Review

HLA-B27: what’s new?

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Abstract

The HLA-B27 molecule is one of the most fascinating in medicine. Its contribution to the aetiopathogenesis of SpA and other diseases, and its protective action in certain infections, continue to challenge our understanding of its immunobiology and physiological roles. Animal studies have helped to cast light on ways in which HLA-B27 exerts its effects. Subtle variations in structure and behaviour between B27 subtypes that are strongly associated with SpA, compared with those whose association is neutral or weak, are helping to elucidate its pathogenetic mechanisms. However, none of the current hypotheses fully explains the observed actions of HLA-B27. Consequently, attention is turning to how haplotype linkages and genetic networks involving other MHC and non-MHC genes influence the penetrance and clinical expression of B27. HLA-B27 gives an intriguing insight into the connection between heredity and disease. As well as its close links with SpA, various other associations have been reported between B27 and diseases of different organs and systems. Evidence is also accumulating that it mitigates the virulence of HIV and other viral infections. The role of HLA-B27 as an aid to diagnosis, prognosis and disease management is gradually becoming clearer.

Key words: HLA-B27, Ankylosing spondylitis, Spondyloarthropathy, Infection.

Introduction

The HLA-B27 molecule is one of the most fascinating in medicine. Since first coming to prominence in 1973 with the discovery of its intimate association with AS [1, 2], much has been learnt about its immunobiology and its involvement both in the aetiopathogenesis and in the prophylaxis of disease. A previous review in 2004 [3] concluded with the prediction that new associations of HLA-B27 and novel uses for it as a diagnostic and prognostic aid would continue to be discovered as our understanding of the functional nature and role of the antigen increased. So, 5 years later, what is new?

Geographical and population variations in the prevalence of HLA-B27 and its subtypes

There has been a steady flow of publications describing the geographical prevalence of HLA-B27 and the frequency and distribution of its subtypes in different populations and ethnic groups [4–18]. Most reports have confirmed the known geographical distribution of the different subtypes of HLA-B27, with HLA B*2705 being common in Caucasians and American Indians, HLA B*2704 in Asians and HLA B*2702 in Mediterranean populations [19]. Each of these alleles shows a strong association with AS, which has also been reported with other rare subtypes, including B*2701, B*2703, B*2707, B*2708, B*2710, B*2713, B*2714, B*2715, B*2719 and B*2725 [19]. HLA-B*2705 is present in nearly all populations and is deemed to be the genetic ancestor from which the other B27 alleles have evolved.

Although a common HLA-B27 subtype in Southeast Asia, comprising more than half of all B27 subtypes found in Indonesia, Malaysia and Thailand [20], B*2706 has been reported only sporadically in AS patients in those countries [14]. Similarly, although HLA-B*2709, which comprises ~20% of the B27 alleles in Sardinia and ~3% in Southern Italy [19], was recently reported in a Sardinian woman with AS, she also possessed another MHC allele which has been found to confer susceptibility to AS [21].

Contrary to their reported association with AS in other populations [19], HLA-B*2707 may be protective against AS and other HLA-B27-related diseases in Greek Cypriots [5], whereas HLA-B*2708 may provide protection in Mestizos [17], since both are found only in healthy controls in these populations.
In contrast to other Asian populations, such as Han [22] and Taiwan [14] Chinese or the Japanese [15], the predominant HLA-B27 subtype associated with AS in Koreans is B*2705 rather than B*2704 [15, 16]. In Taiwan Chinese, susceptibility to AS is determined by homozygosity for HLA-B*2704, whereas B*2705 may confer protection [23]. The first association of B*2724 in a Chinese Han with juvenile AS was reported in 2006 [13]. HLA-B27 homozygosity does not affect the clinical manifestations of AS in Korean patients [24]. HLA-B27 is virtually absent in Zambian patients with AS [25].

**Mechanisms of action of HLA-B27**

How HLA-B27 predisposes to the development of AS and other SpAs remains unknown. The classic role of MHC Class 1 molecules is to present peptides to CD8+ T cells, but HLA-B27 may also possess functions, which are unrelated to antigen presentation [19].

Studies of transgenic rodents, which indicated that HLA-B27 is directly involved in disease pathogenesis rather than merely being a marker for a linked disease-associated gene [26], have spawned various hypotheses attempting to explain how its immunobiological effects are mediated.

