Genetics of spondyloarthritis—beyond the MHC

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Abstract | Ankylosing spondylitis (AS), psoriasis and inflammatory bowel disease (IBD) often coexist in the same patient and in their families. In AS, genes within the MHC region, in particular *HLA-B27*, account for nearly 25% of disease hereditability, with additional small contributions from genes outside of the MHC locus, including those involved in intracellular antigen processing (that is, *ERAP1*, which interacts with *HLA-B27*) and cytokine genes such as those involved in the IL-17–IL-23 pathway. Similar to AS, the strongest genetic signal of susceptibility to psoriasis and psoriatic arthritis also emanates from the MHC region (attributable mostly to *HLA-C*06:02* although other genes have been implicated), and gene–gene interaction of *HLA-C* with *ERAP1*. The remaining hereditary load is from genes involved in cytokine production, specifically genes in the IL-17–IL-23 pathway, the NFκB pathway and the type 2 T-helper pathway. In IBD, similar genetic influences are operative. Indeed, genes important in the regulation of the IL-17–IL-23 pathway and, in Crohn's disease, genes important for autophagy (that is, *NOD2* and *ATG16L1* and *IRGM*) have a role in conferring susceptibility of individuals to these diseases. Thus, AS, psoriasis and IBD seem to share similar pathogenic mechanisms of aberrant intracellular antigen processing or elimination of intracellular bacteria and cytokine production, especially in the IL-17–IL-23 pathway.

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Introduction

After the initial discoveries of the association of *HLA-B27* positivity with ankylosing spondylitis[1] (AS) and of *HLA-Cw6* with psoriasis[2] in the 1970s (which was later refined to *C*06:02*), the importance of genetic factors in disease susceptibility became clear. However, little substantive progress in finding other genes associated with these diseases was made for over 30 years. During the 1990s, microsatellite technology was developed triggering numerous family studies that used affected sibling pair analyses to identify chromosomal regions linked to diseases including AS, psoriasis and inflammatory bowel disease (IBD). These studies enabled the identification of a candidate locus in the MHC region for psoriasis susceptibility (*PSORS1*) and another on chromosome 16q12 for IBD (*IBD1*), which was subsequently found to contain *NOD2* (previously referred to as *CARD15*).[3,4] The sequencing of the human genome during the HapMap project enabled the development of high-throughput automated microarray chip technologies. These technologies facilitated dense genome-wide association and resequencing studies that have led to remarkable advances in gene discovery and genetic characterization of the susceptibility of individuals to spondyloarthritis (SpA) and related diseases. This Review explores advances in our understanding of the genetics of AS that have ensued from these technological approaches, and briefly compares these findings with those in the related diseases psoriasis, psoriatic arthritis (PsA) and IBD. More importantly, common genetic factors or pathways in these diseases that not only underscore similar mechanisms in pathogenesis but also highlight new directions for therapeutic intervention are discussed.

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Genetics of AS

HLA-B27

Family studies,[5] reports of disease concordance in twins,[5] and modeling of genetic risk[6] show that hereditary factors account for the majority of cases of AS; moreover, several genes are likely to be operative in pathogenesis.[6] The strongest genetic association with AS is with the MHC region, particularly *HLA-B27*.[5,7] Since the association of *HLA-B27* with AS was first described nearly 40 years ago, the allele has persisted as one of the best examples of a hereditary marker associated with a complex disease.[7]

How the product of *HLA-B27* contributes to disease susceptibility is only now becoming clear. Initial hypotheses focused on the canonical function of HLA-B27 as a MHC class I molecule in presenting an 'arthritogenic peptide' to $CD8^+$ T cells. Despite numerous studies, however, such a peptide has yet to be discovered. Indeed, as will be discussed in the section on the role of genes outside of the MHC region, aberrant peptide presentation (rather than presentation of a pathogenic peptide) might account for the influence of *HLA-B27*.

One current mechanism for how HLA-B27 could lead to AS is based on the presence of a unique Cys67 residue in the extracellular α1 domain of HLA-B27 heavy

chains that enables them to self associate and form homodimers.[8] HLA-B27 heavy-chain homodimerization, or misfolding, could then cause retention in the endoplasmic reticulum of the nascent molecules by the endoplasmic chaperone BiP, promoting excessive induction of the proinflammatory unfolded protein response.[9]

An alternative mechanism is based on the observation that HLA-B27 homodimers can be expressed on the cell surface (that is, they are not retained in the endoplasmic reticulum) and bind to KIR3DL1, KIR3DL2, and immunoglobulin-like transcript 4 (ILT4) receptors on synovial and peripheral blood monocytes, B cells and T cells.[10] Thus, HLA-B27 heavy-chain homodimers (which exclude β2-microglobulin, the third component of the HLA–antigen complex that activates the T-cell receptor) might activate disease-relevant immunoreceptors and downstream pathways. Lack of involvement of the unfolded protein response is supported by a study published in 2011,[11] which examined blood monocyte-derived dendritic cells from patients with AS, testing the ability of HLA-B27 to form heavy-chain dimers along with the induction of endoplasmic reticulum stress.[11] No substantial difference was noted in the global levels of MHC class I dimers in patients compared with healthy individuals. Moreover, no evidence of stress in the endoplasmic reticulum was found, although lower levels of BiP were observed.

