

## Review

### Progress in spondylarthritis

# Progress in studies of the genetics of ankylosing spondylitis

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## Abstract

The advent of high-throughput SNP genotyping methods has advanced research into the genetics of common complex genetic diseases such as ankylosing spondylitis (AS) rapidly in recent times. The identification of associations with the genes *IL23R* and *ERAP1* have been robustly replicated, and advances have been made in studies of the major histocompatibility complex genetics of AS, and of *KIR* gene variants and the disease. The findings are already being translated into increased understanding of the immunological pathways involved in AS, and raising novel potential therapies. The current studies in AS remain underpowered, and no full genomewide association study has yet been reported in AS; such studies are likely to add to the significant advances that have already been made.

## Introduction

Genetic factors are the primary determinants not only of the risk of developing ankylosing spondylitis (AS) but also of its severity [1], as assessed by radiographic measures or by self-administered questionnaires such as the widely used Bath Ankylosing Spondylitis *Disease Activity* Index and Bath Ankylosing Spondylitis *Functional Index* [2,3]. The disease has long been known to be highly familial, with siblings of a case with the disease having >50 times risk of developing the condition themselves compared with individuals in the general population [4].

The main disease-causative gene in AS, HLA-B27, was the first gene identified to be associated with any common human arthropathy, and the discovery proved that the familiarity of the condition was, to a significant degree, genetically determined. The disease is strongly associated with the gene HLA-B27; however, only 1 to 5% of B27-positive individuals develop AS, and there is increasing evidence to suggest that other genes must also be involved. B27-positive relatives of AS patients have a recurrence risk of

the disease 5.6 to 16 times greater than B27-positive individuals in the general population, implying the presence of non-B27 shared familial risk factors [5,6]. A major non-B27 contribution to susceptibility to AS is suggested by the greater concordance rate of monozygotic twins (63%) than of B27-positive dizygotic twin pairs (23%) [7].

Recurrence risk modeling indicates that the observed pattern of disease recurrence in families best fits an oligogenic disease model [8]. Extensive efforts to identify genes by linkage mapping in families has proven relatively unproductive, with linkage demonstrated at genomewide significant levels to only one region (chromosome 16q (LOD score 4.7)) [9]. No genomewide association study in AS has yet been reported, although a screen of 14,500 common nonsynonymous SNPs has been reported, identifying the association of the genes *ERAP1* (formerly known as *ARTS-1*) and *IL23R* with AS [10]. Through the use of high-throughput microarray-based SNP genotyping techniques in adequately sized cohorts, researchers are making rapid progress in identifying genes in a wide variety of common human diseases, and it is likely that this approach will be similarly successful in AS.

## Major histocompatibility complex and ankylosing spondylitis – progress beyond B27

Whilst HLA-B27 is clearly the primary AS-associated major histocompatibility complex (MHC) gene, studies of HLA-B subtypes, of other HLA-B alleles, and of MHC haplotypes indicate that there are very probably other HLA-B and non-HLA-B MHC genes important in the risk of developing AS.

### HLA-B and HLA-B27 subtypes

The study of HLA-B27 subtypes has accelerated over the past 5 years through improved DNA-based genotyping methods. The Anthony Nolan Trust database (<http://>

AS = ankylosing spondylitis; IL = interleukin; MHC = major histocompatibility complex; SNP = single nucleotide polymorphism; TNF = tumor necrosis factor.

hla.alleles.org/class1.html) now reports 46 B27 subtypes, making B27 one of the more polymorphic of HLA-B alleles.

The significance of the B27-subtype studies is that they provide important information helpful in research into the mechanism by which B27 causes AS. The fact that B27 subtypes exist on very different MHC haplotypes makes the chance of a B27-linked gene being primarily responsible for the association of B27 with AS much less likely. The sequence differences between disease-associated subtypes point to regions of B27 that are less important in causing susceptibility to AS, whereas sequence differences in subtypes that are differentially associated with AS are likely to be in regions critical to the mechanism by which B27 increases the risk of AS. For most subtypes too few carriers have been identified to determine whether they are disease-associated. For some subtypes, however there is evidence of differential strength of association with AS. AS has been reported to occur with the following subtypes: B\*2701, B\*2702 [11], B\*2703 [12], B\*2704 [13], B\*2705 [11], B\*2706 [14], B\*2707 [15], B\*2708 [15], B\*2709 [16], B\*2710 [17], B\*2714 [18], B\*2715 [18], B\*2719 [19] and B\*2730 [20].

