

Genetics and the axial spondyloarthritis spectrum

Matthew A. Brown ¹, Huji Xu^{2,3,4} and Zhixiu Li⁵

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

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.

¹Guy's & St Thomas' NHS Foundation Trust and King's College London NIHR Biomedical Research Centre, London, UK,

²Department of Rheumatology and Immunology, Changzheng Hospital, Second Military Medical University, Shanghai, China,

³Peking-Tsinghua Center for Life Sciences, Tsinghua University, Beijing, China, ⁴Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing, China and

⁵Translational Genomics Group, Institute of Health and Biomedical Innovation, Queensland University of Technology, Translational Research Institute, Brisbane, QLD, Australia

Submitted 15 April 2020; accepted 10 June 2020

Correspondence to: Matthew A Brown, Guy's & St Thomas' NHS Foundation Trust and King's College London NIHR Biomedical Research Centre, London SE1 9RT, UK. E-mail: matt.brown@kcl.ac.uk

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			
			<i>IL23R</i>	<i>ERAP1</i>	<i>ERAP2</i>	<i>MEFV</i>
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]

^aIncluded as a comparator for PsA, although not an axSpA. ^bIBD 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 enthesal 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 enthesal-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.

PRs and axSpA

PRs 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 *ANKK1* 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.

Funding: MAB was funded by a National Health and Medical Research Council (Australia) Senior Principal Research Fellowship (1024879). This research was funded/supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London and/or the NIHR Clinical Research Facility. The views expressed are those of the authors and not necessarily those of the National Health Service, the NIHR or the Department of Health. H.X. was supported by the National Natural Science Foundation of China (grant 31821003) and the China Ministry of Science and Technology (grant 2018AAA0100300). This paper was published as part of a supplement funded by Novartis.

Disclosure statement: The authors have nothing to disclose in relation to this manuscript.

References

- 1 Reveille JD, Zhou X, Lee M *et al.* HLA class I and II alleles in susceptibility to ankylosing spondylitis. *Ann Rheum Dis* 2019;78:66–73.
- 2 Cortes A, Pulit SL, Leo PJ *et al.* Major histocompatibility complex associations of ankylosing spondylitis are complex and involve further epistasis with ERAP1. *Nat Commun* 2015;6:7146.
- 3 Burton PR, Clayton DG, Cardon LR *et al.* Association scan of 14,500 nonsynonymous SNPs in four diseases identifies autoimmunity variants. *Nat Genet* 2007;39:1329–37.
- 4 Li Z, Akar S, Yarkan H *et al.* Genome-wide association study in Turkish and Iranian populations identify rare familial Mediterranean fever gene (MEFV) polymorphisms associated with ankylosing spondylitis. *PLoS Genet* 2019;15:e1008038.
- 5 Sieper J, van der Heijde D, Dougados M *et al.* Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). *Ann Rheum Dis* 2013;72:815–22.
- 6 Okada Y, Han B, Tsoi LC *et al.* Fine mapping major histocompatibility complex associations in psoriasis and its clinical subtypes. *Am J Hum Genet* 2014;95:162–72.
- 7 Capon F, Di Meglio P, Szaub J *et al.* Sequence variants in the genes for the interleukin-23 receptor (IL23R) and its ligand (IL12B) confer protection against psoriasis. *Hum Genet* 2007;122:201–6.
- 8 Cargill M, Schrodi SJ, Chang M *et al.* A large-scale genetic association study confirms IL12B and leads to the identification of IL23R as psoriasis-risk genes. *Am J Hum Genet* 2007;80:273–90.
- 9 Strange A, Capon F, Spencer CC *et al.* A genome-wide association study identifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1. *Nat Genet* 2010;42:985–90.
- 10 Feld J, Ye JY, Chandran V, Inman RD *et al.* Is axial psoriatic arthritis distinct from ankylosing spondylitis with and without concomitant psoriasis? *Rheumatology (Oxford)* 2020;59:1340–6.
- 11 Liu Y, Helms C, Liao W *et al.* A genome-wide association study of psoriasis and psoriatic arthritis identifies new disease loci. *PLoS Genet* 2008;4:e1000041.
- 12 Bowes J, Budu-Aggrey A, Huffmeier U *et al.* Dense genotyping of immune-related susceptibility loci reveals new insights into the genetics of psoriatic arthritis. *Nat Commun* 2015;6:6046.
- 13 Popa OM, Cherciu M, Cherciu LI *et al.* ERAP1 and ERAP2 gene variations influence the risk of psoriatic arthritis in Romanian population. *Arch Immunol Ther Exp (Warsz)* 2016;64:123–9.
- 14 Day TG, Ramanan AV, Hinks A *et al.* Autoinflammatory genes and susceptibility to psoriatic juvenile idiopathic arthritis. *Arthritis Rheum* 2008;58:2142–6.
- 15 Orchard TR, Holt H, Bradbury L *et al.* The prevalence, clinical features and association of HLA-B27 in sacroiliitis associated with established Crohn's disease. *Aliment Pharmacol Ther* 2009;29:193–7.
- 16 Akyuz F, Besisik F, Ustek D *et al.* Association of the MEFV gene variations with inflammatory bowel disease in Turkey. *J Clin Gastroenterol* 2013;47:e23–7.
- 17 Leirisalo-Repo M, Sieper J. Reactive spondyloarthritis: epidemiology, clinical features and treatment. M In: Weisman, D Van der Heijde, J Reveille, eds. *Ankylosing spondylitis and the spondyloarthropathies*. Philadelphia: Mosby Elsevier, 2006:53–64.
- 18 Visser H, Vos K, Zanelli E *et al.* Sarcoid arthritis: clinical characteristics, diagnostic aspects, and risk factors. *Ann Rheum Dis* 2002;61:499–504.
- 19 Ohno S, Ohguchi M, Hirose S *et al.* Close association of HLA-Bw51 with Behçet's disease. *Arch Ophthalmol* 1982;100:1455–8.

