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Review

Genetics of ankylosing spondylitis☆

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ABSTRACT

Ankylosing spondylitis (AS) is a chronic inflammatory arthritis that affects the spine and sacroiliac joints. It causes significant disability and is associated with a number of other features including peripheral arthritis, anterior uveitis, psoriasis and inflammatory bowel disease (IBD). Significant progress has been made in the genetics of AS have in the last five years, leading to new treatments in trial, and major leaps in understanding of the aetiopathogenesis of the disease.

1. Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory arthritis that affects the spine and sacroiliac joints. It causes significant disability and is associated with a number of other features including peripheral arthritis, anterior uveitis, psoriasis and inflammatory bowel disease (IBD). Significant progress has been made in the genetics of AS have in the last five years, leading to new treatments in trial, and major leaps in understanding of the aetiopathogenesis of the disease.

2. Major Histocompatibility Complex Genetics of AS

It has long been known that AS runs strongly in families, with the risk of disease in first-degree relatives of AS cases being >52 times that of unrelated subjects (Brown et al., 2000). Whether this cofamiliality was due to shared environmental or genetic factors was unclear until the demonstration in the early 1970s of association of the HLA-B27 allele with the disease (Brewerton et al., 1973b; Schlosstein et al., 1973). Heterozygote HLA-B27 carriage has an odds ratio of ~50 for AS, and homozygosity with an odds ratio of ~100 (International Genetics of Ankylosing Spondylitis et al., 2013; Jaakkola et al., 2006; Khan et al., 1978). The recurrence risk for AS in monozygotic twins is 63%, first degree relatives 8.2% and second degree relatives 1.0%. The parent–child recurrence risk is 7.9% and the sibling–sibling recurrence risk is 8.2% (Brown et al., 2000).

The HLA-B27 association in AS remains amongst the strongest genetic association with any common human disease, but the molecular mechanism underlying this association remains unclear. In nearly all populations studied worldwide, HLA-B27 is strongly associated with AS. One hundred and thirty subtypes of HLA-B27 have now been reported (European Bioinformatics Database Immuno Polymorphism Database, 2013), and AS has been reported to occur with the following subtypes: B*2702 (MacLean et al., 1993), *2703 (Reveille et al., 2000), *2704 (Lopez-Larrea et al., 1995), *2705 (MacLean et al., 1993), *2706 (Gonzalez-Roces et al., 1997), *2707 (Armas et al., 1999), *2708 (Armas et al., 1999), *2710 (Garcia et al., 1998), *2714 (Garcia-Fernandez et al., 2001), *2715 (Garcia-Fernandez et al., 2001), and *2719 (Djouadi et al., 2001). The vast majority of HLA-B27 subtypes occur in too few individuals to definitively establish their association with disease. Of those studied in sufficient numbers of carriers, HLA-B*2702-5, *2707, *2708 and *2710 clearly significantly increase AS risk. There is some evidence suggesting that HLA-B*2704 may carry higher risk than the ancestral HLA-B*2705 allele, and that the risk associated with B*2703 may be lower. Two subtypes, B*2706 and B*2709, are not associated with disease, but AS has been reported in carriers of each allele, indicating that they are not protective for AS. It is beyond the scope of this article to discuss the potential mechanisms by which HLA-B27 induces AS, but as we and others have proposed previously, any hypothesis as to explain this must also explain how these two subtypes are not AS-associated (Brown, 2009; McLean et al., 1985).

It has also long been suspected that other, non-HLA-B27, MHC alleles are involved in AS-pathogenesis. Whilst many studies have attempted to study this further, the difficulty of distinguishing linkage disequilibrium with HLA-B27 from direct associations across

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the MHC has until recent large scale studies precluded convincing demonstration of any replicated non-HLA-B association with AS. An exception to this has been the association of HLA-B60 with AS, first reported by Robinson et al. in 1986 (Robinson et al., 1989) and confirmed subsequently in populations of both white European (Brown et al., 1996) and east Asian ancestry (Wei et al., 2004).

The International Genetics of AS Consortium has recently extended this observation, using the findings of 10,619 AS cases and 15,145 controls densely genotyped across the MHC to genetically dissect the region further (International Genetics of Ankylosing Spondylitis et al., 2013). A major finding from this study was the identification of a single tagSNP, rs116488202, that is highly sensitive and specific for *HLA-B27* (>98.5%, within the limit of accuracy of direct genotyping of HLA-B27), and which can be genotyped for a small fraction of the cost of typing HLA-B27 itself. This should have a major impact on genetic screening for AS either in high risk or even in the general population. An early application is that it has enabled imputation of HLA-B27 in large cohorts, and thus the ability to study non-*HLA-B27* MHC associations of AS in sufficiently powered studies. These studies have shown genomewide significant association of *HLA-A*0201* with AS with odds ratios of 1.21 and 1.36 in *HLA-B27* positive and negative cases respectively. It is likely that the further associations of MHC genes will be identified in future studies, particularly as better imputation methods for HLA loci become available.

3. Non-MHC genetic associations

Strong epidemiological evidence of the existence of significant non-MHC genetic associations of AS was presented well before any such genes were convincingly identified. HLA-B27 positive first-degree relatives of AS cases are 5.6–16 times more likely to develop disease themselves than HLA-B27 positive carriers in the general community (Calin et al., 1983; van der Linden et al., 1983). Identical twins are much more likely to be concordant for AS (60–75%) than HLA-B27-positive dizygotic twins (24%) (Brown et al., 1997; Pedersen et al., 2008).