The “arthritogenic peptide” hypothesis proposes that particular properties of the HLA-B27 peptide binding groove enable the molecule to display microbial peptides that exhibit molecular mimicry with specific arthritogenic self-peptides. This would allow the response of HLA-B27-restricted cross-reactive cytotoxic T-lymphocytes to a foreign peptide to be directed against self-peptides as well. The autoimmune reaction might then lead to chronic inflammation. The finding of a viral peptide and two self-peptides that exhibit HLA-B27 subtype-dependent molecular mimicry supports the concept of the hypothesis [27], but there is no proof for the involvement of these peptides in the pathogenesis of AS.

Structural and behavioural differences between individual subtypes, with differing strengths of association with AS, are believed to be instrumental in the pathogenesis of SpA. Subtypes HLA-B*2706 and B*2709 are, at most, weakly associated with AS [19]. HLA-B*2706 differs from B*2704 by only two amino acid residues and B*2709 differs from B*2705 by just one [19]. However, while differences in amino acid sequences that involve the peptide binding groove and hence determine peptide specificity could contribute to the different strengths of association with AS, they do not provide the whole answer.

It has been suggested that B*2709 arose in the Mediterranean region by a single mutation from B*2705 on a haplotype associated with low susceptibility for AS and that it is the haplotype that is more important for disease predisposition than the immunobiological differences between B*2705 and B*2709 [19]. In Sardinia, most of the B*2709 and B*2709 alleles are inherited on different haplotypes [20] and it is feasible that B*2709 has remained strongly linked to a low-risk haplotype. Where AS has been reported in association with B*2709, other genetic factors are liable to have been implicated. In two recent cases of AS in Southern Italy and Sardinia, in which the patients carried HLA-B*2709, one had co-existing ulcerative colitis [28] and the other possessed HLA-B*1403, an allele that was found to be associated with AS in a small study of B*27 Togolese (West African) patients [29]. Additional genetic differences between populations possessing B*2709 and B*2705 might also contribute to their differing associations with SpA [19].

Being present in a much larger and probably more genetically diverse population, the case for a lack of association between B*2706 and disease is more compelling, but patients with this subtype and AS have been reported as well [14, 30].

The HLA-B27 heavy chain has a tendency to misfold. Misfolding appears to occur in the endoplasmic reticulum prior to conjugation of the heavy chain with β2 microglobulin (β2m) and its cargo peptide. Formation of disulphide bonds between the cysteine residue at position 67 (cys 67) in the B pocket of the peptide binding groove of two separate heavy chain molecules creates homodimers without the participation of β2m. Endoplasmic reticulum stress resulting from the accumulation of misfolded heavy chains activates the unfolded protein response, which may induce cytokine production by macrophages and thereby promote inflammation [31]. However, while the misfolding hypothesis gains support from the observation that HLA-B*2706 and B*2709 fold much more efficiently than disease-associated subtypes B*2705, B*2704 and B*2702, it is undermined by the fact that HLA-B*2707, which is associated with AS in most populations in which it is found, folds as efficiently as B*2706 and B*2709 [32].

β2m-free homodimers of B27 can also be expressed on the cell surface where they are capable of binding with immunoregulatory receptors of other cells, including killer immunoglobulin-like receptors (KIRs) and leucocyte immunoglobulin-like receptors (LILRs). Ligation of their receptors promotes the survival of NK cells and T cells expressing KIRs, and modulates immune cytokine production [33], LILRs, which are mainly expressed on lymphoid and myelomonocytic cells, are also involved in the activation and regulation of the immune system [34]. Potentially, the interaction of cell surface β2m-free B27 homodimers with these immune receptors could play a part in the pathogenesis of autoimmune disorders, including SpA.

A pathogenetic role has also been mooted for β2m. It has been postulated that, following its release from a subpopulation of cell surface-expressed HLA-B27 molecules, it is deposited within synovial tissues, provoking an inflammatory process that culminates in a destructive arthropathy [35]. This hypothesis is given weight by new findings in transgenic rats [27].

It is well established that AS has a polygenic aetiology. Whereas HLA-B27 accounts for over half of the genetic susceptibility, other genes involved in inflammation, such as ARTS1, IL23R and IL1A, have also been shown to be associated with susceptibility to AS and they may interact...
with HLA-B27 to predispose to the development of SpA [36].