A different mechanism (which is not known to involve heavy chain homodimerization, although investigations are ongoing) is based on the inability of *HLA-B27*-positive individuals to clear certain intracellular pathogens. Interestingly, although *HLA-B27* confers a survival advantage in the face of viral infections such as HIV, hepatitis C, and influenza, carriers of the gene are defective in the killing of intracellular bacterial species of genera including *Yersinia, Salmonella, Shigella,* and *Chlamydia*.[12] These bacteria have been well documented in the triggering of reactive arthritis.[12] Further evidence for persistent bacterial infection having a role in the pathogenesis of SpA was reported in a study from 1998 that revealed the presence of bacterial antigens or DNA in synoviocytes of patients with reactive arthritis.[13]

All of these mechanisms are likely to have a role in predisposing an individual to SpA. Less than one in 20 *HLA-B27*-positive individuals, however, develop SpA, as opposed to 20% of *HLA-B27*-positive relatives of patients with AS.[14] A compilation of the variance supplied by individual genes implicated in AS and confirmed in genome-wide association studies (GWAS) to be linked with AS susceptibility have shown that *HLA-B27* is responsible for only 23.3% of AS heritability.[7] However, as the majority of *HLA-B27*-positive individuals do not develop SpA, the mechanisms I have outlined do not fully explain susceptibility to AS. Clearly, other genetic factors further increase the likelihood of a carrier of *HLA-B27* developing AS or another subtype of SpA.

Other *HLA-B* alleles and MHC genes

More than 220 genes reside in the MHC region, many of which are important in the immune response. The attempt to elucidate the role of other genes in the MHC region in the pathogenesis of AS, however, has been confounded by linkage disequilibrium of these genes with *HLA-B27*. The best evidence for another *HLA-B* allele being operative in AS susceptibility is *HLA-B60* (referred to as *HLA-B*40:01* by DNA typing), which was identified in studies of US[15] and UK[16] patients with AS, as well as in *HLA-B27*-negative patients with AS from Taiwan.[17] The role of other genes in the MHC region, including *MICA*, *TNF, HSP70* and HLA-class II region genes (such as *DRB1* and *LMP2*) have been examined, but defining a definite contribution to AS susceptibility has been confounded by the linkage disequilibrium known to exist in this region.[18] In fact, in a GWAS in 2011, after controlling for the presence of *HLA-B27*, few single nucleotide polymorphisms (SNPs) remained that achieved genome-wide significance except around the *HLA-B* locus, potentially reflecting additional contribution of other *HLA-B* alleles or other genes nearby (including *HLA-C* and *MICA*).[19]

Key points

- Ankylosing spondylitis (AS), psoriasis and inflammatory bowel disease (IBD) exhibit both shared as well as disease-specific genes that are operative in susceptibility
- Genes within the MHC region (especially *HLA-B27*) account for the majority of the currently known susceptibility of individuals to AS
- Genes outside of the MHC region involved in intracellular antigen processing and cytokine production (especially genes in the IL-17–IL-23 pathway), also predispose individuals to AS, although their overall contribution to hereditability is small
- Psoriasis and psoriatic arthritis have similar characteristics to AS: the majority of disease susceptibility is from the MHC region, and most of the remaining susceptibility is from genes involved in cytokine production
- In IBD, genes important in autophagy (in Crohn's disease) and regulation of the IL-17–IL-23 pathway have a large role in disease susceptibility

Genes outside of the MHC region

Three GWAS in AS susceptibility in individuals from the USA, UK and Australia (the Australo–Anglo–American Spondylitis Consortium or TASC, in collaboration with the Wellcome Trust Case Control Consortium) have been published, which have identified more than 14 (and counting) susceptibility genes or genetic loci to date (Supplementary Table 1, Figure 1).[19–21] These genes contribute up to 25.39% of the overall heritability of AS, with the overwhelming majority provided by *HLA-B27* itself (Table 1).[7]

ERAP1

The first report of *ERAP1* (previously known as *ARTS-1*) as a risk factor for AS was in patients from the UK and USA.[20] This finding was replicated in another UK cohort and subsequently confirmed in independent studies from the UK, USA, Canada, Portugal, Hungary, China and Korea.[19,22–27] The primary function of the product of *ERAP1* (endoplasmic reticulum aminopeptidase 1) is to act as a molecular ruler in the endoplasmic reticulum in the trimming of peptides processed in proteasomes to an optimal length of nine amino acids for MHC class I binding and presentation.[28] Thus, these findings

