Exome-wide study of ankylosing spondylitis demonstrates additional shared genetic background with inflammatory bowel disease

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Ankylosing spondylitis (AS) is a common chronic immune-mediated arthropathy affecting primarily the spine and pelvis. The condition is strongly associated with HLA-B*27 as well as other human leukocyte antigen variants and at least 47 individual non-MHC-associated variants. However, substantial additional heritability remains as yet unexplained. To identify further genetic variants associated with the disease, we undertook an association study of AS in 5,040 patients and 21,133 healthy controls using the Illumina Exomechip microarray. A novel association achieving genome-wide significance was noted at CDKAL1. Suggestive associations were demonstrated with common variants in FAM118A, C7orf72 and FAM114A1 and with a low-frequency variant in PNPLA1. Two of the variants have been previously associated with inflammatory bowel disease (IBD; CDKAL1 and C7orf72). These findings further increase the evidence for the marked similarity of genetic risk factors for IBD and AS, consistent with the two diseases having similar aetiopathogenesis.

INTRODUCTION

Ankylosing spondylitis (AS) is an inflammatory arthropathy with a prevalence of 0.1–0.5% in populations of European or Asian descent. The condition primarily affects the sacroiliac joints and the spine, initially causing pain and reversible stiffness. Subsequent ankylosis of these leads to fixed spinal deformity and increasing disability. The condition also has extra-articular manifestations, most commonly in the eye (acute anterior uveitis), and rarely in the aorta, kidneys and lungs. Inflammatory bowel disease (IBD; either Crohn’s disease or ulcerative colitis) is found in 5–10% of AS patients, and ~60% of AS patients have subclinical ileal inflammation. The disease is known to be highly heritable, and to date at least 47 independent genetic variants have been shown to be associated with AS susceptibility. These findings have contributed greatly to increased understanding of the pathogenesis of the disease, and also to the development of new treatments. The genetic variants associated with AS have been discovered using coding variant scans, genome-wide association studies, candidate gene studies and studies targeting immunologically important regions. Generally these associations have been with common variants. For example, in the International Genetics of AS Consortium Immunochip study, which identified 37 AS-associated variants, the mean minor allele frequency (MAF) of the key-associated single-nucleotide polymorphism (SNP) was 32%, and only two low-frequency (MAF 1–5%) AS-associated alleles were identified and one rare allele (MAF < 1%). As with many common heritable diseases, a large proportion of the heritability of AS remains unexplained. The vast majority of human genetic variation consists of low-frequency and rare variants with MAF < 5%. Studies performed to date have not addressed such variants extensively due to the design of genome-wide association study SNP microarrays and the sample sizes of the studies not having power to detect association with low-frequency or rare variants. It is likely that there is a substantial numbers of additional variants in the low-frequency or rare variant range that remain undiscovered.

Exomes are proposed to carry a disproportionately high number of clinically important variants because of their potentially profound effects on the protein function. Much of the variation found in exomes is also rare. Recent exome-sequencing analyses have demonstrated the huge number of rare and potentially damaging variants present in human exomes, with ~313 genes per person predicted to be adversely affected by exonic variants.

In this study, we sought to identify further AS-associated genetic variants focusing on exons using the Illumina Human-Exome Beadchip microarray. In addition to covering common
coding variants, this chip has extensive low-frequency and rare variant content, enabling us to perform a relatively low cost survey of the role of such variants in AS (compared with studies utilising whole-exome or -genome sequencing).

RESULTS

Participants and SNPs

After participant quality control (QC) there were 4,602 AS cases and 20,164 healthy controls. After SNP QC there were 207,193 SNPs. Principal components analysis was performed with 0–1 eigenvectors; the sctree plot of genomic control-1000 statistics for different numbers of eigenvectors is shown in Supplementary Figure 1. Use of one eigenvector produced a genomic control-1000 statistic of 1.045, and use of additional eigenvectors did not reduce the genomic control-1000 statistic further. Therefore, all further analyses used a single eigenvector to control for population stratification. The quantile–quantile plot for the experiment is shown in Supplementary Figure 2.

