Progress in the genetics of ankylosing spondylitis

Matthew A. Brown

Abstract

Ankylosing spondylitis (AS) is a common, highly heritable, inflammatory arthropathy. In addition to being strongly associated with HLA-B27, a further 13 genes have been robustly associated with the disease. These genes highlight the involvement of the IL-23 pathway in disease pathogenesis, and indicate overlaps between the pathogenesis of AS, and of inflammatory bowel disease. Genetic associations in B27-positive and -negative disease are similar, with the main exception of association with ERAP1, which is restricted in association to B27-positive cases. This restriction, and the known function of ERAP1 in peptide trimming prior to HLA Class I presentation, indicates that HLA-B27 is likely to operate in AS by a mechanism involving aberrant peptide handling. These advances point to several potential novel therapeutic approaches in AS.

Keywords: ankylosing spondylitis; spondyloarthritis; genome-wide association study; SNP; heritable

INTRODUCTION

Ankylosing spondylitis (AS) is the prototypic disease of a group of arthropathies called the seronegative spondyloarthropathies. In addition to AS these include psoriatic arthritis, colitic arthritis (in association with either Crohn’s disease or ulcerative colitis) and reactive arthritis. These conditions share an association with HLA-B27, a predisposition to axial arthritis involving the spine and pelvis. They are characterized histopathologically by the presence of inflammation at the site of insertion of tendons or ligaments into bone (the enthesis), and the tendency for inflammation to lead to new bone formation in affected joints. In combination, the spondyloarthropathies are amongst the most common forms of inflammatory arthritis, with a prevalence of up to 1.31%, compared with a prevalence of rheumatoid arthritis of 0.6%, in North Americans [1].

The major involvement of genetic factors in the risk of developing AS has been known for several decades, since the observation of the familial nature of the disease [2], and then the discovery of the association of HLA-B27 [3–5]. Twin studies have formally estimated the heritability of susceptibility to the disease as >90% [6, 7], indicating that in the environment of developed countries where the twin studies were performed, the risk of developing the condition is almost entirely inherited. This implies that the environmental trigger for the disease is likely to be ubiquitous, something supported by the fact that the condition does not occur in epidemics, and has a fairly constant global prevalence in relationship to the prevalence of HLA-B27, with few exceptions. The condition can also arise after bacterial infections of the urinary tract or gut in the setting of chronic reactive arthritis, suggesting that bacterial exposure may similarly induce primary AS. In different environments the heritability of the disease may differ, as is suggested by the observation that whilst AS is rare in Africans [8], even amongst those carrying HLA-B27, American–Africans do develop the disease.

A major clue as to the genetic etiology of AS comes from the observation that the three conditions AS, inflammatory bowel disease (IBD) and psoriasis, tend to run together in families, suggesting shared pathogenic mechanisms. In first-degree relatives of cases with AS, there is a 3-fold increased risk of

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IBD [9]. About 70% of AS cases have subclinical terminal ileitis [10], and overt IBD occurs in ~10% of AS cases. The prevalence of spondyloarthritis is increased in IBD, with axial or peripheral arthritis occurring in up to 30% of IBD cases [11]. Similarly, psoriasis occurs in up to 10% of AS cases compared with the prevalence of psoriasis of 2–3% in the general population. Of psoriasis cases, 7–42% develop an associated inflammatory arthritis, frequently spondyloarthritis [12–14].

Recent advances in the genetics of AS have greatly increased our understanding of the pathogenesis of the disease, including regarding the potential mechanisms by which HLA-B27 may induce AS. HLA-B27 carriage is present in >80% of white European AS cases, compared with ~8% of healthy controls [15]. Only ~1–5% of HLA-B27 carriers develop AS, however [16–18]. It is thought that other genes play a major role in determining which B27-positive individuals develop the condition [6], with modeling in families suggesting the involvement of a moderate number of genes with significant effects in addition to HLA-B27 [19]. In recent years, improvements in genotyping and in study design have revolutionized the field of common disease genetics in general, and have had a major impact in AS, where there have now been 13 genes, other than HLA-B, associated with the disease. These findings provide fascinating insights into the pathogenesis of AS, and validate the hypothesis-free genetics approach to AS-research.