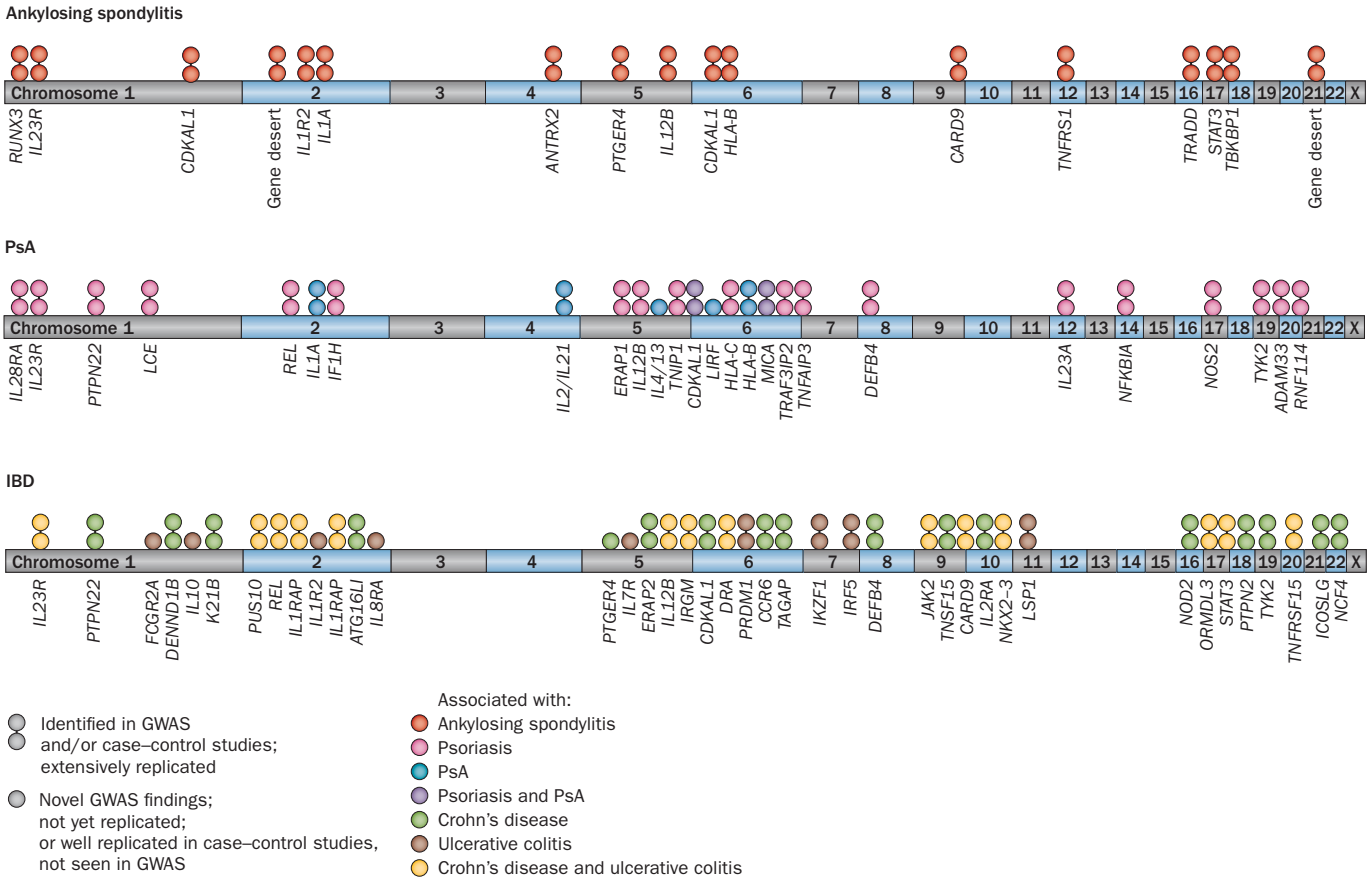

Figure 1 | Innate immunity, antigen presentation and the T_H17 pathway are all implicated in conferring susceptibility to AS, psoriasis/PsA and IBD. Double spheres indicate a gene identified in a GWAS and/or in multiple case–control studies and extensively replicated. Single spheres indicate relatively novel GWAS findings not yet replicated, or genes well-replicated in case–control studies but not identified in GWAS. For psoriasis and PsA, the spheres are colored according to whether they are associated with just psoriasis, just PsA, or both. Similarly, the spheres on the IBD chromosomal depiction are colored according to whether they are associated with Crohn's disease alone, ulcerative colitis alone, or both diseases. Other genes of less clear functional relevance to psoriasis not shown include *PTTG1*, *CSMD1*, *GJB2, SERPINB8* and *ZNF816A*. Similarly, genes whose functional relevance to Crohn's disease or ulcerative colitis has not been established, (such as: *MST1* and *PSMG1;* for Crohn's disease, *DNMT3A*, *PHOX2*B, *BACH2*, and *c11orf30* at chr.11q13.5; and for ulcerative colitis, *OTUD3*, *DAP*, *LYRM4*, *GNA12*, *LAMB1*, *CCNY*, *CUL2*, and *HERC2)* are not shown. Abbreviations: GWAS, genome-wide association study; IBD, inflammatory bowel disease; T_H17, type 17 T helper (cell); PsA, psoriatic arthritis.

suggest that aberrant antigen presentation (rather than a particular antigen) is crucial in AS pathogenesis.