Single variant analysis

Assays for 10 non-MHC SNPs previously associated with AS were included on the HumanExome Beadchip, and each one showed at least suggestive association ($P < 5 \times 10^{-6}$) with AS in the current study (Table 1 and Supplementary Figures 3–13). The associations with SNPs in ERAP1, IL23R, the intergenic regions chromosomes 2p15 and 21q22, GPR35 and I6LR were confirmed at genome-wide significance level ($P < 5 \times 10^{-8}$), SNP associations within ANTXR2, FCGR2A, IL1R1 and NOS2 were confirmed at suggestive levels of significance. At nine of the confirmed loci, association was seen with the primary associated SNP. At NOS2 the association was with rs2297518, which has been reported previously as a secondary signal at the NOS2 locus, the primary associated SNP rs2531875 did not being included on the HumanExome Beadchip. Novel common variant association was identified in CDKAL1 (MAF = 0.22, $P = 1.8 \times 10^{-8}$, OR = 1.2) at a genome-wide level of significance (Table 2 and Supplementary Figure 14). The CDKAL1 SNP rs6908425 has previously been associated with Crohn’s disease, psoriasis and ulcerative colitis again with the C allele being the risk variant. rs6908425 is in strong linkage disequilibrium with variants associated with diabetes and body mass index (Supplementary Table 1). Suggestive associations were seen with common variants in FAM118A ($P = 5.9 \times 10^{-8}$, odds ratio (OR) = 1.2), C7orf72 ($P = 1.9 \times 10^{-7}$, OR = 1.1) and FAM114A1 ($P = 1.4 \times 10^{-6}$, OR = 1.1), and with a rare variant in patatin-like phospholipase domain containing 1 (PNPLA1) (MAF = 0.0017, $P = 1.5 \times 10^{-6}$, OR = 2.6). SNPs in C7orf72, including the same SNP we have identified as being associated with AS (rs1456896), have been associated with Crohn’s disease. FAM118A variants have previously been associated with bone mineral density. Strong linkage disequilibrium exists between the bone mineral density-associated SNP (rs136564) and the AS-associated SNP, rs6007594 ($r^2 = 0.03$, D’ = 0.92). Functional annotation for the variants is shown in Supplementary Table 2.

After conditioning on the primary association signals there were second, independent signals observed in ERAP1 and IL23R (Table 3 and Supplementary Figure 19). The pattern of association at ERAP1 is consistent with previous work that describes two independent haplotypes at ERAP1, tagged by the functional variants rs30187-T (primary signal) and rs10050860-C (primary unconditioned signal, $P = 3.1 \times 10^{-24}$, allele C, OR = 1.4, 95% confidence interval (CI) 1.27–1.43 and conditioned on rs30187 $P = 9.7 \times 10^{-10}$, allele C, OR = 1.2, 95% CI 1.14–1.30). Moderate linkage disequilibrium was observed between rs30187 and rs10050860 ($r^2 = 0.156$ and $D’ = 1.00$). As previously reported, after conditioning on rs30187, association was confirmed with the neighbouring ERAP2 gene (rs2549794, $P = 2.8 \times 10^{-14}$, allele C, OR = 1.2, 95% CI 1.16–1.28). This association remains after controlling for both the rs30187 and rs10050860 ERAP1 variants (rs2549794, $P = 4.7 \times 10^{-14}$, allele C, OR = 1.2, 95% CI 1.16–1.28). No additional associated variants were evident.

At IL23R, the intronic variant rs11465804 was slightly more significantly associated than the previously reported rs11209026 nonsynonymous SNP ($P = 1.3 \times 10^{-22}$ and $P = 4.35 \times 10^{-25}$ respectively). These two SNPs are in high linkage disequilibrium ($r^2 = 0.89$, $D’ = 0.97$), and conditioning for either SNP controlled for the association at the other SNP, suggesting that the rs11465804 variant tags this previously demonstrated functional SNP.23,24 As previously reported, a secondary association is seen at the IL23R locus, evident after conditioning on rs11465804 (rs10889677, $P = 9.8 \times 10^{-9}$, allele A, OR = 1.2, 95% CI 1.10–1.20). No additional associated variants were evident.