**MAJOR HISTOCOMPATIBILITY COMPLEX ASSOCIATIONS OF AS**

Although the recent wave of gene discoveries have involved non-MHC (major histocompatibility complex) loci, it is clear that the MHC is the major disease-associated locus in AS. Linkage studies in families have repeatedly confirmed strong linkage of the MHC with AS, whereas outwith the MHC, only one locus on chromosome 16q is considered to be an established, replicated locus [20–25].

Despite extensive research over the past four decades, the mechanism by which HLA-B27 includes AS is not established. Theories explaining the mechanism underlying the association include:

- Canonical theories, explaining the association of HLA-B27 with AS in terms of the known function of HLA-Class I molecules in peptide presentation to CD8 T-lymphocytes. These include the ‘molecular mimicry’ and ‘arthritogenic peptide’ theories.

- Non-canonical mechanisms. These include:
  - The induction of endoplasmic reticulum stress due to the propensity of HLA-B27 to fold slowly and inefficiently,
  - The occurrence of abnormal forms of HLA-B27 such as homodimers, leading to aberrant immunological reactions,
  - The linked gene theory, which proposes that HLA-B27 is merely a marker for a nearby true AS-susceptibility locus.

The strong association of HLA-B27 with AS in diverse populations strongly suggests that HLA-B27 is the true disease-associated allele in AS, and some support is lent to this by the occurrence of spondyloarthritis in B27-transgenic rats [26]. Furthermore, two subtypes of HLA-B27, B*2706 and B*2709, have been shown to have significantly reduced, or neutral, association with AS [27, 28]. This suggests that the HLA-B27 sequence variations between these subtypes and those associated with AS are likely to be directly involved in AS-risk, although it is also possible that these subtypes have different linkage disequilibrium with another true AS-susceptibility gene.

Recent genetic studies have provided strong evidence that HLA-B is indeed the true AS-associated variant. Dense MHC SNP mapping by the Wellcome Trust Case-Control Consortium (2) and Australo–Anglo–American Spondyloarthritis Consortium (WTCC2-TASC), in a cohort of 3023 AS cases and 9401 controls, identified strong association around HLA-B with AS. A SNP rs4349859 was identified which tagged HLA-B27 within the accuracy of HLA-B27 genotyping (sensitivity 98%, specificity 99%). A second SNP, rs13202464, also showed high sensitivity (98.7%), but slightly lower specificity (98.7%), for HLA-B27 than rs4349859. Controlling for rs4349859, no significant residual association was seen with MHC SNPs, indicating that it is unlikely that polymorphisms in any other locus within the MHC have a significant influence on AS-susceptibility. The SNP rs4349859 lies 41 kb centromeric of HLA-B, and 5.4 kb telomeric of MICA, which neighbors HLA-B. MICA has previously been associated with AS [29, 30], and thus was a potential ‘linked gene’.
Studies of the ability of rs4349859 to tag HLA-B27 in different world populations and with different HLA-B27 subtypes indicated that the SNP tagged white European B27-subtypes well (including B*2702, B*2705, B*2708 and B*2709), but did not tag the African subtype B*2703, or the Asian subtypes B*2704, B*2706 or B*2707. As it did tag B*2709, which is not AS-associated, these findings indicate that rs4349859 tags white European HLA-B27 subtypes, but not AS itself.

These findings indicate that HLA-B27 itself is involved in AS, and not a nearby linked gene. They also provide a fascinating insight into the evolution of HLA-B27 subtypes, indicating that the founder mutation that became the polymorphism rs4349859 occurred in a common ancestor of nearly all HLA-B27 carriers in white European populations, and of nearly all Asians carrying HLA-B*2705. In contrast, the genetic events that led to the development of other HLA-B27 subtypes must have occurred prior to the development of rs4349859.

Additionally, the discovery of a strong tagSNP for European HLA-B27 subtypes provides a cheap and easily genotyped alternative to HLA-B27 typing in this population. HLA-B27 typing is complex and expensive, and therefore not optimal for widespread use. SNP genotyping by contrast is simple, cheap and easily automated, and thus rs4349859-typing should be of significant utility in clinical practice, and potentially, in population screening.