Of particular interest, a statistical gene–gene interaction between *HLA-B27* and *ERAP1* is known to occur in patients with AS (that is, *ERAP1* alleles that predispose to disease only do so in the presence of *HLA-B27*),[19] similar to what has been described between *HLA-Cw*06:02* and *ERAP1* in patients with psoriasis.[29] However, although the product of *ERAP1* interacts with HLA-B27,[19] disease-associated *ERAP1* alleles are in fact loss-of-function variants, suggesting that instead of HLA-B27 itself being pathogenic, aberrant presentation of this peptide contributes to disease development. Loss-of-function polymorphisms in *ERAP1* in patients with AS could affect peptide supply and influence heavy chain dimerization or misfolding of HLA-B27.

Studies using crystal structures of human endoplasmic reticulum aminopeptidase 1 proteins have revealed that a K(528)R mutant, which is strongly associated with AS, has markedly altered peptide processing characteristics, possibly caused by impaired interdomain interactions.[30] The expression of *ERAP1* has been shown to be higher in dendritic cells of patients with AS when compared with healthy controls, suggesting that overexpression of *ERAP1* is a mechanism that promotes the pathogenesis of AS.[19] In addition to antigen processing, the product of *ERAP1* also cleaves cell surface receptors for the cytokines IL-1 (IL-1R2), IL-6 (IL-6Rα) and TNF (TNFR1) to downregulate their proinflammatory signaling.[31] That said, cytokine receptor cleavage is unlikely to have a substantial role in AS susceptibility, as one study in 80 patients with AS found no substantial difference in the level of serum cytokines or soluble receptors between patients with different *ERAP1* and/or *ERAP2* polymorphisms and their haplotypes.[32] Moreover, another study tested the ability of human endoplasmic reticulum aminopeptidase 1 to cleave the cytokine receptors TNFR and IL-6R in *ERAP1* knockout and C57BL/6 control mouse spleens and found no differences

in cleavage over time, indicating that the aminopeptidase does not have a major role in cleaving cytokine receptors.[19]

IL23R

The importance of the IL-17–IL-23 axis in the pathogenesis of SpA and related diseases was apparent early on with the near simultaneous discoveries that the same SNPs within *IL23R* are associated with IBD,[33] psoriasis[34] and AS.[20] IL-23R does not interact with IL-12, but pairs with IL-12RB1 to confer IL-23 responsiveness on cells expressing both subunits of this cytokine. In the case of AS, this finding has been extensively replicated in cohorts of patients with AS from Canada, Spain, Portugal and Hungary.[24,35–38] By contrast, this association was not seen in patients from Korea and China,[26,39,40] which is likely to be because the associated SNPs are not polymorphic in these cohorts.

Intergenic regions

Intergenic regions, also known as 'gene deserts', at chromosomes 2p15 and 21q22 were associated with AS in cohorts of patients with AS from the UK and USA.[21] The association of the 2p15 locus with AS was replicated in other cohorts from Europe, the USA, China and Korea.[19,27,40] In addition to the association seen in adult patients from the US and UK, in pediatric patients with IBD the intergenic region at chromosome 21q22 was also identified[41] (although this observation did not explain the association with AS in the adult cohorts). Whether these regions contain regulatory regions for other AS associated genes in other genomic locations is currently unknown.

IL1 region genes and IL1R2

Genes in the IL-1 locus at chromosome 2p15 were reported to be associated with AS in patients from Europe and the USA over 10 years ago.[42–46] Subsequently, a multicenter study identified *IL1A* as an AS susceptibility gene.[47] However, subsequent GWAS have not confirmed this association with the IL-1 locus,[19–21] potentially owing to methodological or stratification issues. However, a role for genes in the IL-1 region in AS susceptibility was suggested by a GWAS that identified *IL1R2*, located at chromosome 2q12.[21] Its product, IL-1 receptor type 2, inhibits IL-1 activity by acting as a decoy target for IL-1. Nevertheless, the contribution of IL-1 to AS susceptibility, is likely to be small; indeed, an IL-1 receptor antagonist was relatively ineffective in treatment of patients with AS.[48]

ANTXR2

The *ANTXR2* gene at chromosome 4q21 encodes a receptor for anthrax toxin and was associated with AS in patients from the US and UK,[21] although whether this association will be replicated in further studies remains to be seen. The ANTXR2 protein binds to type IV collagen and laminin, suggesting that it is involved in extracellular matrix adhesion. Mutations in *ANTXR2* have been implicated in juvenile hyaline fibromatosis and infantile systemic hyalinosis.[49] Expression of *ANTXR2* does not differ in patients with AS when compared with healthy controls, so its role in AS is unclear.[21]

