Genetics and the Causes of Ankylosing Spondylitis

Aimee Hanson[a], Matthew A. Brown, MBBS, MD, FRACP, FAHMS, FAA[b,*]

KEYWORDS

• Axial spondyloarthritis • Ankylosing spondylitis • Genetics • Association • SNP • Heritability

KEY POINTS

- Ankylosing spondylitis (AS) is a common, highly heritable inflammatory arthritis for which, thus far, 113 non-MHC genetic associations have been identified.
- Human leukocyte antigen (HLA)-B27 contributes approximately 20% of the heritability of AS, and nonmajor histocompatibility complex loci identified to date contribute another approximately 10%.
- The HLA associations of AS are complex and multiple non-B27 HLA alleles have been identified as being involved.
- Key pathways identified by AS genetic studies include the interleukin (IL)-23 and M1-aminopeptidase pathways, but multiple other pathways have been identified as increasing numbers of associations have been identified.
- Preliminary evidence suggesting involvement of killer immunoglobulin-like receptor (KIR) genes in AS pathogenesis needs replication in other cohorts.

INTRODUCTION

Genetic studies of ankylosing spondylitis (AS) have, over the past decade, provided major insights into the etiopathogenesis of the disease that have led to major therapeutic innovations. Some of these new treatments have already entered clinical practice, and others are in trials and undergoing development. It is well known that susceptibility to and severity of AS are largely genetically determined. Extensive progress has been made identifying susceptibility alleles in the disease, with

Disclosure Statement: A. Hanson has nothing to disclose. M.A. Brown has received research support, and acted as an advisor or as part of the speakers' bureau of Abbvie, Janssen, Novartis, Pfizer, and UCB.

[a] Translational Research Institute, Princess Alexandra Hospital, University of Queensland Diamantina Institute, Woolloongabba, Brisbane, Queensland, Australia; [b] Institute of Health and Biomedical Innovation, Translational Research Institute, Princess Alexandra Hospital, Queensland University of Technology, Woolloongabba, Brisbane, Queensland, Australia
* Corresponding author.
E-mail address: matt.brown@qut.edu.au

Rheum Dis Clin N Am 43 (2017) 401–414
http://dx.doi.org/10.1016/j.rdc.2017.04.006 **rheumatic.theclinics.com**

113 established loci identified, contributing roughly 10% of the heritability of AS, over and above the major effect of human leukocyte antigen (HLA)-B27, which determines approximately 20% of the genetic risk. Studies of the genetics of clinical manifestations of AS, such as the extent of bony ankylosis or presence of anterior uveitis, have been more challenging, though some genes have been found to influence uveitis risk beyond their effects on the risk of AS. This article seeks to present the current state of understanding of the genetic influences in AS, focusing on more recent advances and their contribution to understanding mechanisms of disease.

MAJOR HISTOCOMPATIBILITY COMPLEX AND ANKYLOSING SPONDYLITIS

Large scale case-control studies of HLA and other major histocompatibility complex (MHC) genes in AS have demonstrated that the genetic associations at this locus are far more complex than initially thought. Since the discovery of the association of HLA-B27 with AS, there have been many studies suggesting the presence of additional MHC-associated variants.[1–5] With the exception of the association of *HLA-B60* with AS,[6,7] until recently, none of those have been convincingly replicated.

The MHC is under marked genetic selection pressure and HLA frequencies vary substantially between ethnic groups. The development of methods of HLA-typing using imputation from dense single nucleotide polymorphism (SNP) genotyping, together with the availability of large reference sets of subjects genotyped at both HLA loci and MHC SNPs, has enabled analysis of HLA and MHC associations in large case-control cohorts. Another methodologic advance in recent studies is principal components analysis; population stratification can be identified and controlled for, making the findings robust to differences in allele frequencies due to ethnic variation rather than disease affection status. Two such studies have now been published, 1 in subjects of European ancestry[8] and the other in Koreans.[9] Both show convincingly that there are additional HLA-B variants associated with AS, as well as other HLA class I and II variants (**Table 1**). Although these studies do not exclude the presence of other non-HLA MHC genetic associations, they do indicate that it is unlikely that variants of large effect exist within the MHC once the associations of HLA variants are accounted for.

Table 1
Association of *HLA-B* alleles with susceptibility to ankylosing spondylitis in European-descent subjects

Round	*HLA-B* Allele	Odds Ratio (95% CI)	*P*-Value
1	*27:05*	62.41	$<10^{-321}$
2	*27:02*	43.41	1.07×10^{-122}
3	*07:02*	0.82	5.04×10^{-6}
4	*57:01*	0.75	5.13×10^{-4}
5	*51:01*	1.33	2.14×10^{-3}
6	*47:01*	2.35	2.25×10^{-3}
7	*40:02*	1.59	4.65×10^{-3}
8	*13:02*	1.43	4.29×10^{-3}
9	*40:01*	1.22	4.93×10^{-3}

Findings are presented for consecutive conditional analyses, in which, for round 2 and onward, the test conditioned on the previous alleles.