NON-MHC GENETICS OF ANKYLOSING SPONDYLITIS

The development of low-cost (per genotype), high accuracy, microarray based SNP genotyping, and of sophisticated study design and analysis approaches, has in the past 5 years led to a revolution in common disease genetics, largely kicked off by the publication of Wellcome Trust Case-Control Consortium (WTCCC) GWAS in 2007 [31]. GWAS studies in autoimmune diseases have been particularly successful, likely because the genetic variants involved in these diseases have been subject to strong evolutionary pressure related to protection from infection, and possibly, cancer. The first large-scale SNP study in AS led to the identification of associations with \textit{IL23R} and \textit{ERAP1} [32]. This study only involved non-synonymous SNPs that change the translated amino acid sequence. Early in the GWAS-era, it became apparent that most associations actually lay out with the coding regions of genes, and thus this early AS study covered only a small proportion of genetic ‘space’ potentially involved in the disease. This study has been followed by two further GWAS. First, the Australo–Anglo–American Spondyloarthritis Consortium (TASC) reported a GWAS of 2053 AS cases and 5140 controls reported significant association of two intergenic regions, chromosome 2p15 and 21q22, with AS, and two further genes, \textit{ANTXR2} and \textit{IL1R2} [33]. Follow-up studies of these two studies provided suggestive evidence that \textit{CARD9} and \textit{TRADD} were also AS-associated [34, 35]. A study of genetic overlaps between Crohn’s disease and AS then identified robust association of SNPs nearby \textit{KIF21B}, \textit{IL12R}, \textit{STAT3} and suggestive associations with \textit{CDKAL1}, \textit{LRRK2/MUC19}, and an intergenic region on chromosome 13q14 [36]. Recently, the WTCCC2-TASC study described above identified additional associations with \textit{RUNX3}, \textit{TNFR1}, \textit{PTGER4} and \textit{TBKBP1}, as well as confirming the previous hits listed above (Table 1).

\textbf{ERAP1}

\textit{ERAP1} was the first non-MHC gene for which definitive AS-association was observed [32]. Although initial studies were underpowered to exclude associations with the neighboring genes \textit{CAST} and \textit{ERAP2}, those have now been excluded. \textit{ERAP1} variants are associated with AS in a wide variety of ethnic groups, including Han Chinese [37, 38], Koreans [39], Portuguese [40] and Hungarians [41]. The diverse ethnic associations, involving the same main haplotype, indicate a common variant underlying the association, rather than multiple rare variants. The WTCCC2-TASC study demonstrated that the main associated variant in white Europeans in rs30187 (Lys528Arg), and that a second haplotype bearing the SNPs rs10050860 (Asp575Asn) and rs17482078 (Arg725Gln) was independently also disease-protective. The latter haplotype could not be broken down genetically, as in white Europeans the two SNPs were in perfect linkage disequilibrium; transethnic studies may be helpful here.

\textit{ERAP1} was initially thought to trim cytokine receptors from cell walls, this has now been shown not to be a significant physiological role. Studying \textit{ERAP1}\textsuperscript{−/−} mice in comparison with wild-type controls, the WTCCC2-TASC group showed that
TNFR and IL-6 R levels in supernatants of cultured splenocytes, either unstimulated or stimulated, did not vary according to ERAP1 status. Thus the known role of ERAP1 as a molecular ruler, trimming peptides down to nine amino acids in length before presentation by HLA Class I molecules, is the likely function involved in the association of ERAP1 with AS. Using recombinant ERAP1, it was shown that in vitro rs31087 and rs17482078 were associated with markedly reduced peptide trimming, whereas rs10050860 and other non-synonymous variants were neutral.

