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Genetics and the axial spondyloarthritis spectrum

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Abstract

The axial SpAs (axSpAs) are clearly clinically a heterogeneous set of diseases with markedly varying extra-articular features. These diseases are all highly heritable and have overlapping but differing genetic origins. Shared features include association with HLA class I alleles and genes of the IL-23 pathway, among other things. Significant differences do exist however, both in the genetic loci involved and at specific loci in the individual genetic variants associated with each disease. These similarities and differences are of great interest in regards to disease pathogenesis and treatment development, although individually they are too small in effect to be of prognostic or diagnostic value. Polygenic risk scores, which capture a high proportion of the genetic variation between disorders, have been shown to have clinically useful discriminatory capacity in axSpA. This suggests they have the potential to enable improved disease classification, incorporating basic pathogenic features such as genomics, and ultimately benefitting clinical care. The aim of this article is to review the genetic characteristics of the spectrum of axSpAs and to discuss how this influences our understanding of the disease pathogenesis and the clinical implications of this understanding.

Key words: acute anterior uveitis, AS, axial spondyloarthritis, Behçet's disease, FMF, heritability, IBD, polygenic risk score, PsA, SNP

Rheumatology key messages

- The axial spondyloarthritides are both clinically and genetically heterogeneous.
- Differences in genetic associations of axial spondyloarthritides may explain differences in responses to therapies.
- Genetic data indicate that non-radiographic axial spondyloarthritis is aetiopathogenically more heterogeneous than ankylosing spondylitis.

SUPPLEMENT

Introduction

Common disease genetic studies continue to rapidly develop as a tool for investigating in an hypothesis-free manner the architecture of human diseases. The early emphasis in this field has been on identification of disease-associated genetic loci, and from that, developing a better understanding of disease pathogenesis and identification of novel therapeutic targets. This has been extensively reviewed elsewhere. The availability of more powerful genomics resources such as larger-sized cohorts and extensively phenotyped biobank datasets and of novel statistical methods such as Mendelian randomization approaches, polygenic risk scores (PRSs) and methods to assess heritability of individual diseases and co-heritability between diseases using case–control cohorts has greatly expanded the scope of genetics to address key questions about the relationships between diseases, the genetic architecture of disease and the role of environmental factors in disease. In this review we will address key questions about the relationship between the clinically defined SpAs and gender-related aspects of axial SpAs (axSpAs) enabled by these novel genomics approaches.

The spectrum of axSpA

AxSpA is known clinically to be a heterogeneous group of related disorders that have shared clinical, genetic, histopathological and likely aetiopathogenic features.

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The group of conditions includes AS, IBD-associated arthritis, psoriatic axSpA and reactive arthritis. AxSpA also occurs in a subset of patients with a sarcoidosis, Behçet's disease (BD) and FMF. The ability to identify patients with at least moderate specificity with non-radiographic axSpA (nr-axSpA) has further broadened the group of clinically defined conditions that form this group, making at least eight different clinically defined though clearly related subsets of axSpA (Table 1). Further heterogeneity is evident if you consider patients with associated acute anterior uveitis (AAU) or peripheral SpA, even before you consider disease activity levels, severity of ankylosis and treatment response variation.

There is good evidence that genetic factors are significant determinants of these different disease subsets. The revolution of the genome-wide association study (GWAS) era has identified hundreds of genes associated with these conditions, and there is clear evidence of a differential association of specific loci between conditions. In some cases the differences relate to differences in association with any variant at individual loci, and in others, while the locus in question is associated with both diseases, the variant(s) involved is different. One of the surprises of the GWAS era has been the extent of pleiotropy (i.e. that genetic variants are associated with multiple traits and diseases) [24]. This is particularly evident among the SpAs, with extensive sharing of associated loci between IBD, psoriasis and AS noted early on in the GWAS era [25]. Surprisingly, the extent of sharing between these diseases, even though they affect largely different tissue types, is far greater than between different forms of arthritis, such as RA and AS, with a 2013 analysis showing only one shared association between AS and RA (rs4129267 in *IL6R*) [25]. In contrast, the shared heritability between AS, IBD and psoriasis has been shown to be high and the number of genetic loci with concordant associations (same variant, same direction of effect) is also high. For example, the genetic correlation between AS and Crohn's disease (CD) and ulcerative colitis (UC) is respectively 0.49 and 0.47 (on a scale of 0–1), indicating a high degree of genetic correlation even though the diseases have very different clinical manifestations. This also explains why a proportion of AS patients have clinical IBD, whereas there is no similar association between RA and IBD.