Table 1 | Contribution to heritability of AS of confirmed susceptibility genes

Gene name or chromosomal region	Most highly associated SNP	Odds ratio	Overall contribution to AS heritability (%)[12]
HLA-B27	rs4349859	90.4	23.3
IL23R	rs11209026	1.90	0.31
LTBR-TNFRSF1A	rs11616188	1.38	0.075
2p15	rs10865331	1.36	0.54
ERAP1	rs30187	1.35	0.34
KIF21B	rs2297909	1.25	0.25
21q22	rs378108	1.25	0.035
TBKBP1	rs8070463	1.24	0.054
ANTXR2	rs4389526	1.21	0.054
PTGER4	rs10440635	1.20	0.052
RUNX3	rs11249215	1.19	0.12
IL12B	rs6556416	1.18	0.11
CARD9	rs10781500	1.18	0.034
IL1R2	rs2310173	1.18	0.12
Total	–	–	25.39

Abbreviations: AS, ankylosing spondylitis; SNP, single nucleotide polymorphism.

RUNX3

In 2011, data from GWAS implicated *RUNX3* (located at chromosome 1p36) in AS susceptibility.[19] The transcription factor this gene encodes is involved in $CD8^+$ T cell differentiation[50] suggesting that this process is involved in the effect of HLA-B27. In a previous GWAS of peripheral blood cell subsets, SNPs in *RUNX3* associated with AS in the 2011 study were also associated with decreased $CD8^+$ T cell counts.[19]

IL12B

IL12B, located at chromosome 5q33, encodes the IL-12p40 protein, which is a shared component of both IL-12 and IL-23 and was shown to be associated with AS in the TASC cohort.[19] Of note, ustekinumab—a monoclonal antibody that targets *IL12B* was successful in the treatment of patients with psoriasis and SpA.[51]

TNF pathway associated genes

Data from TASC and the WTCCC2 revealed associations between SNPs in a region of chromosome 12p13 encompassing the genes *LTBR* and *TNFRSF1A* and AS.[19] This association was confirmed in Han Chinese patients with AS.[52] Furthermore, mice in which TNF is constitutively overexpressed develop IBD and SpA. Interestingly, SpA development was dependent on *TNFR1* expression; moreover, *TNFR1* expression in mesenchymal tissue alone was sufficient to promote disease.[53] Further functional and genetic studies, however, will be required to determine if the genetic polymorphisms at this locus are associated with AS owing to effects on *LTBR* or *TNFR1*, or both.

Studies in the TASC and WTCCC2 cohorts have also implicated nearby *TBKBP1* on chromosome 17q21[19] —which encodes an adaptor protein that binds to serine/threonine-protein kinase TBK1 and is part of the

interaction network in the TNF–NFκB pathway[54] in the pathogenesis of AS.

The product of *TRADD*, located on chromosome 16q22, is also part of the TNF signaling pathway. This gene showed a potential association with AS in the TASC/WTCCC2 dataset;[19,21] further evidence for this association was provided by data from an additional UK cohort.[55]

CARD9

Nonsynonymous SNPs in *CARD9* on chromosome 9q34 were also identified as having a role in susceptibility to AS in GWAS[19,21] and this association was later confirmed in a study in 730 UK patients with AS.[56] The product, caspase recruitment domain-containing protein 9 (hCARD9) is an adaptor molecule that oligomerizes with BCL10 and the paracaspase MALT1 to form a trimolecular complex that transduces signaling to the canonical NFκB pathway[57] and has an essential role in protection against fungal and bacterial pathogens. hCARD9 has an important role in the IL-17–IL-23 pathway, signaling via NFκB to induce production of TNF, IL-6 and IL-23 (but not IL-12), and differentiation of T cells secreting IL-17 and IL-23.[58] Examination of an mRNA expression database revealed that the SNPs most strongly associated with AS (or in strong linkage disequilibrium) were those most associated with *CARD9* expression.[56]

PTGER4

The protein product of the *PTGER4* locus, prostaglandin E_2 (PGE_2) receptor EP4 subtype, stimulates dendritic cells to produce IL-23, which, in turn, promotes expansion of T cells secreting IL-17 and IL-23. Expression of *PTGER4* is increased in response to mechanical stress, and, as PGE_2 is bone anabolic, this locus potentially links inflammation and bone formation in AS. Moreover, β-glucan, via its receptor dectin-1 (involved in TLR2-mediated inflammatory responses), induces PGE_2 production.[59] This induction has substantial implications for the pathogenesis of AS, in which the anabolic processes of syndesmophyte formation and spinal fusion are important manifestations of the disease.