This finding is of critical importance in determining the mechanism of association of HLA-B27 and AS. If true, this is consistent with the reduced function of protective ERAP1 variants on AS, HLA-B27 misfolding should be reduced where ERAP1 function is diminished. Data demonstrating a mechanistic association between ERAP1 and HLA-B27 homodimer association will need to be presented to investigate theories linking HLA-B27 homodimer formation with AS. Lastly, the demonstration that the association of ERAP1 variants with psoriasis in HLA-Cw6-positive, but not Cw6-negative [46], cases, suggests that the mechanism by which HLA-Cw6 is involved in psoriasis is similar to that by which HLA-B27 is involved in AS. Comparison of data from the behaviour of these two HLA Class I proteins, particularly with regard to non-canonical mechanisms of action such as misfolding and homodimer formation, are likely to be instructive.

Clearly more research is required in this field, including examining the influence of inhibiting or stimulating ERAP1 expression/function in mouse models of AS. If the in vitro suggestion is true, this finding raises the potential of ERAP1 inhibitors as therapeutic agents in AS.

### Table 1: Summary of genetic associations with AS

<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>Discovery study</th>
<th>Level of confidence</th>
<th>Contribution to AS heritability (%)</th>
<th>Likely function</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-B27</td>
<td>6p21.3</td>
<td>[3–5]</td>
<td>Confirmed</td>
<td>23.3</td>
<td>Presentation of peptides to T cells</td>
</tr>
<tr>
<td>IL23R</td>
<td>1q31</td>
<td>[32]</td>
<td>Confirmed</td>
<td>0.31</td>
<td>Activation/differentiation of IL-23 R expressing cells</td>
</tr>
<tr>
<td>RUNX3</td>
<td>1q36</td>
<td>[62]</td>
<td>Confirmed</td>
<td>0.12</td>
<td>Reduction in CD8 lymphocyte counts</td>
</tr>
<tr>
<td>KIF21B</td>
<td>1q32</td>
<td>[36]</td>
<td>Confirmed</td>
<td>0.25</td>
<td>Unknown</td>
</tr>
<tr>
<td>IL2Q22</td>
<td>2q22</td>
<td>[33]</td>
<td>Confirmed</td>
<td>0.035</td>
<td>Unknown</td>
</tr>
<tr>
<td>2q15</td>
<td>2q15</td>
<td>[33]</td>
<td>Confirmed</td>
<td>0.543</td>
<td>Unknown</td>
</tr>
<tr>
<td>IL1R2</td>
<td>2q11</td>
<td>[33]</td>
<td>Confirmed</td>
<td>0.12</td>
<td>Influence on IL-1 cytokine response</td>
</tr>
<tr>
<td>ANTRX2</td>
<td>4q21</td>
<td>[33]</td>
<td>Confirmed</td>
<td>0.054</td>
<td>Unknown</td>
</tr>
<tr>
<td>PTGER4</td>
<td>5p13</td>
<td>[62]</td>
<td>Confirmed</td>
<td>0.052</td>
<td>Induction of IL23 expression, in turn driving activation/differentiation of IL-23 R expressing cells. Bone anabolism.</td>
</tr>
<tr>
<td>ERAP1</td>
<td>5q15</td>
<td>[32]</td>
<td>Confirmed</td>
<td>0.34</td>
<td>Peptide trimming prior to HLA Class I presentation</td>
</tr>
<tr>
<td>IL2B</td>
<td>5q33</td>
<td>[36]</td>
<td>Confirmed</td>
<td>0.11</td>
<td>Activation/differentiation of IL-23 R expressing cells</td>
</tr>
<tr>
<td>CARD9</td>
<td>9q34</td>
<td>[33, 34]</td>
<td>Confirmed</td>
<td>0.034</td>
<td>T&lt;sub&gt;H&lt;/sub&gt;17 activation after β-glucan exposure</td>
</tr>
<tr>
<td>TNFR/LTBR</td>
<td>12p13</td>
<td>[33, 71]</td>
<td>Confirmed</td>
<td>0.075</td>
<td>TNF signaling</td>
</tr>
<tr>
<td>TBKBP1</td>
<td>17q21</td>
<td>[62]</td>
<td>Confirmed</td>
<td>0.054</td>
<td>TNF signaling</td>
</tr>
<tr>
<td>TNFSF15</td>
<td>9q32</td>
<td>[63]</td>
<td>Suggestive</td>
<td></td>
<td>T&lt;sub&gt;H&lt;/sub&gt;17 activation/differentiation</td>
</tr>
<tr>
<td>TRADD</td>
<td>16q22</td>
<td>[33]</td>
<td>Suggestive</td>
<td></td>
<td>TNF signaling</td>
</tr>
<tr>
<td>STAT3</td>
<td>17q21</td>
<td>[36, 71]</td>
<td>Suggestive</td>
<td></td>
<td>Activation/differentiation of IL-23 R expressing cells</td>
</tr>
<tr>
<td>KIR3DL1/F</td>
<td>KIR3DS1</td>
<td>19q13</td>
<td>[67]</td>
<td>Suggestive</td>
<td>NK cell inhibition/activation</td>
</tr>
</tbody>
</table>

