

Quantifying the genetic risk for the development of axial SpA - could this become a diagnostic tool?

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Abstract

Purpose of review: To assess the utility of recent genetic findings in ankylosing spondylitis and axial spondyloarthropathy in relation to diagnostic testing, prognosis and responses to biologic treatment and the development of new therapies.

Recent Findings: Ankylosing spondylitis and other forms of spondyloarthropathy are polygenic with more than 100 genes contributing to disease susceptibility. The role of genes in determining the outcome of the disease and response to treatment is less clear. Here we review some of the progress that has been made over the past decade in understanding the genetic contribution to these diseases and how this may be used to inform the development of new treatments. In those with a high pre-test probability of spondyloarthropathy HLA-B27 testing can increase the post-test predictive value to almost 100% in some cases. There are currently no reliable genetic predictors of disease severity or response to treatment.

Summary

The utility of HLA-B27 as a diagnostic tool when coupled with careful clinical assessment is well established but other genetic markers probably have relatively little to add. In contrast, novel drug targets are likely to be identified from genetic association studies.

Key words:

Spondyloarthropathy, ankylosing spondylitis, genetic markers, HLA-B27

Introduction

As a fourth year medical student at London's Westminster Hospital in the early 1970s one of us was lucky enough learn about ankylosing spondylitis (AS) from Derrick Brewerton, little realizing that it

would subsequently occupy much of his working life. At that time Brewerton and others were just about to publish the iconic association between AS and HLA-B27 (then known as HL-Aw27) [1, 2]]. Arguments about the relative importance of nature and nurture in the aetiology of many rheumatic diseases were already being rehearsed, particularly in relation to rheumatoid arthritis [3] but the tools for investigating the genetic component of any disease (even monogenic disorders) were then so limited that to call them rudimentary seems generous. The key insight of Brewerton and his colleague Frank Dudley Hart was that the relatively high frequency of familial recurrence of AS (sibling recurrence risk about 7%) indicated a strong genetic predisposition to the disease. Crucially, their research was facilitated by the increasing range of transplantation antigens for use as genetic markers. Collaboration with David James, a transplant immunologist at the Anthony Nolan Centre just around the corner from The Westminster, underpinned much of this HLA-B27 work and the rest, as they say, is history. The HLA-B27 association with AS (relative risk~120) is still one of the strongest genetics risks for a polygenic disorder and actually prompted many to believe that AS was monogenic. Subsequently we have demonstrated by twin studies that most of the population variance for AS can be explained by genes but that only about one-third of this can be accounted for by HLA-B27 [4]. Genetic factors also make a contribution to the severity of the disease [5]. Many of the questions from that era about the genetic contribution to AS are as relevant today as they were then. What is the mechanism behind the HLA-B27 association? Are other genes involved? If so, how many? How useful is this genetic knowledge for determining the diagnosis or prognosis of AS, and can we use this knowledge to develop new therapies? Well – we still don't know the mechanism of the HLA-B27 association after 45 years; there are probably well over 100 genetic influences involved, some of which have given us useful insights into potential therapies; and the role of these genes in facilitating diagnosis and/or prognosis is somewhat controversial.

Spondyloarthropathies and ankylosing spondylitis

For the purposes of this article I use the term spondyloarthropathy (SpA) to refer to those arthropathies with a variable predilection for the spine and sacroiliac joints, and axial SpA (axSpA) to embrace a range of disorders that includes AS, psoriatic arthritis, reactive arthritis and some of the arthropathies associated with inflammatory bowel disease. For practical purposes I do not believe that semantic arguments relating to the nosology of these conditions materially affect my conclusions about the utility of our increasing genetic knowledge about these conditions. According to the Assessment of Spondyloarthritis international Society (ASAS) individuals may be classified as having non-radiographic axSpA (nr-AxSpA) according to criteria that either include magnetic resonance imaging (imaging criteria) or not (clinical criteria); HLA-B27 testing is an absolutely crucial component of the latter [6]. To what extent those with nr-axSpA represent a form of early ankylosing spondylitis is a moot point but not all cases of nr-axSpA ultimately appear to develop AS over time [7]. Further, there are reservations about the robustness of the “clinical” (non-imaging) criteria for the diagnosis of nr-axSpA. In this regard it is interesting that there are differences in the genetic makeup of two distinct but related cohorts with SpA – one fulfilling the ASAS imaging criteria for axSpA and the other the modified New York radiographic criteria for AS [8].

HLA-B27 and AS/axSpA

Broadly speaking the HLA-B27 association with SpA is maintained across different ethnic groups, and the prevalence of the disease generally reflects the frequency of HLA-B27 in different populations.