KIF21B and STAT3

A study of 53 markers selected from 30 Crohn's disease-associated genomic regions in patients of European ancestry with AS identified a region around chromosome 1q32 near *KIF21B*, as well as *STAT3* at 17q21, as AS susceptibility loci.[52] Although the relevance of *KIF21B* to AS pathogenesis is less clear, *STAT3* encodes a key signaling molecule within the IL-17–IL-23 T cell differentiation pathway, which underscores the key role of this T-cell subset in AS pathogenesis. The association of *STAT3* with AS was subsequently confirmed in 775 Han Chinese patients with AS from Shanghai and Nanjing.[40]

HLA-B27 negative genetics

More than 10% of patients with AS do not express *HLA-B27*.[1,18] Except for a lower frequency of uveitis and a later age at disease onset, *HLA-B27*-negative patients with AS have similar clinical symptoms as those who are *HLA-B27* positive.[60] No consistent association with any *HLA* gene has been described in *HLA-B27* negative patients with AS. In one study, the first to examine non-*HLA* genes in *HLA-B27*-negative patients, *ERAP1* was associated with AS only in those who were *HLA-B27* positive, whereas no association was seen with *ERAP1* in *HLA-B27* negative patients.[19] By contrast, other genes with established associations with AS, including *IL23R* and the intergenic regions 2p15 and 21q22, *IL12B*, *KIF21B* and *TBKBP1*, were associated with AS in both *HLA-B27*-positive and *HLA-B27*-negative disease.[19] These findings are the first convincing evidence of an association in *HLA-B27*-negative AS, and indicate both considerable overlap and divergence in genetic susceptibility between *HLA-B27*-positive and *HLA-B27*-negative AS.

Genetics of psoriasis

Genes in the MHC region

By virtue of the high degree of familial aggregation and associations with *HLA-B13*, *HLA-B37* and *HLA-B57* (reflecting linkage disequilibrium with *HLA-C*06:02*), the important role for genetic factors in psoriasis susceptibility has long been recognized.[2] *HLA-C*06:02* also seems to be a prognostic marker of disease severity, and is associated with a younger age of disease onset, familial aggregation and more severe disease.[61] The major locus in psoriasis susceptibility is a region in the MHC around *HLA-C* known as *PSORS1*.[62] This region has been extensively studied and *HLA-C* itself has been implicated in conferring susceptibility.[63] In 2011, data demonstrating gene–gene interaction between *HLA-C*06:02* and *ERAP1* in psoriasis[29], similar to that reported between *HLA-B27* and *ERAP1* in AS,[19] further implicated aberrant MHC peptide processing as a mechanism in psoriasis susceptibility.

A role for other MHC loci has also been suggested, including the region around C6orf10 (a potential downstream effector of TNF) and *MICA*, a distant homolog of MHC class I genes, in a large study of patients with psoriasis of European and Chinese ancestry.[64] MICA is of particular interest because it can be induced by cellular or metabolic stress in the epithelia, providing ligands for the activatory T-cell receptor, NKG2D.[65] In psoriasis, *MICA* is downregulated in lesional skin when compared with nonlesional skin.[66]

Genes outside of the MHC region

A number of GWAS and candidate gene studies in patients of European and Chinese descent have been published in the past three years and have implicated genes outside of the MHC region in conferring susceptibility to psoriasis, including those in the IL-17–IL-23 axis, the NFκB pathway[29,67–70] and the type 2 T-helper pathway (*IL4, IL13*) (Supplementary Table 2, Figure 1).[29,67–74] As discussed above, *ERAP1* is also implicated in predisposing individuals of Chinese and European ancestry to psoriasis.[29,74]

Other immunologically relevant genes associated with psoriasis include *TRAF3IP2*,[29,75,76] which encodes the NFκB activator ACT1,[77] as well as *ADAM33*, *PTPN22* (Table 1) and *CDKAL1*, whose role in psoriasis

pathogenesis is less clear. Another nonimmunologically relevant locus is the *LCE* gene cluster, in which gene deletions (copy number variants, CNVs) have been implicated in psoriasis susceptibility in patients of European and Chinese ancestry[78,79]. A number of other genes of unclear functional relevance to psoriasis have also been identified (Table 1).

Genetics of PsA

Genes in the MHC region

The genetics of PsA are not as well defined as those of psoriasis, probably owing to phenotypic heterogeneity and case ascertainment in patients with PsA. Associations of the disease with *HLA-B* alleles have been reported (that is, *HLA-B38*, *HLA-B39* and *HLA-B27*), yet these associations are not as strong as the association of *HLA-C*06:02* with psoriasis.[2,18] A study in Canadian patients with PsA found that, after controlling for linkage disequilibrium with the nearby *HLA-B* locus, *MICA*016* influenced the risk of individuals developing psoriasis without arthritis, and that homozygosity for *MICA*0801* increased the risk of patients with psoriasis developing PsA.[80] Another gene in the MHC region was implicated in PsA susceptibility in a large cohort of Canadian patients with PsA: *RNF39*, also known as *LIRF*, which is located near *HLA-A*.[81] Its function is unknown, although it is associated with HIV1 disease progression.