- 20 Remmers EF, Cosan F, Kirino Y *et al.* Genome-wide association study identifies variants in the MHC class I, IL10, and IL23R-IL12RB2 regions associated with Behçet's disease. *Nat Genet* 2010;42:698–702.
- 21 Kirino Y, Bertsias G, Ishigatsubo Y *et al.* Genome-wide association analysis identifies new susceptibility loci for Behçet's disease and epistasis between HLA-B*51 and ERAP1. *Nat Genet* 2013;45:202–7.
- 22 Wu Z, Zhang S, Li J *et al.* Association between MEFV mutations M694V and M680I and Behçet's disease: a meta-analysis. *PLoS One* 2015;10:e0132704.
- 23 French F. A candidate gene for familial Mediterranean fever. *Nat Genet* 1997;17:25–31.
- 24 Ellinghaus D, Jostins L, Spain SL *et al.* Analysis of five chronic inflammatory diseases identifies 27 new associations and highlights disease-specific patterns at shared loci. *Nat Genet* 2016;48:510–8.
- 25 Parkes M, Cortes A, van Heel DA, Brown MA. Genetic insights into common pathways and complex relationships among immune-mediated diseases. *Nat Rev Genet* 2013;14:661–73.
- 26 Garcia-Vicuna R, Brown MA. Vedolizumab for inflammatory bowel disease: a two-edge sword in the gut-joint/enthesitis axis. *Rheumatology (Oxford)* 2019;58:937–9.
- 27 Cua DJ, Sherlock JP. Autoimmunity's collateral damage: gut microbiota strikes 'back'. *Nat Med* 2011;17:1055–6.
- 28 Kenna TJ, Brown MA. Immunopathogenesis of ankylosing spondylitis. *Int J Clin Rheumatol* 2013;8:265–74.
- 29 Hanson AL, Nel HJ, Bradbury L *et al.* T-cell receptor immunosequencing reveals altered repertoire diversity and disease-associated clonal expansions in ankylosing spondylitis patients. *Arthritis Rheumatol* 2020; doi: 10.1002/art.41252.
- 30 Ruutu M, Yadav B, Thomas GP *et al.* Fungal β -glucan triggers spondyloarthropathy and Crohn's disease in SKG mice. *Arthritis Rheum* 2010;52:1446.
- 31 Stuart PE, Nair RP, Tsoi LC *et al.* Genome-wide association analysis of psoriatic arthritis and cutaneous psoriasis reveals differences in their genetic architecture. *Am J Hum Genet* 2015;97:816–36.
- 32 Bowes J, Orozco G, Flynn E *et al.* Confirmation of TNIP1 and IL23A as susceptibility loci for psoriatic arthritis. *Ann Rheum Dis* 2011;70:1641–4.
- 33 Baeten D, Ostergaard M, Wei JC *et al.* Risankizumab, an IL-23 inhibitor, for ankylosing spondylitis: results of a randomised, double-blind, placebo-controlled, proof-of-concept, dose-finding phase 2 study. *Ann Rheum Dis* 2018;77:1295–302.
- 34 Deodhar A, Gensler LS, Sieper J *et al.* Three multicenter, randomized, double-blind, placebo-controlled studies evaluating the efficacy and safety of ustekinumab in axial spondyloarthritis. *Arthritis Rheumatol* 2019;71:258–70.
- 35 Coates LC, Baraliakos X, Blanco FJ *et al.* The phenotype of axial spondyloarthritis: is it dependent on HLA-B27 status? *Arthritis Care Res (Hoboken)* 2020; doi: 10.1002/acr.24174.