Lost in the detail underpinning these overall estimates of genetic correlation are fascinating insights provided by analysis of concordant and discordant genetic associations in relation to disease mechanisms and therapeutics. For example, the gene *TLR4* is associated with both AS, psoriasis, primary sclerosing cholangitis (PSC), UC and CD, with the same variant rs4876790 associated in each disease, but with opposite directions of effect (minor allele reduces risk of UC/CD and increases the risk of AS, psoriasis and PSC) [24]. This gene encodes an innate immune receptor for lipopolysaccharide and the differential association is consistent with differing mechanisms by which bacterial exposure drives these diseases. This hints at potential explanations as to why treatment with vedolizumab, aimed broadly at reducing gut mucosal immunity by reducing the traffic of lymphocytes into the gut mucosa, is therapeutic in IBD but may induce axSpA [26]. By reducing gut mucosal immunity, increased exposure to pro-inflammatory pathogen-associated molecular patterns in vedolizumab-treated patients with IBD is likely, potentially leading to increased innate and adaptive autoimmune responses. This mechanism has been proposed to cause axSpA in both mouse models and humans [27–30].

The recent finding that IL-23-specific inhibition is not effective in AS may also have genetic underpinnings. While *IL23A* encoding the IL-23-specific IL-23p19 subunit is associated with psoriasis [31] and PsA [32], it is not associated with AS [24], suggesting that in AS,

Table 1 AxSpAs: key genetic features

axSpAs	HLA-B27 association	Other HLA-associations	Non-MHC associations			
			IL23R	*ERAP1*	*ERAP2*	*MEFV*
AS	89% [1]	Risk: B40, B47, B51, A2, DRB1*0103 Protective: B7, B57 [2]	Yes [3]	Yes [3]	Yes [3]	Yes [4]
nr-axSpA	Radiographic arm 58% [5]	Unknown	Unknown	Unknown	Unknown	Unknown
Psoriasis[a]	No	C*0602, C*1203 [6]	Yes [7, 8]	Yes [9]	Yes [9]	Unknown
PsA	64% (axial disease) [10]	C*0602, A2, B38, B39 [6]	Yes [11]	Yes [12]	Probable [13]	Probable [14]
IBD-associated SpA	41% (axial disease) [15]	Unknown	Yes[b]	No[b]	Yes[b]	Probable [16][b]
Reactive arthritis	16–80% [17]	Unknown	Unknown	Unknown	Unknown	Unknown
Sarcoidosis arthritis	Unclear	DQ2-DR3 [18]	Unknown	Unknown	Unknown	Unclear
Behçet's disease	No	B51 [19]	Yes [20]	Yes [20]	No [21]	Probable [22]
FMF	Unknown	Unknown	Unknown	Unknown	Unknown	Yes [23]

[a]Included as a comparator for PsA, although not an axSpA. [b]IBD overall, not restricted to those with arthritis. Probable means $P > 0.05$–$< 10^{-5}$. Unclear means contradictory studies exist.

factors involving IL-23R and downstream of this receptor are what drive the disease more than in psoriasis. This potentially explains the lack of efficacy of IL-23p19 inhibitors [33] and the lower efficacy of IL-12p40 inhibitors [34] in the disease.