Genes outside of the MHC region

Studies from the UK and Canada have implicated genes in the IL-1 gene complex in conferring susceptibility to PsA,[82,83] although, as in AS, these associations have not been confirmed in GWAS. As in psoriasis, genetic variants in *IL23A, TNFAIP3* and *TNIP1* have also been described as conferring risk of PsA.[84] The association of the *IL13, IL4* gene locus at chromosome 5q31 has been reported to be more specific for PsA than for psoriasis as a whole.[85,86] Other potential PsA susceptibility factors are *LCE* gene deletions on chromosome 1q31, which were associated with PsA in one study[87] but not another.[88] Finally, one GWAS[70] implicated a region at chromosome 4q27 containing the genes *IL2* and *IL21*, which have been implicated in the pathogenesis of a number of other autoimmune diseases, in PsA susceptibility. These findings require confirmation in further studies.

Genetics of IBD

The importance of IBD in the pathogenesis of SpA is underscored by the fact that sacroiliitis and spondylitis occur in up to 20% of patients with IBD. Furthermore, up to 70% of patients with AS or another subtype of SpA will have microscopic evidence of gut inflammation, although only ~7% develop Crohn's disease.[89]

Family studies of microsatellite markers revealed an association between *NOD2* on chromosome 16q12 and Crohn's disease.[3,4] The NOD2 protein serves as an intracellular receptor for bacterial products in monocytes and transduces signals leading to NFκB activation.[90] *NOD2* accounts for approximately 20% of the overall Crohn's genetic susceptibility[3,4] People carrying *NOD2* variant alleles show reduced localization of bacteria in autophagolysosomes.[90] A number of GWAS, and meta-analyses thereof, have been conducted that have implicated more than 99 genes in IBD susceptibility,[91–99] including 71 for Crohn's disease, 47 for ulcerative colitis and a minimum of 28 shared association signals between Crohn's disease and ulcerative colitis (Supplementary Table 2, Supplementary Table 3, Figure 1). *ATG16L1*, which is expressed in intestinal epithelial cell lines, has been identified in GWAS and widely confirmed as an important factor in Crohn's disease susceptibility.[91,92] Dendritic cells from patients with Crohn's disease carrying alleles of *NOD2* or *ATG16L1* that are associated with susceptibility are deficient in autophagy induction, suggesting that these genes influence bacterial degradation and interact with the MHC class II antigen presentation machinery.[85] Another autophagy gene that has been implicated in susceptibility to Crohn's disease and ulcerative colitis is *IRGM* at chromosome 5q33,[100] a gene implicated in the control of intracellular pathogens and in the reduction of intracellular bacillary load.[101] The association of Crohn's disease with the *IRGM* locus has been attributed to an alteration in regulation of *IRGM* expression that affects the efficacy of autophagy; a common insertion/deletion polymorphism upstream of *IRGM* is likely to be the causal variant.[101]

A number of other genes, some associated with Crohn's disease (Supplementary Table 3, Figure 1), others with ulcerative colitis (Supplementary Table 4), and some common to both gut diseases (Table 2) have been described and validated in patients of European and Asian ancestry.[102]

Although most of the differences in Crohn's disease when compared with ulcerative colitis susceptibility reside in genes associated with sensing of intracellular bacteria and with autophagy (processes that are not implicated in the pathogenesis of ulcerative colitis), disparity is also seen in other genes involved in the innate immune response or pattern recognition pathways. For example, the associations of *HLA-DRA*, *IRF5*, *FcGRIIa* and *IL10* with ulcerative colitis are not seen in Crohn's disease.[97]

Genes common to AS, psoriasis, PsA and IBD

AS, IBD, and psoriasis and PsA not only tend to occur in the same families, but also clearly share common genetic and immunologic mechanisms (Table 2).[98] One example is the potentially defective intracellular processing of antigens (indicated by the association of the *ERAP1* and *HLA-B27* gene–gene interaction in AS, and of *ERAP1* and *HLA-Cw6* in psoriasis); another is defective autophagy (implicated by the *NOD2, ATG16L1*, and *IRGM* associations in Crohn's disease). Shared associations with genes in the IL-17-IL-23 axis (*IL23R, IL12B, STAT3, JAK2, PTGER4, PUS10* and *IL18RAP)* and in the NFκB pathway (*REL, CARD9*) suggest that alterations in these signaling cascades are also common to the pathogenesis of these related diseases. Associations with genes whose relevance to SpA is less clear (*DEFB4, CDKAL1, KIF21B, ORMDL3, MST1* and *PSMG*) are also common to these disorders.