An independent signal supported by multiple SNPs was demonstrated after conditioning on the main SNP at the FAM114A1 locus; these SNPs sit in the TLR10 gene (Table 3 and Supplementary Table 2).
Supplementary Figure 22). SNPs in TLR10 have previously been associated with Crohn’s disease,\textsuperscript{5,26} and the peak-associated SNP in our study, rs1109695, is in strong linkage disequilibrium with the most strongly associated, previously reported, Crohn’s disease TLR10 SNPs, rs7658893 ($r^2 = 0.64, D’ = 1.0$) and rs6841698 ($r^2 = 0.64, D’ = 0.83$).

Rare variant burden tests
Using the SKAT-O test, no genes were significantly associated with AS at either a genome-wide or suggestive level of significance. This was the case for all the sets of variants incorporated into the burden equation including the following: (a) ‘Damaging set’, (b) ‘Polyphen set’ and (c) all variants. No association was identified even after removing the restrictive minor allele filter of 0.05 and including SNPs of all frequencies.

With sample sizes of 4,602 AS cases and 20,164 controls used in this study, the power to detect the association was good for low MAF variants, but low for rare variants (Supplementary Figure 23). Assuming a prevalence of 0.55%, allele risk of 1.5 and alpha of $5 \times 10^{-5}$, and equal MAF for the disease-causative and genotyped markers, the study had 100% power for MAF = 0.05, but only 9% power for MAF = 0.01 and close to zero ($6.1 \times 10^{-5}$%) power for the median MAF in this study ($2.0 \times 10^{-4}$).

DISCUSSION
This study re-demonstrates a number of known AS genetic associations both within and outside the MHC (ERAP1, IL23R, chromosome 2p15, chromosome 21q22, KIF12B-GPR25, GPR35, IL6R, ANTXR2, IL1R1, FCGR2A and NOS2). It also describes a common novel AS-associated non-MHC variant that achieved genome-wide significance (CDKAL1), and three novel common variants that achieved a suggestive level of significance (FAM118A, C7orf72, FAM114A1). One new suggestive rare variant association in PNPLA1 was identified in single marker analyses, in addition to low-frequency associations observed with rs11465804 in IL23R and rs4349859 in HLA-B*27. However, no rare variant associations were noted using burden tests.

In the current study, we identify three AS-associated variants that have previously been associated with IBD, namely variants in or near CDKAL1, C7orf72 and TLR10. There is a high prevalence of IBD in patients with AS,\textsuperscript{7,28} around 10% of AS patients have clinical IBD and up to 70% have subclinical bowel inflammation demonstrated histologically.\textsuperscript{29} In addition, reactive arthritis, which is a type of spondyloarthritis that can progress to AS, can be triggered by enteric infections such as Campylobacter, Salmonella and Shigella. Strong co-familiarity between AS and IBD exists, the sibling recurrence risk ratio for IBD in first-degree relatives of AS probands being 3.0,\textsuperscript{30} not dissimilar to the overall familiality of rheumatoid arthritis.\textsuperscript{31} There is extremely strong correlation between AS and IBD genetic associations, with a 2013 analysis indicating that the two diseases shared at that point 22 SNP associations, of which 21 were concordant (same SNP, same direction of association).\textsuperscript{32,33} Nonetheless, major differences exist between genetic associations of the two diseases pointing to differences in disease-specific aetiopathogenesis; for example, the absence of association of IBD with HLA-B*27, and the absence of association of AS with the major IBD loci NOD2/CARD15 and ATG16L1. The finding of three more concordant genetic associations further strengthens the evidence of shared aetiopathogenesis between these diseases.