Clearly the biggest genetic differences between these diseases are due to HLA allelic variation, though even there, fascinating overlaps exist. For example, HLA-B51 is the major risk factor for BD, but it is also a minor risk factor for AS [2]. Similarly, HLA-B27 is the major risk factor for AS and also influences the risk of axSpA in psoriasis [35, 36] and IBD [15, 37], and HLA-DRB1*0103 is a risk factor for IBD [38] as well as for AS [2]. The association with HLA-B27 may drive the tissue specificity for entheseal arthritis in each of these conditions. However, HLA-B27 is also the major risk factor for AAU over and above its association with AS [39], and even in the absence of axSpA. While the iris may represent a form of enthesis-like tissue, it remains unexplained how HLA-B27 alone leads in some cases to axial joint inflammation and in others to ocular inflammation, with or without associated axSpA.

Part of the complexity relates to *ERAP1* and *ERAP2* associations with these diseases. While *ERAP1* is associated with each of the HLA class I–associated diseases (AAU [40], AS [3], BD [21], psoriasis [9] and the rare HLA-A29-associated uveitis birdshot retinopathy) [41], the *ERAP2*-associated diseases also include IBD [42], though its association with psoriasis is not clear at this point. The key *ERAP1*-associated variant rs30187 (K528R) is a risk factor for AS only in the presence of HLA-B27 or HLA-B40 [2, 43] and for psoriasis only in the presence of HLA-Cw6 [9], but it is a protective factor for BD only in the presence of HLA-B51 [21]. This is very likely mediated through effects on peptides presented by the HLA class I proteins, with clear differences in protein pools having been demonstrated not only between the different HLA class I proteins, but also depending on the *ERAP1* genetic background [44–46]. It seems very likely that this influences the tissue specificity of these related diseases.

As GWAS datasets have grown, the ability to distinguish primary and secondary associated variants at specific loci has increased. It has become apparent that many loci harbour multiple disease-associated variants and that these themselves have differential associations between SpAs. An example is the *IL23R* locus, which has complex associations of multiple variants with AS, BD, psoriasis, CD and UC, which overlap but are not identical. Thus AS, psoriasis, CD and UC, but not BD, share an association with rs11292026 (R381Q) [3, 7, 47], which is known to influence IL-23-driven IL-17 production but not Th17 differentiation [48]. However, all five diseases share a second independent association with rs11209032 at the same locus [20, 24], which influences methylation of an enhancer region [20, 24, 49, 50], thereby affecting Th17 differentiation [49, 50], potentially through effects on either *IL23R* or *IL12RB2*, which flank it.

This locus is undoubtedly more complex than even this, with different variants associated with AS, IBD and psoriasis in East Asians (where rs11209026 is not found) and multiple rare variants known to be disease associated but for which functional mechanisms underpinning the association are as yet unknown [51–54]. In addition to some genetic loci being specifically associated only with either PsA or cutaneous-only psoriasis (e.g. *PTPN22* [55]and *NFKB1A* [56]), differences have been demonstrated in the key *IL23R* and *TNFAIP3* variants associated with PsA and those with cutaneous-only psoriasis [12, 31]. It is likely that these variants have differences in the mechanism of their association with disease and that these differences contribute to the phenotypic differences between diseases and between cases of specific diseases.

Understanding these differences is likely to contribute to our understanding of disease pathogenesis and prediction of therapeutic efficacy in clinical trials. It is already well established for example that HLA-B27 status is associated with response to TNF inhibitor therapy [57] and, as mentioned above, that diseases with IL-23 pathway genetic associations benefit from therapies targeting this pathway, unlike the situation in RA that is neither genetically associated with this pathway nor responds to its inhibition as well as does axSpA [58, 59]. Pharmacogenetic analyses in large cohorts of patients, such as in registries or long-term cohort studies, will be required to develop predictors of response and toxicity for clinical purposes. A better understanding of the genetic architecture of axSpA, including both the associated loci and the variants within loci and how they operate, will ultimately lead to a better ability to predict response of the disease overall to therapies.