Level of confidence—Confirmed' indicates P < 5 × 10⁻⁷ in one study, with replication in a second cohort. 'Suggestive' indicates 10⁻⁵ < P < 5 × 10⁻⁷ in one study, or P < 5 × 10⁻⁷ but no replication. Contribution to AS heritability is calculated from findings of the confirmation arms of the WTCCC2-TASC GWAS [62] or TASC GWAS [33].
**IL23R and associated genes**

The finding of association of IL23R with AS was the first indication of the involvement of the pathway that this gene tags in the development of this condition. Since then, several other genes in the pathway have been associated with the disease, including IL12B, STAT3, CARD9 and PTGER4. Whilst these genes have many functions, their shared association with AS and the fact that they all interact through one pathway, suggests that it is their actions on that pathway by which they influence AS. IL12B encodes IL-12p40, a component of both the heterodimeric cytokines IL-12 and IL-23. STAT3 encodes part of the JAK-STAT signaling pathway downstream of IL-23 R; of note, association has been demonstrated between JAK2, which encodes the partner of STAT3 in this pathway, and Crohn’s disease [47], and suggestive association has been seen with AS [48]. CARD9 encodes a component of the dectin-1 innate immunity signaling pathway. Dectin-1 recognizes β-glucan, a component of fungal and some bacterial cell wall, and signals to the nucleus through CARD9, leading to activation of TH1 and TH17 lymphocyte subsets, thereby linking the innate and adaptive immune systems [49]. This is particularly relevant given the recent demonstration that in skg mice, β-glucan exposure induces spondyloarthritis, episodic unilateral uveitis, and IBD resembling Crohn’s disease [50]. PTGER4 is also associated with Crohn’s disease [51].

The association of PTGER4 with AS is particularly fascinating. PTGER4 encodes the PGE2EP4 receptor, one of four known PGE2 receptors (named EP1-4), which have different effects and are expressed in different tissues. Both EP2 and EP4 are G-protein coupled receptors, being linked with the stimulatory Gαs subunit, activating adenylate cyclase leading to increases in cAMP production [52]. EP4, but not EP2, also signals through phosphatidylinositol 3-kinase (PI3K), inhibiting protein kinase A. EP1 acts by influencing intracellular calcium, and protein kinase C, and EP3 signals via the inhibitory Gαi subunit. PGE2 is produced in response to dectin-1 recognition of β-glucan, and both PGE2 and PGE2EP4 have been shown to stimulate dendritic cell production of IL-23, in turn activating TH17 lymphocytes, and potentially other IL-23 R expressing cell types [53]. PGE2EP4 agonists have been shown to restore IL-17 production in response to Candida albicans exposure, where PGE2 synthesis has been blocked using NSAIDs [54]. As mentioned above, β-glucan exposure in skg mice induces spondyloarthritis in a TH17 dependent model; the involvement of PGE2EP4 in this model warrants further study. Collagen-induced arthritis, an IL-23 dependent inflammatory arthritis model, is significantly attenuated in PGE2EP4/4 knockout mice [55], and PGE2EP4 inhibition has been shown to attenuate CIA in both prophylactic and therapeutic models [53]. PGE2 is also part of the mechanostat, the biological network that transduces mechanical stress to influence bone formation and resorption. Repetitive mechanical stress has been shown to upregulate PGE2 production at entheses, and this in turn has been shown to induce new bone formation [56]. Thus PGE2EP4 links inflammation and new bone formation at entheses, something of obvious potential relevance to AS pathogenesis. There is modest evidence that non-steroidal anti-inflammatory drugs, which inhibit PGE2 production, may retard the bony ankylosis which characterizes the condition, consistent with a role for prostaglandins in the development of ankylosis in AS [57]. More specific targeting of EP4 receptors therefore represents an exciting potential therapeutic approach.