Little is known about FAM114A1. It may be responsible for the described association, but the corresponding protein NOXP20 contains a predicted caspase recruitment (CARD) domain suggesting that it may be involved in apoptosis.\textsuperscript{34} CARD9 has previously been associated with AS and NOXP20 may have a similar role. In addition, neighbouring genes include the Toll-like receptors that are intimately involved in innate immunity and so are strong biological candidates for involvement in AS. The second independent signal at the FAM114A1 locus was in the toll-like receptor 10 gene (TLR10). This missense variant (rs11096955) is predicted by Polyphen-2 to cause a benign change (isoleucine to leucine), but it may tag other more functional variants. This association implicates this important component of the innate immune system in AS aetiology. Toll-like receptors recognise evolutionary conserved sequences on pathogens and trigger immune responses. TLR10 has recently been identified to induce pro-inflammatory cytokine production and interferon in response to influenza infection.\textsuperscript{35} It has recently been suggested that immunodeficiency to gut organisms may trigger AS; if the
association with TLR10 impairs innate immune responses, this would be consistent with this theory.26

FAM118A is a protein-coding gene of unknown function that encodes a single-pass transmembrane protein (www.uniprot.org). The AS-associated SNP (rs6007594) is a missense mutation causing an arginine to be replaced by a histidine. This missense change is predicted to be probably damaging with a Polyphen-2 score of 0.999 (sensitivity: 0.14; specificity: 0.99).37 Kwan et al.22 demonstrated that FAM118A is expressed in lymphoblastoid cell lines as well as human osteoblasts, and in both cell types showed major SNP effects on FAM118A expression levels. How this impacts on AS aetiology is not immediately evident and larger studies studying SNPs across this locus will be required to determine the genetic variant(s) responsible for the association observed here.

The PNLPA1 gene belongs to a family of genes, the members of which have diverse lipolytic and acyltransferase activities. The function of PNLPA1 itself is not well understood. It is expressed in epidermal keratinocytes, and has a role in glycerophospholipid metabolism in the cutaneous barrier. Variants in PNLPA1 are associated with the skin disorder ichthyosis.38 The rs141744967 variant is a missense polymorphism that causes a change from alanine to valine. The functional effect is not available from the study had excellent power to detect common variant association analyses with one eigenvector as a covariate for population

Finally, rare variants do not share linkage disequilibrium with many other surrounding variants to the extent that common variants do. Therefore if identified in a study such as this, a good check of association is manual inspection of the genotype intensity clustering, and, in addition, considering the biological plausibility. However, probes can map to other areas of the genome without our knowledge giving well-clustered intensity plots. Biological plausibility is not necessarily a good measure of a true association as the association may be the first association in a pathway not previously known to be involved in disease aetiology. This makes independent replication studies essential, although it is particularly challenging for low-frequency or rare variants because of the sample size requirements.

This study has re-demonstrated many known AS risk loci, and also identified a novel common variant at a genome-wide level of significance, and four suggestive associations, including one rare variant association. The finding of further concordant associations with IBD genes increases the evidence of shared aetiopathogenesis between the diseases and the potentially important role of intestinal dysbiosis in AS.40,41 The major overlap between AS and IBD is also supported by another study showing similar genetic variants but differing effect sizes between variants associated with AS and anterior uveitis.32 Whether low-frequency and rare genetic variants are major contributors to the aetiopathogenesis of AS remains unclear and will likely require much larger studies with more comprehensive coverage of these variants types to resolve.

**MATERIALS AND METHODS**

Patient cohorts

AS patients of European descent who met the modified New York criteria43 from the United Kingdom, Australia and New Zealand were recruited (n = 5,040). Healthy controls were provided by the following groups:

1. 1958 British Birth Cohort (n = 5,964); 2. GoDarts type 2 diabetes cohort (n = 1,793); 3. Oxford Biobank (n = 4,522); 4. Twins UK cohort (n = 1,189); 5. Anglo-Australasian Osteoporosis Genetics Consortium (n = 7,665). All patients gave written informed consent and ethical approval was provided by all appropriate institutional review boards.

