Editorial
Future Rheumatology

Recent advances in the genetics of ankylosing spondylitis

"*HLA-B27* is the primary disease susceptibility gene for AS ... (but) is not a prerequisite for AS, as the disease also affects individuals who do not possess this genetic marker"

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The precise cause of ankylosing spondylitis (AS) remains unknown, but there is strong evidence that genetic factors play a pivotal role in disease susceptibility, and that they interact with non-genetic (environmental) factors to lead to immune-mediated mechanisms that result in the release of proinflammatory cytokines such as TNF-α [1–9].

Genetic factors

More than 90% of the risk of developing AS is determined genetically, indicating the highly heritable nature of this disease [1–5]. There is a strong association with the genetic marker *HLA-B27*, which lies in the major histocompatibility complex (MHC) region on the short arm of chromosome 6 (6p21 region). *HLA-B27* is the primary disease susceptibility gene for AS, contributing approximately 40% of the population-attributable genetic risk of AS in Caucasians [1,2]. However, *HLA-B27* is not a prerequisite for AS, as the disease also affects individuals who do not possess this genetic marker.

The precise explanation for the association of *HLA-B27* and AS, one of the strongest between a MHC molecule and a disease, has eluded researchers for more than 35 years.

Several hypotheses have been proposed that are based not only on the fact that the HLA-B27 molecule, besides having its peptide-presenting specificity, folds slowly, tends to misfold and can form covalent heavy chain homodimers amenable to recognition by leukocyte receptors that might predispose to disease through immunomodulation of both innate and adaptive responses to arthritogenic pathogens [5–8]. However, none of the proposed theories have as yet satisfactorily explained the underlying mechanism and the differential association of HLA-B27 subtypes with AS. There are more than 52 alleles of *HLA-B27* based on nucleotide sequence differences, but at the translated protein level the number of subtypes are smaller and can be encompassed by *HLA-B*2701* to *HLA-B*2743*. The common subtypes *B*2702*, *B*2704* and *B*2705* are strongly associated with AS. Among the other subtypes, most of which are relatively uncommon, *B*2701*, *B*2703*, *B*2707*, *B*2708*, *B*2714*, *B*2715* and *B*2719* are known to be disease associated (or, at least, AS patients possessing these subtypes have been observed) [3,5–7]. *B*2706*, a subtype occurring in Southeast Asia, does not predispose to AS, and this may also be the case with *B*2709*, a rare subtype primarily observed among Italians living on the island of Sardinia [5–8].

The recent development of the genome-wide association study approach has revolutionized genetic studies of AS by finding some non-MHC disease genes, some of which also confer susceptibility to psoriasis and chronic inflammatory bowel diseases, such as the gene for the interleukin-23 receptor (IL-23R) [1–4,9]. It is of interest that IL-23 is selectively overexpressed in subclinical intestinal inflammation sites in patients with AS at levels similar to those seen in patients with Crohn's disease. IL-23R is a key factor in the regulation of a newly defined proinflammatory effector T-cell subset, Th17 cells.

Successful treatment of psoriasis and Crohn's disease has been reported with the human anti-IL-12p40 monoclonal antibody ustekinumab, which blocks both IL-12 and IL-23, as these cytokines share the IL-12p40 chain [10,11]. Sequence variants in the *IL-23R* gene and its ligand have also been found to play a role in psoriasis. The *IL-23R* gene has recently been found to contribute approximately 9% of the population-attributable genetic risk for AS in Caucasians [1–2,4]. Altogether, these recent findings indicate that genes participating in IL-23 signaling may be a common susceptibility factor for AS, Crohn's disease and psoriasis by playing a prominent role in the pathogenesis of the chronic epithelial inflammation observed in these diseases.

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Another gene, *ARTS1* (also called *ERAAP* and *ERAP1*), which encodes a transmembrane aminopeptidase with diverse immunologic functions and is located on chromosome 5, shows a strong association with AS, contributing roughly 23% of the population-attributable genetic risk for AS among Caucasian populations [1,2]. *ARTS1* is involved in trimming peptides to the optimal length in the endoplasmic reticulum for presentation by MHC class I proteins, and that includes HLA-B27. It also cleaves cell surface receptors for the proinflammatory cytokines IL-1 (IL-1R2), IL-6 (IL-6R-α) and TNF (TNFR1), thereby downregulating their signaling. It is possible that genetic variants of *ARTS1* could have proinflammatory effects through this mechanism.

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Regions on chromosomes 2 (2p15) and 21 (21q22) also harbor susceptibility genes for AS. One of the members of the *IL-1* gene cluster, *IL1A*, contributes approximately 5% of the population-attributable genetic risk for AS among Caucasian populations [12]. Thus, the population-attributable genetic risks for *HLA-B27* (40%), *ARTS1* (23%), *IL23R* (9%) and *IL1A* (5%) add up, and one can conclude that approximately three-fourths of the total genetic risk of developing AS has been uncovered. These findings may lead to a better understanding of the pathogenesis of AS and related spondyloarthropathy, and may also provide insight into potential new therapeutic approaches.

Environmental triggers

Among the possible environmental triggers for AS onset, infections have long been suspected. It has been speculated that AS may be triggered by gut infection with *Klebsiella* bacteria. However, the evidence is circumstantial, based on the observation by some, but not all, investigators of elevated levels of antibodies against *Klebsiella pneumoniae* in the blood of patients with active disease. More convincing proof has been lacking. Thus, the environmental triggers for AS remain unknown, but the close relationships between AS and psoriasis and clinical and asymptomatic forms of Crohn's disease suggest the potential involvement of an immune reaction in the gut or skin that may be influenced by reactions to microbial infections.

Disease heterogeneity

Heterogeneity of AS has been known for many years, first exemplified by the difference between HLA-B27-positive and HLA-B27-negative patients [13–15]. Although there are many similarities, HLA-B27-negative AS is later in its onset; is significantly less often complicated by acute anterior uveitis and more frequently accompanied by psoriasis, ulcerative colitis and Crohn's disease; and it less often shows familial aggregation [13–15]. In fact, it is unusual to observe families among people of northern European extraction with two or more first-degree relatives affected with HLA-B27-negative AS in the absence of psoriasis, ulcerative colitis or Crohn's disease in the family. A recent genetic study supports the existence of an HLA-B27-independent common link between gut inflammation and AS [9].

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Individuals who are homozygous for HLA-B27 are more than three-times as likely to get the disease as those who are heterozygotes [16]; this has recently been confirmed in a study from Finland [17]. There are many possible explanations that can account for this increased disease penetrance in individuals who are homozygous for HLA-B27. These include, for example, possible increased cell surface expression of HLA-B27 or a potentially increased effect of linked genes that may have influence on the disease process or occurrence of the disease.

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