A recent GWAS of Turkish–Iranian AS has confirmed that the FMF gene *MEFV* M694V coding polymorphism is associated with a substantially increased risk of AS in these populations, consistent with previous candidate gene studies and reports of sacroiliitis complicating FMF [4]. The association was found in both HLA-B27-positive and negative cases, but was particularly strong in HLA-B27-negative cases (odds ratio 7.8 in HLA-B27-negative cases), making it the strongest non-MHC association reported to date with AS. This genetic evidence both increases the spectrum of axSpA and also has potential therapeutic implications in AS. The M694V *MEFV* polymorphism is known to lead to autoinflammation, driving IL-1 production, and in the GWAS study, AS patients carrying the M694V variant had increased serum IL-1, IL-17 and IL-23 levels. While the studies of IL-1 inhibition in AS have so far been small and inconclusive, there is no doubt this therapy is highly effective in FMF [60]. These data suggest that in subsets of AS patients, notably in *MEFV* M694V carriers, but perhaps more broadly in HLA-B27-negative AS in particular, IL-1 inhibition deserves further consideration as a therapy.

PRSs and axSpA

PRSs are quantitative measures that use findings from tens to tens of thousands of genetic variants to assess

the risk of disease in individuals. Algorithms to calculate the scores are developed from large GWAS cohorts, assessing the strength of genetic variants with the disease or trait of interest. Individual scores are then calculated by adding the results for each genetic variant included in the PRS, weighted by the effect they have on the disease or trait, to create a quantitative output. Within a population, these scores tend to have normal distributions. As they are a genetic test, they can be used at any point in the patient's clinical course, including prior to the development of disease. It needs to be understood that very few genetic tests, even in monogenic diseases, are diagnostically definitive. Thus, even though PRS may have high discriminatory capacity [e.g. receiver operator characteristics analysis area under the curve (AUC) >0.9], as with any other biomarker test, they do not have 100% specificity and sensitivity. As with all screening or diagnostic tests, their performance depends on the prior probability of the outcome and thus, for example, in population screening they perform less well. Initially developed PRSs focused only on genetic variants that were definitely associated with disease. These performed moderately well but were suboptimal, as the variants tested only captured a small proportion of the overall disease heritability.

Tests that involve hundreds to thousands of markers capturing a higher proportion of the disease heritability performed better, even though they include among those markers a proportion of markers that were not actually disease associated. In AS and psoriasis therefore, tests that only include genome-wide significant (definitely associated) genetic variants do not have much better performance than HLA alone [61, 62]. In contrast, true PRSs in AS, involving thousands of markers, perform very well (AUC = 0.90–0.95), and better overall than CRP, MRI or HLA-B27 alone [63]. This raises the possibility that PRSs could be used to define patients with true inflammatory axSpA, rather than phenocopies (diseases that appear clinically similar but have different aetiologies and pathogenesis). In psoriasis, a PRS involving 226 markers had good discriminatory capacity between PsA and PsC (AUC = 0.80) compared with markers capturing HLA variants alone (AUC = 0.58) [64]. As with most PsA studies, this study did not distinguish between different subtypes of PsA (e.g. axial *vs* peripheral), and it is likely that better performing tests will be developed when more precisely phenotyped cohorts are available and when larger discovery datasets are available from which to develop the PRSs.

PRSs have also been developed to investigate the relationship between AAU and AS. While PRSs have little capacity to distinguish AS cases that have or will develop AAU (AUC = 0.56), they have strong discriminatory capacity to identify AAU patients who have or will develop AS (AUC = 0.96) [65]. These tests perform significantly better than HLA-B27 testing alone and, even if done just for the one indication, can cost less than commercial HLA-B27 testing, which they should ultimately replace.