The recent report of cases of AS occurring in individuals carrying the B\*2709 subtype has raised the question of whether this subtype is protective against AS, or is simply less strongly associated with the disease. No case of AS had been reported with B\*2709 until these reports, suggesting that this subtype is protective for AS [21]. Three cases have now been reported with axial AS in B\*2709 carriers. One woman with ulcerative colitis and pre-radiographic AS has been reported. This lady may have developed AS as a consequence of other susceptibility factors related to ulcerative colitis, such as genetic variation in *IL23R*, and her HLA-B\*2709 carriage may not have been involved in her developing AS [22]. In a second AS case reported from Sardinia carrying B\*2709, the other HLA-B allele was B\*1403, potentially explaining the development of AS [23]. B\*1403 has also been reported to possibly be associated with AS [24,25]. This subtype has similar sequence to B27 around the B pocket of the peptide binding groove, carrying a cysteine residue at position 67. This residue is thought to be involved in B27-homodimer formation, potentially explaining the association of these alleles with AS. A third case has been reported from Tunisia, although no clinical details or other genetic information were available [16]. These cases confirm that whilst B\*2709 has a weaker association with disease in comparison with B\*2705, it is not absolutely protective for AS

The B\*2706 subtype similarly has been shown to be less strongly associated with AS than B\*2704 in South-East Asia [13]. As with B\*2709, however, cases of AS have been reported in B\*2706 carriers, confirming that this subtype is also not protective against AS but rather has a weaker strength of disease association [26]. This is consistent with

previous family studies that demonstrate B\*2704/\*2706 compound heterozygotes can still develop AS [27]. The Taiwanese study and others have also suggested that B\*2704 may be more strongly associated with AS than B\*2705.

These studies suggest that there is a hierarchy of strength of association of B27 with AS, with B\*2704 equally or more strongly associated than B\*2705, B\*2702 and probably B\*2707, which are more strongly associated than either B\*2706 or B\*2709. The author also thinks it is likely that B\*2703 is less strongly associated with disease than B\*2705, but sufficient data in African Americans do not yet exist to make this conclusion firm. None of the other subtypes are sufficiently common for any comment to be made about their relative strength of association with AS. Most studies to date reporting subtype frequencies have been quite limited, with fewer than 200 AS cases reported. Much larger studies of different ethnic group should be encouraged in order to clarify the level of association of less frequent B27 subtypes, as this could be very informative with regard to the mechanism of association of B27 with AS.

HLA-B27 is clearly not the only HLA-B allele associated with AS. Association with HLA-B60 has been reported by many groups in both B27-positive cases and B27-negative cases [28-30]. The strength of association of HLA-B60 with AS is much weaker than the association with B27, with an odds ratio of 3.6 [29]. It is uncertain whether HLA-B60 is also disease-causing itself, or is a marker of an MHC haplotype bearing other disease-causing genes. This is also the case for B\*1403, for which the strength of evidence for its genetic association is modest and not fully established.

#### **Major histocompatibility genes other than HLA-B**

There is strong evidence from studies of association of other MHC class II and class III genes with AS for the existence of other MHC-encoded AS susceptibility genes. Pinpointing the specific genes involved is a challenging task, given that the MHC is characterized both by extreme diversity of specific loci, and by extreme and complex linkage disequilibrium patterns that must be tightly controlled for to avoid confusing findings due to linkage disequilibrium from true association. Several small association studies have implicated other MHC genes in AS, although the studies have been too small and targeted to determine whether these are primary associations or are due to linkage disequilibrium with other loci (reviewed in [31]).

Studying MHC markers (SNPs and microsatellites) on HLA-B27-DRB1 haplotypes, we recently showed convincing evidence for the existence of non-B27 MHC genes in AS carried on both B27-positive and B27-negative strands [32]. Comparing B27-matched case and control haplotypes, strong association was observed with DRB1 irrespective of whether the haplotype carried HLA-B27 (B27-positive strand,

$P=4 \times 10^{-4}$ ; B27-negative strand,  $P=5 \times 10^{-8}$ ). The effect size of these associations is substantial, with the attributable risk from these haplotypes being 34%. This study, although quite large, was not adequately powered to identify the specific gene variants involved.

