility. Rather, we hypothesize that the chromosome 2p15 and 21q22 regions harbor either noncoding RNA species or hitherto unreported protein-coding genes that are likely to be involved in susceptibility to ankylosing spondylitis. To investigate this further, we performed a transcriptome-wide profiling study of expressed sequence tags and small RNAs derived from PBMCs from four active ankylosing spondylitis cases and three healthy controls using Illumina's deep sequencing approach. No small regulatory RNAs such as microRNAs were seen within the regions of highly associated SNPs at either locus, although, consistent with recent findings[13], these were identified in association with transcription start sites of flanking genes outside the disease-associated region (Supplementary Fig. 4). At both loci, we identified sequence tags derived from long RNAs. These either represent long mRNA-like noncoding RNA species or, alternatively, previously undescribed mRNA isoforms originating from distal promoters of adjacent protein-coding genes.

Fourteen SNPs in a 61-kb region encompassing *IL1R2* achieved nominal significance, with the strongest association observed with genotyped markers at rs2310173 ($P = 8.3 \times 10^{-6}$) and with imputed markers at rs10185424 ($P = 5.4 \times 10^{-6}$) (Supplementary Fig. 3a). Marker rs2310173 was also associated with ankylosing spondylitis in the replication study ($P = 0.018$) and showed a high level of significance in the combined analysis ($P = 4.8 \times 10^{-7}$). IL-1R2 is cleaved from cell membranes, possibly by ERAP1 (ref. 14) and acts as a decoy receptor, interfering with the binding of IL-1 to IL-1RI. One possible explanation for the associations of *ERAP1* and *IL1R2* with ankylosing spondylitis is that the disease-associated genetic variants affect cleavage of IL-1R2 from the cell surface. In this respect, we note that several SNPs in *TNFRSF1A* achieved moderate levels of association in the discovery set (strongest associated SNP, rs1800693, $P = 6.9 \times 10^{-5}$). *TNFRSF1A* encodes tumor necrosis

factor receptor 1, which may also be cleaved from the cell surface by ERAP1 (ref. 15). No support for this association was seen in our replication study, but SNPs in *TNFRSF1A* have been associated with both ulcerative colitis and Crohn's disease previously[16,17], providing some support for this association with ankylosing spondylitis. Tumor necrosis factor overexpression in mice leads to inflammatory bowel disease and to sacroiliitis resembling ankylosing spondylitis, and is dependent on expression of *TNFRSF1A* (ref. 18).

ANTXR2, recessive mutations of which cause juvenile hyaline fibromatosis (MIM228600) and infantile systemic hyalinosis (MIM236490), encodes capillary morphogenesis protein-2 (CMP2). The SNP rs4333130 was associated with ankylosing spondylitis in both the discovery cohort ($P = 7.5 \times 10^{-7}$) and replication cohort ($P = 0.029$) as well as overall ($P = 9.3 \times 10^{-8}$). In the imputed data set, no markers were more strongly associated (Supplementary Fig. 3b). A functional explanation for this association with ankylosing spondylitis is not clear.

The power of this study to detect small to moderate genetic effects was modest. We calculate that the discovery phase of the study has 2%–21% power to identify SNPs conferring an additive allelic odds ratio of 1.2 with minor allele frequencies of 0.1–0.5 at $\alpha = 5 \times 10^{-7}$, assuming $D' = 0.9$ and the marker and disease-associated allele frequencies are equal. Further GWAS with larger sample sizes will therefore be useful and likely to identify more genes associated with ankylosing spondylitis. The identification of four genetic loci newly associated with ankylosing spondylitis extends our understanding of the genetic etiology of this disorder and provides an important foundation for future hypothesis-driven research into the pathogenesis of this common and debilitating condition.

METHODS

Methods and any associated references are available in the online version of the paper at http://www.nature.com/naturegenetics/.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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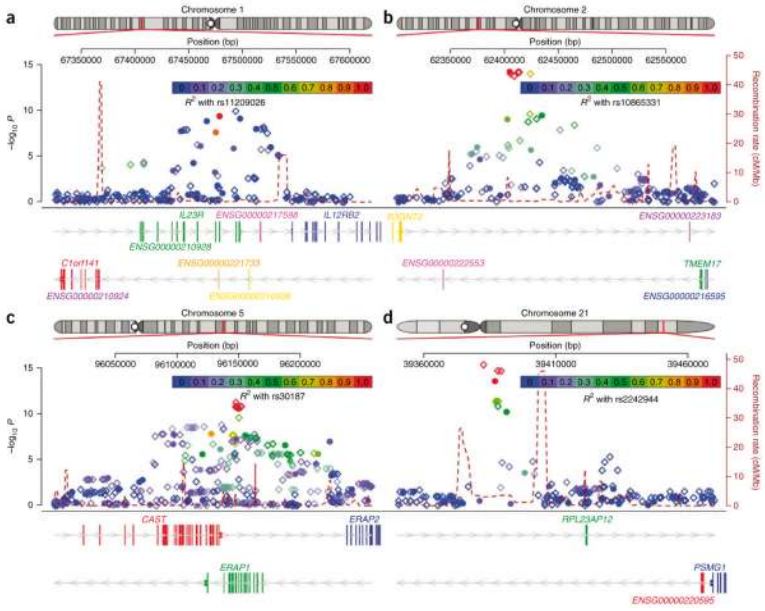

Figure 1.