- 36 Roux H, Mercier P, Maestracci D *et al.* Psoriatic arthritis and HLA antigens. *J Rheumatol Suppl* 1977;3:64–5.
- 37 Orchard TR, Thiyagaraja S, Welsh KI *et al.* Clinical phenotype is related to HLA genotype in the peripheral arthropathies of inflammatory bowel disease. *Gastroenterology* 2000;118:274–8.
- 38 Roussomoustakaki M, Satsangi J, Welsh K *et al.* Genetic markers may predict disease behavior in patients with ulcerative colitis. *Gastroenterology* 1997;112:1845–53.
- 39 Robinson PC, Claushuis TA, Cortes A *et al.* Genetic dissection of acute anterior uveitis reveals similarities and differences in associations observed with ankylosing spondylitis. *Arthritis Rheumatol* 2015;67:140–51.
- 40 Robinson PC, Leo PJ, Pointon JJ *et al.* The genetic associations of acute anterior uveitis and their overlap with the genetics of ankylosing spondylitis. *Genes Immun* 2016;17:46–51.
- 41 Kuiper JJ, Van Setten J, Ripke S *et al.* A genome-wide association study identifies a functional ERAP2 haplotype associated with birdshot chorioretinopathy. *Hum Mol Genet* 2014;23:6081–7.
- 42 Franke A, McGovern DP, Barrett JC *et al.* Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. *Nat Genet* 2010;42:1118–25.
- 43 Evans DM, Spencer CC, Pointon JJ *et al.* Interaction between ERAP1 and HLA-B27 in ankylosing spondylitis implicates peptide handling in the mechanism for HLA-B27 in disease susceptibility. *Nat Genet* 2011;43:761–7.
- 44 Sanz-Bravo A, Campos J, Mazariegos MS, Lopez de Castro JA. Dominant role of the ERAP1 polymorphism R528K in shaping the HLA-B27 peptidome through differential processing determined by multiple peptide residues. *Arthritis Rheumatol* 2015;67:692–701.
- 45 Guasp P, Alvarez-Navarro C, Gomez-Molina P *et al.* The peptidome of Behçet's disease-associated HLA-B*51:01 includes two subpeptidomes differentially shaped by endoplasmic reticulum aminopeptidase 1. *Arthritis Rheumatol* 2016;68:505–15.
- 46 Martín-Esteban A, Guasp P, Barnea E, Admon A, López de Castro JA. Functional interaction of the ankylosing spondylitis-associated endoplasmic reticulum aminopeptidase 2 with the HLA-B*27 peptidome in human cells. *Arthritis Rheumatol* 2016;68:2466–75.
- 47 Duerr RH, Taylor KD, Brant SR *et al.* A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. *Science* 2006;314:1461–3.
- 48 Di Meglio P, Di Cesare A, Laggner U *et al.* The IL23R R381Q gene variant protects against immune-mediated diseases by impairing IL-23-induced Th17 effector response in humans. *PLoS One* 2011;6:e17160.
- 49 Roberts AR, Vecellio M, Chen L *et al.* An ankylosing spondylitis-associated genetic variant in the IL23R-IL12RB2 intergenic region modulates enhancer activity and is associated with increased Th1-cell differentiation. *Ann Rheum Dis* 2016;75:2150–6.
- 50 Roberts AR, Vecellio M, Cortes A *et al.* Investigation of a possible extended risk haplotype in the IL23R region