For example, its prevalence is particularly high in circumpolar regions where the general population prevalence of HLA-B27 may be in excess of 25% in some ethnic groups; in contrast, the disease is uncommon in sub-Saharan Africa where the prevalence of HLA-B27 is typically <0.5%. There are more than 100 distinct allelic variants of HLA-B27 at the DNA level, many of which have only been described in AS cases. However, many of these alleles are so rare that formal population studies to establish causality are impossible. Nevertheless, population studies demonstrate pretty convincingly that most of the more common variants (B*2705, B*2702, B*2704, B*2707, B*2708) are associated with AS and that the strength of this association appears to be quite similar (if not identical). In contrast, the associations with HLA-B*2703 (in West Africa), B*2706 (in Asia) and B*2709 (in Sardinia) do appear to be weaker or even absent. The HLA-B27 association may also be weaker in southern than northern Europe. For example, a recent study from Turkey [9] indicates that the frequency of HLA-B27 among AS cases is only 70% compared with 85% in our UK sample of 8,500 cases. This study confirmed earlier reports of a somewhat weaker association with AS in Turkey where there is also a lower HLA-B27 frequency (2.6%) in the general population [10]. There also seems to be a broader range of HLA-B27 subtypes in the Turkish AS patients than in more northerly European populations (including HLA-B*2702, *2705, *2707, *2711, *2713, *2715, and *2723); none of the Turkish AS cases had HLA-B*2701 or *2708 despite the presence of these alleles in the general population at frequencies of 4 and 2.7%, respectively [10]. The explanation(s) for the HLA-B27 association with AS remains as elusive as ever. Possible mechanisms include: (1) the arthritogenic peptide hypothesis; (2) inflammatory stress responses in the endoplasmic reticulum due to accumulation of abnormally folded HLA-B27; and/or (3) unusual activity of the immune system due to interactions between HLA-B27 homodimers and killer immunoglobulin-like receptors (KIR) on some CD4 positive T-cells. These have been extensively reviewed elsewhere [11, 12]. The role of HLA class 1 molecules like HLA-B27 in the pathogenesis of AS has been further emphasized in recent years by the association of other components of the antigen processing and presentation pathway with AS. In particular, the endoplasmic reticulum associated amino peptidases ERAP1, ERAP2, and LNPEP (leucyl/cystinyl aminopeptidase) show strong associations with AS and there is a high degree of synergistic interaction with HLA-B27 in the case of ERAP1 [13, 14, 15]. Further, within the major histocompatibility complex there are several additional AS associations (much weaker than with HLA-B27), including with other HLA-B genes, the HLA-A, HLA-DR and HLA-DP loci [15]. Disease associated variants of ERAP1 can alter the repertoire of peptides available for binding to and presentation by HLA-B27, which in turn could have a significant influence on any of the pathogenic mechanisms proposed above [16]. One interesting proposal suggested that the ERAP1 association could be attributed unusual rare *ERAP1* alleles and haplotype combinations restricted largely to AS cases; this was hypothesised to have a major potential effect on the HLA class 1 peptide repertoire [17]. However, this has now been disproved and the *ERAP1* is actually restricted to the different functional effects of a few relatively common variants on HLA class 1 peptide antigen trimming [18].

Other genes in AS

More than 100 genetic associations have now been proposed in AS [19] but only a few of these result in amino acid substitutions that affect function, such as the coding change in the IL-23 receptor cytoplasmic tail that affects signalling and the ERAP1 variants that affect peptide trimming in the endoplasmic reticulum [13, 14, 15, 16, 20]. The vast majority of associated SNPs are in non-coding regions of the genome where it seems likely that many have regulatory functions although these remain to be precisely defined [21, 22]. At least some of these appear to cluster in related functional groups such as the IL23 related pathways [14]. The observation that loss of function variants of ERAP1 are protective against AS raises the possibility that small molecule inhibitors of these endopeptidases could be developed as drugs for AS and related disorders [12,13].

Utility of genetic markers in diagnosis

Extrapolation from the results of AS recurrence in twins suggests that well over 90% of the population variance (broadly speaking what determines whether you or I will develop AS) is genetically determined [4]. This does not exclude an extrinsic trigger but suggests that any such factor is likely to be so common that most of us will encounter it at some time in our lives (twin studies may underestimate the importance of such shared environmental factors). Given our greatly increased knowledge of the genetic component of AS over the past decade it is therefore easy to suppose that we should therefore be in a much stronger position to use this knowledge for diagnostic and prognostic purposes. However, the reality is rather different. The strength of the association between AS and HLA-B27 is remarkable but it still contributes only about one-third of the genetic component of the disease. The remaining polygenic contribution therefore accounts for the majority of the population variance for AS. Although the precise genes responsible for most of the single nucleotide polymorphism (SNP) associations with AS are still unresolved one can still use these markers to define an individual's overall susceptibility. Theoretically, high throughput genotyping platforms could allow us to type all the known AS associated SNPs quickly and, these days, relatively cheaply to give a more accurate assessment of risk in a given individual. While this is true it fails to take account of a fundamental statistical rule that when applying a test of this sort its value is determined by the pre-test probability of obtaining a positive result. This is well exemplified by the example of HLA-B27 testing alone in the diagnosis of AS/axi SpA. Assuming a prevalence of axSpA of about 5% in those with chronic back pain [23, 24] estimated that in the absence of any other features suggestive of SpA the pre-test probability of SpA was 14% but if HLA-B27 was present the post-test probability of axial SpA increased to 59%. If 1 or 2 other SpA features were present the pre-test probability of axial SpA was 35-70%, increasing to 80-90% if HLA-B27 was positive. The presence of 3 or more additional features had a pre-test probability of >90%, which increased to nearly 100% in the presence of HLA-B27. So, while it may be true that a battery of genetic tests may give better sensitivity for diagnosing AS/axial SpA than HLA-B27 alone this is highly unlikely to supplant the judicious application of some very simple questions in the clinical setting.