Relationship between nr-axSpA and AS

It is self-evident that AS has a pre-radiographic phase, as it is known that it takes many years from the onset of symptoms before patients develop the changes seen on plain pelvic radiographs that are a required component of the modified New York AS criteria [66, 67]. New classification criteria have been developed to capture earlier cases prior to changes on plain radiographs, with the commendable goal of enabling research and, in turn, improved diagnosis and treatment of patients with early axSpA. All such criteria developed to date, including the widely used Assessment of SpondyloArthritis International Society (ASAS) criteria, have improved sensitivity in early disease, at the cost of reduced specificity, compared with the modified New York AS criteria [68, 69]. Classification criteria are developed to define diseases that share clinical characteristics, disease pathogenesis, natural history and response to treatment to a maximal extent. Less-specific criteria have adverse performance both in research and in clinical practice. It is becoming increasingly evident that the most widely used axSpA criteria currently employed in clinical practice, the ASAS classification criteria, also capture many patients who do not actually have true axSpA. This is reflected in lower response [70] and treatment retention rates seen in nr-axSpA than AS cohorts [70, 71] and has required additional criteria to be added to ensure adequate specificity for use in clinical trials, such as elevation of ESR/CRP, MRI positivity and/or short disease duration.

The fact that the ASAS criteria were capturing patients with diseases other than true axSpA was clearly demonstrated using PRSs to compare nr-axSpA patients from the ASAS criteria validation study with primarily community-recruited patients with AS [72]. PRSs developed in AS cases performed poorly in nr-axSpA cases meeting the ASAS criteria. While a PRS involving 31 single-nucleotide polymorphisms (SNPs) performed well when comparing AS cases with healthy controls (AUC = 0.90), the same PRS performed less well in MRI-positive axSpA cases (AUC = 0.78) and even had moderate distinguishing capacity between AS and MRI-positive axSpA cases (AUC = 0.67). As we know that these SNPs are not associated with disease severity as assessed by radiographic change, and that the AS cohort has a similar gender distribution to community cohorts, this difference in discriminatory capacity between AS and nr-axSpA is unlikely to be due to the AS cohort being different from general population AS [73, 74]. Even comparing cohorts meeting the ASAS criteria from different sites within the one study, the prevalence of HLA-B27 varied considerably, from 44 to 100% of axSpA cases meeting the ASAS criteria ($P = 0.00085$), again confirming that the ASAS criteria led to classification of quite different patients in different settings [72].

It is possible that some nr-axSpA patients have a form of axSpA that is genetically distinct from AS,

TABLE 2 Comparison of AS patient HLA-B27 prevalence in European and East Asian ethnicities

Ethnicity	Male		Female	
	B27 positive, %	Non-MHC, PRS (S.E.)	B27 positive, %	Non-MHC PRS (S.E.)
European	83.5	0.118 (0.00367)	78.9	0.109 (0.00357)
East Asian	93.7	0.0964 (0.00728)	85.0	0.0859 (0.00666)

Subjects were randomly selected from a larger case–control cohort to ensure an equal gender ratio (1:1) among both cases ($n = 4872$ European, 2430 East Asian) and healthy controls ($n = 12\,400$ European, 2568 East Asian). HLA-B27 prevalence is higher in male than female cases in both European (odds ratio 1.35, $P = 4.7 \times 10^{-5}$) and East Asian (odds ratio 2.64, $P = 4.7 \times 10^{-12}$) datasets; no difference is observed in the controls. PRSs are non-significantly different between males and females in either ethnic group, with a trend for higher scores in males (Europeans $P = 0.079$; East Asians $P = 0.29$; two-tailed *t*-test).

however, the PRS will identify from among nr-axSpA patients those that actually have early AS. In the absence of a better-performing biomarker or imaging test, with the possible exception of MRI if there is substantial inflammation present, PRSs therefore have great potential in axSpA clinical and research studies. However, the development of a PRS specifically for nr-axSpA will be challenging, as it will require the recruitment of large case cohorts (several hundred to thousands) who definitely have inflammatory axial arthritis, using quite specific but sensitive diagnostic criteria to both avoid inclusion of patients with non-inflammatory causes of pain while remaining representative of the disease in the community. These cohorts would then need to be followed longitudinally to study progression to AS, spontaneous remission and response to therapy, as has been done with AS itself.