- associated with ankylosing spondylitis. *Genes Immun* 2017;18:105–8.
- 51 Davidson SI, Jiang L, Cortes A *et al.* Brief report: high-throughput sequencing of *IL23R* reveals a low-frequency, nonsynonymous single-nucleotide polymorphism that is associated with ankylosing spondylitis in a Han Chinese population. *Arthritis Rheum* 2013;65:1747–52.
 - 52 Davidson SI, Wu X, Liu Y *et al.* Association of *ERAP1*, but not *IL23R*, with ankylosing spondylitis in a Han Chinese population. *Arthritis Rheum* 2009;60:3263–8.
 - 53 Rivas MA, Beaudoin M, Gardet A *et al.* Deep resequencing of GWAS loci identifies independent rare variants associated with inflammatory bowel disease. *Nat Genet* 2011;43:1066–73.
 - 54 Beaudoin M, Goyette P, Boucher G *et al.* Deep resequencing of GWAS loci identifies rare variants in *CARD9*, *IL23R* and *RNF186* that are associated with ulcerative colitis. *PLoS Genet* 2013;9:e1003723.
 - 55 Bowes J, Loehr S, Budu-Aggrey A *et al.* PTPN22 is associated with susceptibility to psoriatic arthritis but not psoriasis: evidence for a further PsA-specific risk locus. *Ann Rheum Dis* 2015;74:1882–5.
 - 56 Zhao Q, Sun Y, Fu X *et al.* Identification of a single nucleotide polymorphism in *NFKB1A* with different effects on psoriatic arthritis and cutaneous psoriasis in China. *Acta Derm Venereol* 2019;99:84–8.
 - 57 Rudwaleit M, Claudepierre P, Wordsworth P *et al.* Effectiveness, safety, and predictors of good clinical response in 1250 patients treated with adalimumab for active ankylosing spondylitis. *J Rheumatol* 2009;36:801–8.
 - 58 Dokoupilova E, Aelion J, Takeuchi T *et al.* Secukinumab after anti-tumour necrosis factor-alpha therapy: a phase III study in active rheumatoid arthritis. *Scand J Rheumatol* 2018;47:276–81.
 - 59 Brown MA. Breakthroughs in genetic studies of ankylosing spondylitis. *Rheumatology (Oxford)* 2007;47:132–7.
 - 60 Gul A, Ozdogan H, Erer B *et al.* Efficacy and safety of canakinumab in adolescents and adults with colchicine-resistant familial Mediterranean fever. *Arthritis Res Ther* 2015;17:243.
 - 61 Rostami S, Hoff M, Brown MA *et al.* Prediction of ankylosing spondylitis in the HUNT study by a genetic risk score combining 110 single-nucleotide polymorphisms of genome-wide significance. *J Rheumatol* 2020;47:204–10.
 - 62 Yin X, Cheng H, Lin Y *et al.* A weighted polygenic risk score using 14 known susceptibility variants to estimate risk and age onset of psoriasis in Han Chinese. *PLoS One* 2015;10:e0125369.
 - 63 Li Z, de Guzman E, Harris J *et al.* Genetic risk score prediction in ankylosing spondylitis. *Arthritis Rheum* 2018;70(Suppl 9):1–3553.
 - 64 Patrick MT, Stuart PE, Raja K *et al.* Genetic signature to provide robust risk assessment of psoriatic arthritis development in psoriasis patients. *Nat Commun* 2018;9:4178.
 - 65 Huang X-F, Li Z, de Guzman E *et al.* Genomewide association study of acute anterior uveitis identifies new susceptibility loci. *Invest Ophthalmol Vis Sci* 2020;61:3.
 - 66 Mau W, Zeidler H, Mau R *et al.* Clinical features and prognosis of patients with possible ankylosing spondylitis. Results of a 10-year followup. *J Rheumatol* 1988;15:1109–14.
 - 67 van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984;27:361–8.
 - 68 Robinson PC, Wordsworth BP, Reveille JD, Brown MA. Axial spondyloarthritis: a new disease entity, not necessarily early ankylosing spondylitis. *Ann Rheum Dis* 2013;72:162–4.
 - 69 van der Linden S, Akkoc N, Brown MA, Robinson PC, Khan MA. The ASAS criteria for axial spondyloarthritis: strengths, weaknesses, and proposals for a way forward. *Curr Rheumatol Rep* 2015;17:62.
 - 70 Ornbjerg LM, Brahe CH, Asklind J *et al.* Treatment response and drug retention rates in 24 195 biologic-naive patients with axial spondyloarthritis initiating TNFi treatment: routine care data from 12 registries in the EuroSpA collaboration. *Ann Rheum Dis* 2019;78:1536–44.
 - 71 Grintborg B, Sorensen IJ, Ostergaard M *et al.* Ankylosing spondylitis versus nonradiographic axial spondyloarthritis: comparison of tumor necrosis factor inhibitor effectiveness and effect of HLA-B27 status. An observational cohort study from the nationwide DANBIO registry. *J Rheumatol* 2017;44:59–69.
 - 72 Thomas GP, Willner D, Robinson PC *et al.* Genetic diagnostic profiling in axial spondyloarthritis: a real world study. *Clin Exp Rheumatol* 2017;35:229–33.
 - 73 Cortes A, Maksymowych WP, Wordsworth BP *et al.* Association study of genes related to bone formation and resorption and the extent of radiographic change in ankylosing spondylitis. *Ann Rheum Dis* 2015;74:1387–93.
 - 74 International Genetics of Ankylosing Spondylitis Consortium, Cortes A, Hadler J *et al.* Identification of multiple risk variants for ankylosing spondylitis through high-density genotyping of immune-related loci. *Nat Genet* 2013;45:730–8.
 - 75 West HF. Aetiology of ankylosing spondylitis. *Ann Rheum Dis* 1949;8:143–8.
 - 76 Lee W, Reveille JD, Davis JC Jr *et al.* Are there gender differences in severity of ankylosing spondylitis? Results from the PSOAS cohort. *Ann Rheum Dis* 2007;66:633–8.
 - 77 Rudwaleit M, Landewe R, van der Heijde D *et al.* The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. *Ann Rheum Dis* 2009;68:770–6.
 - 78 Ward MM, Hendrey MR, Malley JD *et al.* Clinical and immunogenetic prognostic factors for radiographic severity in ankylosing spondylitis. *Arthritis Rheum* 2009;61:859–66.