SNP association plots for ankylosing spondylitis–associated regions. Discovery cohort association significance is plotted against the left hand *y* axis as $-\log_{10}$ (*P*-value). Genetic coordinates are as per NCBI dbSNP genome build 128 (October 2007). Filled circles, genotyped SNPs; open diamonds, imputed SNPs; color scale, LD; purple dotted line and right *y* axis, recombination rate (cM/Mb as per HapMap data). Positions of gene exons and ESTs are indicated below the *x* axis, with their direction of translation (gray arrows). (**a**) Chromosome 1p31 region. SNP association plot for a 295-kb region (67,325 kb to 67,620 kb) of chromosome 1. LD is in relation to marker rs11209026. (**b**) Chromosome 2p15 region. SNP association plot for a 295-kb region (62,300 kb to 62,595 kb) of chromosome 2. LD is in relation to marker rs10865331. (**c**) Chromosome 5q15 region. SNP association plot for a 258-kb region (96,000 kb to 96,258 kb) of chromosome 5. LD is in relation to marker rs30187. (**d**) Chromosome 21q22 region. SNP association plot for a 245-kb region (39,350 kb to 39,595 kb) of chromosome 21. LD is in relation to marker rs2242944.

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Table 1

Genome-wide significant loci typed in both discovery cohort and replication study

					Discovery cohort				Replication cohort				Combined cohorts
Chromosomal band	**SNP**	**Position**	**Candidate gene**	**Minor allele**	**Control MAF**	**Case MAF**	**OR (95% CI)**	***P*-value**	**Control MAF**	**Case MAF**	**OR (95% CI)**	***P*-value**	***P*-value**
1p31.3	rs11209026	67478546	*IL23R*	A	0.062	0.035	0.53 (0.44–0.64)	4.2×10^{-10}	0.081	0.050	0.60 (0.47–0.77)	4.8×10^{-5}	9.1×10^{-14}
2p15	rs4672495	62374748	–	C	0.33	0.38	1.18 (1.09–1.27)	9.9×10^{-7}	0.32	0.36	1.24 (1.09–1.40)	8.4×10^{-3}	3.2×10^{-9}
2p15	rs10865331	62404976	–	A	0.40	0.46	1.27 (1.18–1.37)	6.1×10^{-15}	0.36	0.43	1.32 (1.18–1.49)	5.5×10^{-6}	1.9×10^{-19}
2q11.2	rs2310173	102030060	*IL1R2*	A	0.45	0.50	1.18 (1.10–1.27)	8.3×10^{-6}	0.47	0.51	1.16 (1.03–1.30)	1.8×10^{-2}	4.8×10^{-7}
4q21.21	rs4333130	81168853	*ANTXR2*	G	0.36	0.31	0.82 (0.76–0.89)	7.5×10^{-7}	0.38	0.35	0.87 (0.77–0.99)	2.9×10^{-2}	9.3×10^{-8}
5q15	rs27037	96120450	*ERAP1*	A	0.29	0.33	1.23 (1.14–1.33)	2.5×10^{-6}	0.28	0.34	1.36 (1.19–1.54)	2.7×10^{-6}	8.2×10^{-11}
5q15	rs27434	96155268	*ERAP1*	A	0.23	0.26	1.19 (1.10–1.30)	2.2×10^{-8}	0.21	0.26	1.33 (1.16–1.52)	5.0×10^{-5}	5.3×10^{-12}
6p22.2	rs3734523	26033966	*MHC*	A	0.10	0.082	0.82 (0.72–0.94)	1.6×10^{-6}	0.12	0.09	0.75 (0.61–0.91)	2.7×10^{-3}	1.6×10^{-8}
21q22.2	rs2242944	39387048	–	A	0.37	0.29	0.72 (0.67–0.78)	2.7×10^{-14}	0.38	0.30	0.72 (0.63–0.82)	5.6×10^{-7}	8.3×10^{-20}

Position is as NCBI dbSNP genome build 128 (October 2007) in base pairs. MAF, minor allele frequency; OR, odds ratio, CI, confidence interval.

'–' indicates not genotyped in that study.