AxSpA in men and women

Several decades ago it was thought that AS was as much a disease of men as SLE is a disease of women, with ~90% of reported cases being male [75]. There has been substantial improvement over time in awareness of the disease and in the sensitivity of diagnostic methods. Associated with that, there has been a reduction in the observed gender ratio in cohorts, with a large-scale multicentre study with central reading of radiographs recently reporting a 3:1 male predominance [76]. In contrast, among patients with nr-axSpA, the reported gender ratio has been close to unity [77]. It has previously been shown that male AS patients have more extensive radiographic changes [73, 76, 78]. Female AS patients have higher self-reported disease activity, similar functional incapacity and lower CRP levels (reviewed in Rusman et al. [79]).

To date, no convincing evidence that specific genetic variants are responsible for the more extensive radiographic changes in male AS patients has been reported. Nominal association of *ANKH* and *TNAP* variants with female AS has been reported [80, 81], however, these genes are not associated with radiographic severity in a large AS study ($n = 1537$) [73] nor has the finding been replicated in large AS GWASs [43, 82].

The reduction in the observed gender ratio in more recent studies of AS, and in axSpA, may be due to improved diagnosis of radiographically less severe cases, greater awareness of axSpA in women or, theoretically, due to a change in disease prevalence in one or the other sex. PRS studies shed some light on this. In the early 20th century it was unknown how discrete units of inheritance (genes) following Mendel's laws could lead to continuous trait distributions in the population, as well as dichotomous disorders. The famous 20th century mathematician Roland Fischer demonstrated that polygenic disorders with each gene following Mendelian rules could lead to polygenic trait distributions, and he hypothesized that individuals with more than a threshold level of susceptibility would then develop the disease concerned [83]. This theory is widely accepted in genetic studies and underpins modern genetic statistical methods assessing disease heritability in dichotomous traits. From this theory it is apparent that where a gender bias with a disease exists, the gender with the lower prevalence requires a higher genetic risk before it develops the disease. Thus, overall, women with AS should have a higher genetic risk than men with the disease.

Prior to the availability of large genetically characterized AS cohort studies, this was only testable by studying disease recurrence rates in offspring of affected men and women; where the disease is less common in women, the theory predicts that the recurrence rate will be higher in the offspring of women than men. It has previously been demonstrated however that HLA-B27 carriage rates are lower in women than men [84]. To study this further we examined HLA-B27 and PRS measures in gender-matched AS case–control cohorts (Table 2) [24, 63]. This shows that not only do women with AS have a lower prevalence of HLA-B27, but they also do not have increased non-HLA PRSs, both findings being contrary to Fischer's theory.

Possible explanations for this include the presence of substantial X-chromosome genetic associations with AS, as this chromosome is not included in PRS

currently. However, this hypothesis would suggest that female children of male AS patients would be more likely to develop AS; evidence to date suggests that the converse is true [85]. Alternately, it is consistent with a lower clinical diagnostic threshold for women in recent decades, leading to an increase in the misdiagnosis rate in women with AS compared with men. This would be consistent with the higher female prevalence in nr-axSpA [5, 86], lower proportion of women with objective MRI evidence of sacroiliac inflammation among cohorts with clinical nr-axSpA [87] and the shorter retention rate of women with axSpA with biologic therapy [70, 71, 88].

Conclusions

Genetic variation is a major determinant of the clinical pattern of axSpA. This is determined by differences in specific associated genes as well as variation within associated loci between axSpA subtypes. Larger and better phenotyped cohorts are likely to be very productive for research into determinants of important clinical parameters, such as prognosis, extra-articular manifestations and treatment response. PRSs are valuable clinical biomarkers and powerful research tools for investigation of axSpA epidemiology and pathogenesis.

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