Although there is good evidence that the severity of AS is at least in part heritable the contribution of individual genes towards this has been relatively little explored to date. HLA-B27 positivity is associated with earlier age of onset and strongly with uveitis, of course [25]. Radiographic severity (assessed by the modified Stoke AS spine score in 1537 cases) has been tentatively associated with the candidate genes RANK- receptor activator of NF kappa B and cyclooxygenase-1 but such studies will require replication [26]. Of interest, no association was observed between radiographic severity and HLA-B27 in this study.

Genetic markers for predicting severity and responses to treatment

The value of individual genetic markers or combinations of markers for predicting response to treatment is often proposed as a means of delivering "personalised medicine" to individual patients [27]. Certainly genetic analysis offers a realistic way of achieving this in oncology where the nature of the mutations in the tumour can guide the most appropriate form of therapy and help to change therapies in the event of tumour relapse. However, in the case of a systemic disease like AS this seems unlikely to me. No two patients with AS are likely to have exactly the same set of genetic predispositions to the disease but this does not help to predict response to therapy. For example, the identification of an AS protective effect from the *IL23R* rs11209026 polymorphism in the cytoplasmic tail of the interleukin-23 receptor, which disrupts its signalling, served to highlight the importance of IL23 driven pathways in the pathogenesis of AS [13, 14, 15, 20]. This led to the targeting of IL-17 by therapeutic monoclonal antibodies as a highly successful therapeutic strategy for AS [28, 29]. However, the successful targeting of IL-17 in this way is not restricted to cases with

the normally functioning, pro-inflammatory, AS-risk *IL23R* genotype. One of the reasons for this lies in the fact that there are several other disease associated polymorphisms lying within the IL23 pathway of T-cell development, including *IL6*, *IL12*, *IL12B*, *TYK2*, *STAT3*, *IL27*, *IL1R1*, *IL1R2*, and *RUNX3* [12, 14]. Of interest, although the AS association with rs11209026 is robust in Caucasian populations it is monomorphic in Chinese with the consequence that there is, of course, no corresponding disease association in this population. Yet, as far as we can tell secukinumab is effective in Chinese patients, certainly when used for the treatment of psoriasis [30].

Predicting the outcome of treatment

Attempts to use genetic markers of susceptibility to a disease like AS to predict response to treatment have been limited to date and potentially would require large cohorts to distinguish subtle differences. Unfortunately this is made even more difficult by the fact that many of the descriptors of disease activity and severity are fairly blunt instruments (the high degree of correlation between the Bath AS functional and disease activity indices bear testimony to the difficulty of distinguishing current disease activity from chronic disease damage). Further, the use of radiographic criteria of disease severity is plagued by the slow rate of radiographic progression (as judged by new syndesmophyte growth. There are occasional exceptions, such as the reported value of the *ERAP1* rs30187 SNP in predicting AS responses to secukinumab in a small study [28] but these demand replication and validation in large data sets. We have recently been interested in the possibility that the rs1800693 SNP in *TNFRSF1A* (encoding a truncated soluble form of the tumour necrosis factor receptor) because it could have anti-inflammatory properties and is associated with protection against AS (but susceptibility to multiple sclerosis). As such it seemed a good candidate for influencing the severity of AS. However, we were unable to demonstrate any influence on age of onset, disease severity scores, intention to treat with biologics or the efficacy of biologics in a sample of nearly 3000 cases [31].

Conclusion

The utility of HLA-B27 in the diagnosis of AS/SpA is undeniable but the utility of additional genetic markers in making the diagnosis or predicting outcome is unclear. In current clinical practice the application of careful clinical questioning coupled with HLA-B27 testing and MRI of the sacroiliac joints when appropriate, provides a diagnostic sensitivity of approaching 100 per cent [6, 23, 24, 32]. Genetic association studies are likely to continue to contribute significantly to the identification of new drug targets in AS/SpA.

Summary Points

- Ankylosing spondylitis is a polygenic disease with contributions from more than 100 genes
- HLA-B27 testing is diagnostically very valuable in cases with a high pre-test probability
- Other genetic markers currently add little to HLA-B27 testing
- AS susceptibility markers do not usefully predict severity of AS or response to treatment
- The genetics of AS/SpA can help to identify potential drug targets for treatment

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***of interest**

****of special interest**

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