- 79 Rusman T, van Vollenhoven RF, van der Horst-Bruinsma IE. Gender differences in axial spondyloarthritis: women are not so lucky. *Curr Rheumatol Rep* 2018;20:35.
- 80 Tsui HW, Inman RD, Paterson AD, Reveille JD, Tsui FW. ANKH variants associated with ankylosing spondylitis: gender differences. *Arthritis Res Ther* 2005;7:R513–25.
- 81 Tsui HW, Inman RD, Reveille JD, Tsui FW. Association of a TNAP haplotype with ankylosing spondylitis. *Arthritis Rheum* 2007;56:234–43.
- 82 Reveille JD, Sims AM, Danoy P *et al.* Genome-wide association study of ankylosing spondylitis identifies non-MHC susceptibility loci. *Nat Genet* 2010;42:123–7.
- 83 Fischer R. The correlation between relatives on the supposition of Mendelian inheritance. *Trans R Soc Edinb* 1918;52:399–433.
- 84 van der Horst-Bruinsma IE, Zack DJ, Szumski A, Koenig AS. Female patients with ankylosing spondylitis: analysis of the impact of gender across treatment studies. *Ann Rheum Dis* 2013;72:1221–4.
- 85 Calin A, Brophy S, Blake D. Impact of sex on inheritance of ankylosing spondylitis: a cohort study. *Lancet* 1999;354:1687–90.
- 86 Kiltz U, Baraliakos X, Karakostas P *et al.* Do patients with non-radiographic axial spondylarthritis differ from patients with ankylosing spondylitis? *Arthritis Care Res (Hoboken)* 2012;64:1415–22.
- 87 Rusman T, John MB, van der Weijden MAC *et al.* Presence of active MRI lesions in patients suspected of non-radiographic axial spondyloarthritis with high disease activity and chance at conversion after a 6-month follow-up period. *Clin Rheumatol* 2020;39:1521–9.
- 88 Gulfe A, Kapetanovic MC, Kristensen LE. Efficacy and drug survival of anti-tumour necrosis factor-alpha therapies in patients with non-radiographic axial spondyloarthritis: an observational cohort study from Southern Sweden. *Scand J Rheumatol* 2014;43:493–7.