This evidence strongly suggests that further studies of the MHC for AS-susceptibility genes other than B27 are likely to be quite fruitful, although the sample sizes required to differentiate linkage disequilibrium effects from true association are substantial. A model example of how to perform such studies comes from research in type 1 diabetes MHC genetics, where convincing evidence that HLA-A and HLA-B are associated with disease susceptibility has recently been reported in a disease hitherto considered HLA class II restricted [33]. To achieve this evidence, over 13,000 controls were studied using dense SNP maps, and the analysis was controlled for linkage disequilibrium with known diabetes HLA class II associations. By contrast, most studies of AS have either been quite small, involving a few hundred samples, or have had inadequate control for the HLA-B associations of the disease (that is, B27, B60 and potentially other HLA-B alleles). Whilst smaller studies may provide tantalizingly suggestive evidence of specific MHC genes associated with AS, and may actually be correct, the past record of such studies in AS and other rheumatic diseases such as RA indicates that these findings are rarely replicated.

### Nonmajor histocompatibility complex genes and ankylosing spondylitis

As discussed in the Introduction, twin and family studies have long suggested the existence of non-MHC susceptibility genes for AS. In 2007 a study of 14,500 nonsynonymous SNPs (that is, single-base polymorphisms that change the amino acid sequence of a protein) by the Wellcome Trust Case Control Consortium and the Australo-Anglo-American Spondyloarthritis Consortium made the first robust identifications of non-MHC susceptibility genes in AS, with the identification of the associations with *ERAP1* and *IL23R* [10]. This study of 1,000 AS cases and 1,500 healthy controls was at the time the largest association study in AS. Nonetheless it still only screened <15% of the human genome, and was only powered to identify moderately large genetic effects compared with the magnitude of genetic associations that are typically found in common diseases.

The association of AS with *IL23R* has been replicated in a Spanish population [34], in a Canadian population [35] and in a further English study [36], but as yet no replication has been reported in Asian populations. To date, no replication study of *ERAP1* (formerly known as *ARTS1*) has been published in AS, although associations have been reported with type 1 diabetes [37] and cervical cancer [38].

*IL23R* has been shown to have pleiotropic effects, also being associated with inflammatory bowel disease [39,40] and

psoriasis [41]. The primary associated polymorphism in these diseases is thought to be the nonsynonymous SNP, rs11209026, although that has yet to be formally established. No association of *IL23R* was seen with Crohn's disease in a Japanese study, and it was noted that rs11209026 was nonpolymorphic in that population [42], potentially explaining the lack of association of the gene with the disease in that ethnic group.

This genetic finding has led to substantial research activity into the involvement of the TH17 lymphocyte pathway in AS. Hitherto TH17 had been studied in mouse models of multiple sclerosis (experimental autoimmune encephalomyelitis) and rheumatoid arthritis (collagen-induced arthritis), yet to date there is little to no evidence for either disease that genetic variation in TH17-related genes such as *IL23R*, *STAT3* or *JAK2* influences disease susceptibility. This lack of evidence highlights again the uncertain relevance of many mouse disease models to the human conditions they may phenotypically resemble.

Research into the mechanism by which *IL23R* polymorphisms influence susceptibility to autoinflammatory diseases is in its early days, and it is not yet clear which cell type is mainly functionally affected by the *IL23R* polymorphisms. *IL23R* is expressed on several immunological cell types in addition to TH17 cells, including macrophages, microglia, natural killer cells and natural killer T cells, and it is not yet clear which cell type is primarily affected by the *IL23R* disease-associated variant. The demonstration of increased TH17 lymphocyte numbers [43] and serum IL-17 levels [44] in AS is consistent with a direct role of TH17 lymphocytes in AS, but formal proof that this is the critical functional cellular subset is awaited. Nonetheless, inhibition of TH17 activity is being investigated as a possible therapeutic approach for autoimmune disease. Antibodies to the IL-12p40 subunit (the shared IL-23/IL-12 subunit) have been successfully trialed in psoriasis [45,46] and in Crohn's disease [47], and trials with anti-IL-17 antibodies are shortly to commence in AS.

As with *IL23R*, we have much yet to learn about the association of *ERAP1* with AS and its underlying mechanism. *ERAP1* may affect disease risk either through its function to trim peptides prior to loading into nascent HLA class I molecules, or alternatively through its role in cleaving pro-inflammatory cytokine receptors from the cell wall, including TNF receptor 1, IL-1 receptor 2 and IL-6 receptor. There is clear *in vivo* evidence that *ERAP1* is important in HLA-class-I-mediated immunity, with *ERAP1*<sup>-/-</sup> mice being shown more prone to infection with *Toxoplasma gondii*, a vacuolar parasite, due to defective presentation of parasite antigen by the murine HLA class I system to CD8 T cells [48]. The effect on cytokine receptor cleavage has been debated and as yet there are no *in vivo* data to support this function. The key next steps are to determine the main associated variant(s) of *ERAP1*, and to assess its expression in health and disease. *ERAP1*

expression is strongly affected by *cis*-acting SNPs, and there are also multiple splice variants of *ERAP1* known; whether AS-associated variants affect either of these properties is unknown. Resolution of the structure of *ERAP1* would also probably be highly informative about its true function.