The GWAS era has enabled rapid progress in identifying non-MHC associations of AS to be made. These findings have highlighted a number of important pathways in AS pathogenesis including the IL-23 pathway, aminopeptidases and peptide presentation, innate immune stimulation and the interaction and homeostasis of resident microbial communities. Included among them are pathways for which we currently have therapeutics available, particularly in the IL-23 pathway, and it will be important to test these therapeutics in AS patients.

3.1. Ubiquitination, aminopeptidases and MHC class I presentation

Ubiquitination is the process of adding ubiquitin groups onto proteins that directs them to a specific sub-cellular compartment or for degradation via the multi-catalytic complex called the proteasome (Pickart, 2001). The proteasome degrades the protein and either recycles the resultant products or the peptides can be presented on MHC class I molecules on the cell surface. Ubiquitination therefore plays an important role in determining what antigens are presented to the immune system. *UBE2E3* and *UBE2L3* have recently been associated with AS and these genes encode the enzymes UbcH9 and UbcH7 respectively (International Genetics of Ankylosing Spondylitis et al., 2013). However, UbcH9 is unable to form bonds with ubiquitin but can with a similar protein SUMO (Desterro et al., 1997). When a protein undergoes sumoylation it is not degraded, it may enhance the proteins stability, change its location or direct involvement in other cellular processes like signal transduction (Muller et al., 2001). Variants in *UBE2L3* are involved with NF-κβ regulation and *UBE2L3* has been associated with a number of other inflammatory diseases implicating this intracellular signalling pathway as a shared pathogenic pathway (Wang et al., 2012).

Two loci (chromosomes 5p15 and 17q21) containing genes encoding four aminopeptidases have now been implicated in AS aetiology (International Genetics of Ankylosing Spondylitis et al., 2013). The chromosome 5p15 locus contains genes that encode the aminopeptidases endoplasmic reticulum aminopeptidase (ERAP)-1, ERAP2, and insulin regulated aminopeptidase (IRAP or LNPEP). The chromosome 17q21 locus contains the *NPEPPS* gene that encodes puromycin-sensitive aminopeptidase. The same primary *ERAP1* haplotype associated with AS is also associated with psoriasis (Strange et al., 2010), and the AS-associated *ERAP2* haplotype is also associated with both psoriasis and inflammatory bowel disease (Chapman et al., 2010). Suggestive evidence has been presented that ERAP1 variants may be associated with type 1 diabetes and cervical cancer but these findings have not been universal and in no study have definitive associations been reported (Dendrou et al., 2009; Mehta et al., 2007).

ERAP1 and 2 are resident in the endoplasmic reticulum (ER) and are an integral part of the MHC class I presentation pathway. Once peptides have been processed through the proteasome, the Transporter associated with Antigen Processing (TAP) takes the resultant peptide from the cytoplasm into the ER. ERAP1 and ERAP2 then trim any N-terminally extended peptides longer than 9 amino-acids down to that length (Chang et al., 2005; York et al., 2002), which is the favoured length for subsequent loading onto MHC class I molecules such as HLA-B27.

ERAP1 was the first aminopeptidase associated with AS (Burton et al., 2007). The association has been widely replicated with similar allelic and haplotypic associations reported in both populations of white European ancestry and in east Asians, implying that common variants are involved rather than multiple rare variants (Choi et al., 2010; Davidson et al., 2009, 2011; Harvey et al., 2011; Li et al., 2010; Lin et al., 2011; Maksymowych et al., 2009; Pimentel-Santos et al., 2009).

Recently interaction between HLA-B27 and ERAP1 variants has been described in AS, such that variants of *ERAP1* were shown only to influence AS disease risk if HLA-B27 is present (Evans et al., 2011). This suggests that *ERAP1* associated variants operate by effects on peptide processing prior to HLA Class I presentation. It had previously been reported that ERAP1 is involved in cleavage of cytokine receptors from cell membranes (Cui et al., 2002, 2003a,b; Goto et al., 2011), but studies comparing serum levels of receptor levels in wild type and ERAP knockout mouse found no differences (Evans et al., 2011). Further, in humans there is no association between *ERAP1* polymorphisms and serum cytokine receptor levels (Haroon et al., 2010). Fine-mapping studies indicate that the SNP rs30187 (Lys528Arg) is directly disease-associated, and that the variation rs10050860 (Asp575Asn) marks an AS-associated haplotype that also carries rs17482078 (Arg725Gln) (Evans et al., 2011). The linkage disequilibrium between rs10050860 and rs17482078 is very tight, and it has not been possible thus far to determine which of these two polymorphisms is the key AS-associated variant, or if both are actually disease associated. Certainly they have a profound effect, with a reduction in AS risk in HLA-B27 positive homozygous carriers of *ERAP1* protective variants of 3–4 fold (Evans et al., 2011).

In vitro studies of peptidase activity of ERAP1 and its variants show that the protective variants of rs30187 and rs17482078 are associated with a 40% reduction in peptidase function, whereas rs10050860 has no effect (Evans et al., 2011). This suggests that rs10050860 is not the true disease-associated variant but rather rs17482078 is. Using recombinant ERAP1 and comparing wild type protein with rs30187 and rs27044 (Q730E) variants, Evnouchidou