Table 2 | Genetic factors shared between susceptibility to AS, psoriasis and IBD

Genetic factors by functional pathway and disease	AS	Psoriasis	IBD	
			Crohn's disease	Ulcerative colitis
Intracellular antigen processing	*HLA-B27, ERAP1*	*HLA-Cw6, ERAP1*	*ERAP2*	*HLA-DRA*
Autophagy	–	–	*IRGM*	*IRGM*
T_H17 pathway	*IL23R, IL12B, STAT3, PTGER4*	*IL23R, IL12B*	*IL23R, IL12B, STAT3, JAK2, PTGER4, PUS10 IL18RAP*	*IL23R, IL12B, STAT3, JAK2, IL18RAP, PUS10*
NFκB pathway	*CARD9*	*REL*	*REL, CARD9*	*REL, CARD9*
Immune response	*IL1R2, ORMDL3*	*DEFB4, IL2/IL21, PTPN22, TYK2*	*DEFB4, IL2/IL21, NKX2-3, ORMDL3, PTPN22, TNFRSF6B, TYK2*	*IL2/IL21, IL1R2, NKX2-3, ORMDL3, TNFRSF6B*
Genes of unclear immune relevance	*CDKAL1, KIF21B*	*CDKAL1*	*CDKAL1, KIF21B, MST1, PSMG1*	*MST1, PSMG1*

Abbreviations: AS, ankylosing spondylitis; IBD, inflammatory bowel disease; T_H17, type 17 T helper (cell).

Environmental factors and SpA

Non-genetic causes of SpA have been examined, particularly *Klebsiella* spp. in AS. Early studies indicated that these bacteria could have a pathogenic role,[12] although this hypothesis has not been confirmed. Furthermore, although environmental factors are likely to participate in disease initiation, those that have been implicated are thought to be ubiquitous and nonspecific (such as gut bacteria) and are thus likely to have only a minor role in triggering pathology.[5,6] Roles for infectious triggers, such as streptococcal pharyngitis, and other environmental factors such as trauma and stress have been proposed in the onset of psoriasis also, but a detailed discussion of these influences are beyond the scope of this Review.

Future directions

GWAS have been successful in characterizing only part of the genetic variance in the incidence of SpA. In AS, for example, only 25% of the heritability has been elucidated (Table 1). One reason for this shortfall is the requirement for large sample sizes (in the tens of thousands or higher) for the discovery of genes that have a small impact on overall susceptibility (associations with disease with an odds ratio of 1.1 or less). Further analysis is likely to lead to the discovery of currently unmapped common variants. Other sources of genetic contribution are rare variants, discovery of which will require extensive resequencing studies, as has already been shown for variants of *IL23R* in IBD.[104] Gene CNVs have already been described in the β-defensin 4 locus in patients with psoriasis and Crohn's disease[105,106] and in the *LCE* gene cluster in PsA.[87] Small CNVs and insertions/deletions are extremely difficult to genotype using current high-throughput array technology (which is optimized for SNP genotyping), and thus remain a potential source of missing heritability. Epigenetic factors, such as differences in methylation patterns, might also have a role in conferring susceptibility, but the heritability of such influences is minor. Finally, epistasis (gene–gene interaction) is an area of recent investigation. Heritability estimates such as those listed in Table 1 are calculated from models of pathogenesis that allow for only additive effects, that is, in the absence of gene–gene interaction. Validation studies that use multi-marker, as opposed to single-marker, analyses in independent cohorts are reported to have an improved capacity for risk prediction;[107] such studies are the focus of ongoing investigations as the statistical methodologies are being developed and refined.

Also lacking at present are functional studies that show how the genes implicated in disease susceptibility actually affect AS, psoriasis and IBD pathogenesis. Until such data are available, it remains possible that the disease associations of some of the genes identified in GWAS might be attributable to other genes with which they are linked.

Conclusions

A consistent picture is emerging of the role of genetic factors in susceptibility to AS, psoriasis and PsA, and IBD. In AS and psoriasis, associations with *HLA-B27* and *HLA-C*06:02* and their interaction with *ERAP1* implicate aberrant intracellular peptide processing, leading to altered peptide presentation, in the development of pathology.[4] In IBD, especially in Crohn's disease, defective autophagy of intracellular bacteria has a role. Superimposed onto these disease-specific associations are shared genetic factors, some of which are important in the IL-17–IL-23 network (*IL23R, IL12B, STAT3, PTGER4*), the NFκB pathway (*CARD9, REL*), and other aspects of innate immunity (*IL2*, *IL21*), whereas others are of less clear immunologic relevance (*CDKAL1*). Thus, both shared and disease-specific genes are operative in conferring susceptibility to AS, psoriasis, PsA and IBD, suggesting common mechanisms of susceptibility and pathogenesis.

Review criteria

This Review was based on selected full-text English language papers published from 2000 and listed in PubMed, as well as additional references found by reading the reference lists of the papers identified. Search terms used included "ankylosing spondylitis AND genetics", "psoriasis AND genetics", "psoriatic arthritis AND genetics", "inflammatory bowel disease AND genetics", "ulcerative colitis AND genetics", and "Crohn's disease AND genetics". Papers reporting associations that have not been replicated or which have been refuted have not been included here unless of particular relevance to the discussion.

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Supplementary information
Supplementary information is linked to the online version of the paper at www.nature.com/nrrheum