**KIF21B**

The mechanism underlying the association of KIF21B and AS is unclear. KIF21B encodes a member of the kinesin family involved in neuronal transport of cellular components. It is widely expressed, but its function in non-neuronal tissue is unclear. KIF21B is also associated with Crohn’s disease and multiple sclerosis [47, 58], and another member of the same family, KIF5A, is in a region associated with type 1 diabetes [59] and rheumatoid arthritis [60], and is close to a multiple sclerosis susceptibility locus [61]. This suggests that this family has some immunological function, which remains as yet unknown.

**TNF-pathway genes**

Genetic studies provide strong evidence of the involvement of TNF-pathways in AS pathogenesis. TNF-antagonists are highly effective in suppressing inflammation in AS, and mice over-expressing TNF develop spondyloarthritis [62]. In the WTCCC2-TASC study, association was observed with SNPs at chromosome 12p13 between the genes LTBR (lymphotoxin beta receptor) and TNFRSF1A (tumor necrosis factor receptor 1, TNFR1) [63]. A mouse model with constitutive over-expression
of TNF that develops IBD and spondyloarthritis has been reported, in which the arthritis has been shown to be dependent on TNFR1 expression, and in which TNFR1 expression in mesenchymal tissue alone is sufficient to permit disease [62]. This is consistent with a role for TNFR1 in AS, but further studies will be required to determine if the genetic polymorphisms at this locus are associated with AS because of effects on LITBR or TNFR1, or both. Association in the same study was observed at chromosome 17q21 near TBKBP1 (encoding TBK binding protein 1), a component of the TNF receptor signaling pathway. Association has also been observed across a broad region of chromosome 16q, a locus encompassing TRADD (tumor necrosis factor receptor type 1 associated death domain protein), in several studies. Although TRADD is the outstanding candidate gene at the locus, this has yet to be fully established.

In a study of families with undifferentiated spondyloarthritis (USpA), rather than AS per se, association was reported with SNPs nearby TNFSF15 [64]. This gene has previously been associated with Crohn’s disease [65], but the SNPs associated with USpA were different. No association was seen with TNFSF15 in a recent study of Crohn’s disease genes in AS [36], and no association was seen either with the Crohn’s disease associated SNPs or the USpA associated SNPs in either of the two GWAS studies reported to date in AS [33, 63]. This association is thus of uncertain significance. It will be further investigated by the Immunochip study described below.

**RUNX3**

The association of RUNX3 with AS provides direct evidence of a role for CD8 lymphocytes in the disease pathogenesis. Expression of RUNX3 in immature CD4/CD8 double positively lymphocytes is triggered by IL–7 R signaling, in turn leading to suppression of CD4 and upregulation of CD8 expression [66]. The polymorphisms associated with AS were noted by the WTCCC2-TASC group also to be associated in healthy controls with reduced CD8 counts [63]. The same investigators then showed that AS cases had lower CD8 counts than age- and gender-matched healthy controls. Suggestive association of SNPs nearby IL7R was also observed in the WTCCC2-TASC study. Although RUNX3 has multiple functions, these findings suggest that variants influencing CD8 lymphocyte development also influence AS risk, providing further support for disease models in which HLA-B27 operates in AS by presenting peptides to CD8 lymphocytes.

**Other genes of interest**

Several association studies have been reported investigating the role of KIR genes in susceptibility to AS. For the most part these have either been negative, or too small to be definitive (reviewed in [67]). A recent study has reported a protective effect of the allele KIR3DL1.F that encodes an inhibitory KIR, and positive association with KIR3DS1, encoding an activating KIR, in AS, across several different cohorts, and achieving strong statistical significance overall (P < 10^{-7}) [68]. This is an extremely complex area to genotype, and will be addressed in a very large sample size by the Immunochip consortium (see below). If confirmed it will be an exciting observation, suggesting a further mechanism by which the innate immune system may be involved in the pathogenesis of AS.