Genotyping and quality control

Each cohort was genotyped using the Illumina Infinium HumanExome BeadChip version 1.2. This Illumina microarray has ~240,000 markers, made up of exonic variants, splice variants, stop altering variants, ancestry informative markers and MHC tag SNPs. Genotype calling was performed using zCall.44 Each cohort had QC completed separately, assessing missingness by individual (threshold < 3%), missingness by genotype (threshold < 3%), Hardy-Weinberg equilibrium in controls (Chi-square test threshold P = 0.01), extreme heterozygosity (threshold > 3 standard deviations from mean) and identity by descent threshold of PI_HAT 0.20 was used. After laboratory QC that excluded ~3,000–5,000 SNPs per cohort, 20,714–22,864 SNPs were removed from each set to form a common SNP basis, 1,033 SNPs were removed due to excess missingness, 526 SNPs were removed from control sets due to not being in Hardy-Weinberg equilibrium and 11,711 SNPs were removed due to allele and frequency inconsistencies between the cohorts. 979 subjects were removed due to excess relatedness, 207 were excluded due to extreme heterozygosity and 2 were excluded due to excessive missingness (after SNP QC).

Shared genotyped SNPs between cohorts with MAF >0.05 were then used to perform principal component analysis for ethnicity identification using SHELFISH (http://www.stats.ox.ac.uk/~davison/software/shellfish/shellfish.php). Unsupervised model-based clustering implemented in R with MCLUST was used to exclude patients deemed to be non-European after plotting with HapMap controls. This model assigns a cluster to each individual based on their principal component analysis values and in consideration to the weighted centre of each cluster and therefore assigns non membership status to those who don’t cluster with core HapMap groups. The analysis identified 219 subjects who were removed due to non-European ethnicity. Supplementary Figures 24 and 25 show the principle component analysis after quality control both with and without the addition of Hapmap Samples.

The genomic control measure (GC or λ) was calculated using the design suggested random set of 5,000 synonymous variants (http://genome.sph.umich.edu/wiki/Exome_Chip_Design#Random_set_of_synonymous_variants_28as_comparator_29).
stratification control. Significance levels used were, genome-wide 
$P < 5 \times 10^{-8}$, and suggestive $5 \times 10^{-6} > P < 5 \times 10^{-8}$.

For low-frequency variant analysis we used the sequence kernel association test–Optimal (SKAT-O) test that computes the SKAT test$^{46}$ and a burden test$^{27,50}$ and then selects the test with the best power.$^{51}$ This was implemented with the ‘skatMeta’ R package. For the low-frequency variant analysis, we used variants with a frequency of < 5%. We also only included gene-based tests where there were at least two variants contributing each with MAF > 0.008%, thus ensuring there were at least 40 copies of the minor alleles in the test. Three sets of variants were sequentially used as inputs into the SKAT-O test. This is because non-damaging variants can reduce the power to detect associations in burden tests. The sets used were (a) All variants, (b) ‘Polyphen2 set’: Polyphen-2$^{27}$ predicted possibly damaging or probably damaging, and (c) ‘Damaging Set’: Variants causing the following consequences: frameshift substitution, nonframeshift substitution, nonframeshift deletion, nonframeshift insertion, frameshift deletion, frameshift insertion, non synonymous single-nucleotide variant, stop gain single-nucleotide variant, stoploss single-nucleotide variant, missense variant, splice acceptor variant, splice donor variant, splice region variant, initiator codon variant, stop retained variant and incomplete terminal codon variant.

Cluster plots for reported SNPs were checked manually in the case cohort and the 1958 British Birth Cohort. Association of classical alleles was completed with imputed SNP2HLA classical alleles and one principal component by logistic regression in R. The level of significance for this analysis was 1.2 $\times 10^{-8}$, reflecting Bonferroni correction for the 424 HLA alleles that were tested for association. Conditional analyses were completed by adding the allele being conditioned as a covariate to the logistic regression model. Power calculations were performed with the online Genetic Power Calculator.

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Supplementary Information accompanies the paper on the npj Genomic Medicine website (http://www.nature.com/npjgenmed)

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