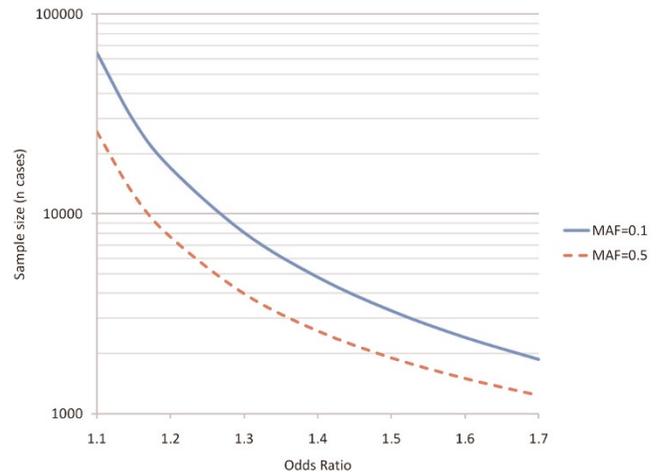
Many other regions and genes have been implicated in candidate gene or linkage mapping studies, which will not be reviewed in depth here. Of these, the strongest associated region is the IL-1 complex on chromosome 2p. Association with this region has been reported by several groups [49-55], making it unlikely that this is a false positive finding – although definitive statistical evidence establishing the association cannot yet be said to have been achieved. The primary associated gene remains unknown.

### Where to next in ankylosing spondylitis genetics?

Clearly the next major steps in defining the genes involved in AS are the completion of genomewide scans for susceptibility to the disease and for its clinical manifestations. Initial scans for disease-susceptibility loci are well advanced, but the record in other diseases indicates that further scans in new cohorts both in the same and different ethnic groups are likely to be further informative. That is, the first susceptibility scans in AS should not be expected to be definitive. Most scans nowadays aim for ~2,000 cases and controls, but as can be seen from Figure 1 this only provides adequate power for quite high odds ratios (additive odds ratios of >1.5 to 1.7 depending on the minor allele frequency). Such large genetic effect sizes are infrequent in common human diseases.

Scans will also probably be fruitful when investigating disease manifestations such as occurrence of uveitis, although it is not yet known whether that is independently heritable from AS. There is evidence of strong heritability (>60%) for radiographic change in AS, age of disease onset, and severity scores such as the Bath Ankylosing Spondylitis Disease Activity Index and the Bath Ankylosing Spondylitis Functional Index. These quantitative traits will require even larger numbers of cases to study, since they will be investigated as cohort studies rather than in a case-control design, where the costs are generally lower because of the use of previously genotyped historic controls. A further difficulty will be that the measures available to characterize disease manifestations, such as the radiographic scores, have been designed with their intended use as outcome measures in clinical trials, and it is readily apparent that, despite their heritability, they do not accurately assess the disease process in AS. For example, the radiographic modified Stoke Ankylosing Spondylitis Spine Score provides equal weighting to radiographic disease in the cervical and lumbar spine, when there is major diversity amongst patients in the extent to which these sites are affected. It is to be hoped that future AS outcome measures will be developed aiming to more closely assess the biological processes

Figure 1



Sample size requirements for genomewide scans. Sample size (number of cases, assuming equal number of controls) to achieve 80% power at  $\alpha = 5 \times 10^{-7}$ , assuming  $D' = 0.8$  and that the minor allele frequency of the marker SNPs and disease-associated variants are equal. MAF, minor allele frequency.

involved in AS pathogenesis rather than the more limited scope of utility for intervention studies.

In most human diseases it has been accepted by researchers that international collaboration will be required to achieve the requisite sample sizes and to not waste resources. The Wellcome Trust Case Control Consortium/Australo-Anglo-American Spondyloarthritis Consortium study has encouraged collaboration by making all genotype data in cases and controls publicly available to *bona fide* researchers [10], an unprecedented gesture in AS research. This open approach is designed to ensure that the greatest value is made of the public resources expended in these studies and, perhaps more importantly, of the DNA samples and clinical information provided by our most important stakeholders, the AS patient community.

### Competing interests

The author declares that they have no competing interests.

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