**HLA-B27-negative AS**

There has always been a concern that HLA-B27 negative AS may have a different etiopathogenesis to B27-positive disease. Very few families have been reported with B27-negative disease, raising the possibility that genetics had at most a small role in familiality of the disease. B27-negative cases also had later age of onset [69] and were less likely to respond to TNF-inhibitor medications [70]. The WTCCC2-TASC study has demonstrated and replicated association of B27-negative AS with IL23R, LITBR/TNFR1, KIF21B, and the 2p15 and 21q22 gene deserts [63]. These are the first loci confirmed in B27-negative disease, and indicate significant genetic overlap between B27-positive and -negative disease forms. This confirms that the two conditions have overlapping etiopathogenesis.

**IMMUNOCHIP**

Organised by the International Genetics of Ankylosing Spondylitis Consortium (IGAS), a case-control association study involving >13 000 AS cases and >20 000 healthy controls is underway, using a 200 000 SNP microarray termed Immunochip. This chip is designed to cost-efficiently perform follow-up genetic studies in immunogenetics conditions, including deep replication of immunogenetics conditions, investigation of pleiotrophic genetic effects between
related conditions, and fine-mapping of established loci (reviewed in [71]). The chip also contains SNPs designed to impute HLA types, and has a dense coverage of the KIR/LILR locus on chromosome 19, from which imputation methods for KIR genotypes are being developed by the Immunochip consortium. This study will provide unprecedented data regarding common genetic variants and AS, and of rare-variants at known loci. A weakness of the chip is that it was designed using white European genetic data, and thus although it will be informative in Asians, its coverage won’t be as good in that ethnic group. Therefore there is still a significant need for GWAS studies in Asian populations. Furthermore, the chip will not study rare variants at loci not already known to be associated with AS via common variant studies. Sequencing studies will be required to pick up such variants.

CONCLUSION
The rapid pace at which genetics studies are advancing our understanding of the pathogenesis of AS is rekindling the excitement of the early 1970s, when the discovery of the association of HLA-B27 with the disease first raised the possibility that it would be solved. Certainly the findings reviewed here provide firm foundations for hypothesis driven research in the field, and point to exciting potential therapeutic targets, some of which are already being targeted in trials. For example, the discovery of the association of the IL23R with AS is responsible for the current trials of anti-cytokine blockade of the IL-23 and its downstream pathway. Whilst a significant proportion of the heritability of AS remains unexplained, and many more genes are likely to be identified in the coming years, there is a strong likelihood of early translation of these genetic findings, justifying the effort and resources that have gone into establishing them.

Key Points
- Genetic factors are major determinants of susceptibility to ankylosing spondylitis (AS), and to its severity.
- Genome-wide association studies (GWAS) have now identified 13 genes, in addition to HLA-B27, which are associated with disease in white Europeans.
- These studies indicate that in both B27-positive and -negative disease, polymorphisms influencing the IL-23 signaling pathway are major susceptibility determinants, pointing to likely therapeutic benefits targeting this pathway.
- Strong overlap is seen between genes influencing AS and IBD, and some overlap is seen with genes influence psoriasis, indicating shared pathogenic pathways.
- The known function of ERAP1, and the restriction of the association of ERAP1 polymorphisms with B27-positive AS, indicates that HLA-B27 is most likely to influence AS via a mechanism involving aberrant peptide presentation.

FUNDING
MAB is funded by an NHMRC Principal Research Fellowship.

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63. Wellcome Trust Case Control Consortium 2 & (TASC) Australo-Anglo-American Spondyloarthritis Consortium Genome-wide association study in ankylosing spondylitis identifies further non-MHC associations and demonstrates that the ERAP1 association is restricted to HLA-B27 positive cases, implicating peptide presentation as the likely mechanism underlying the association of HLA-B27 with the disease. Nature 2010 (Submitted).