Although there is evidence that HLA-B27 modulates the interaction between ReA-triggering bacteria and the host cell [37], the finding that the presence of HLA-B27 on the surface of human cells does not alter the degree of bacterial invasion by *Salmonella typhimurium* or *Yersinia enterocolitica* suggests that this factor should not necessarily be implicated in the pathogenesis of ReA triggered by these bacteria [38].

**Effect of HLA-B27 on disease presentation in inflammatory arthritis**

The antiquity of the link between AS and HLA-B27 has been highlighted by the identification of HLA-B27 sequences in the mediaeval skeletal remains of a man with classical features of AS [39]. In contrast with an early report [40], a recent Finnish study showed that HLA-B27 homozygosity is associated with a moderately increased risk of AS compared with B27 heterozygosity [41].

AS develops at an earlier age in patients who are HLA-B27+ than in those who are HLA-B27− [42, 43]. In a Chinese population, the earliest age of onset of AS is associated with the HLA-B*2715 subtype [43]. Nonetheless, HLA-B27 is associated with the severity and the persistence of MRI-demonstrated inflammatory changes in the SI joints and the lumbar spine in early SpA [45].

Expression of HLA-B27 mRNA correlates with clinical disease activity in patients with HLA-B27+ AS compared with unaffected B27+ family members and unrelated healthy B27+ control subjects [46].

In a recent study, HLA-B27+ individuals were at greater risk of experiencing severe joint pain following gastrointestinal infection. However, a significant association between self-reported reactive joint pain and HLA-B27 was found only for *Salmonella*, *Shigella* and *Yersinia* and not for *Campylobacter* or *Escherichia coli* [47].

As well as conferring increased susceptibility to psoriatic SpA, HLA-B27 is associated with earlier age of onset of psoriasis and arthritis, bilateral sacroiliitis and male gender, but not with severity or extent of the spondylitic process or with functional impairment [48]. In a study of Brazilian patients with PsA, carriage of HLA-B27 was associated positively with spondylitis and negatively with oligoarthritis [49].

Sacroiliitis is common in patients with established Crohn’s disease and is symptomatic in the majority of cases. In this disease, possession of HLA-B27 is associated with the development of AS but not with isolated sacroiliitis [50, 51].

The HLA-B27 antigen is detected in patients with RA no more often than would be expected by chance [52]. However, when present, most studies have shown that possession of B27 influences the radiographic features in subjects with classical seropositive RA, particularly predisposing to an increased frequency of SI joint involvement [52, 53]. In an early study, HLA-B27+ patients with classical RA also had more subcutaneous nodules, worse functional class and higher ESR and haptoglobin levels [53], but these findings have not been confirmed.

Ochronotic SpA, especially axial involvement, may be more severe in HLA-B27+ individuals [54]. Although the spinal changes resemble those of AS, erosion and fusion of the SI joints, annular ossification and syndesmophytes do not occur [54].

Clinical and laboratory features are of limited help in predicting the course and severity of juvenile idiopathic arthritis. In a Scandinavian study [55], the presence of HLA-B27 was associated with an older age of onset and a higher risk of more joint involvement, including involvement of small joints in the lower extremities in boys. In the first 3 years of disease, B27 was also associated with enthesitis in boys and with inflammatory back pain in both sexes [55].

In patients with juvenile SpA in India, urinary tract infection, diarrhoea and constipation were more common in HLA-B27+ cases [56]. In Indian patients with severe haemophilia, HLA-B27 is a strong risk factor for chronic synovitis [57].

**Organ disease associated with HLA-B27**

**Ocular**

Recent studies have confirmed that an HLA-B27-associated extra-ocular disorder, most commonly AS or undifferentiated SpA, occurs in three-quarters of cases of B27-associated uveitis in French [58] and Chinese [59] patients. Uveitis is frequently the first indication of a previously undiagnosed HLA-B27-associated extra-ocular disease [58].

In Turkish citizens, HLA-B27+ acute anterior uveitis (AAU) is more common in males and B27− AAU in females. Unilateral or bilateral alternating AAU as well as fibrinous reaction and hypopyon formation are more common in B27+ patients [60].

HLA-B27+ is the predominant allele in Brazilian patients with SpA and anterior uveitis [61], whereas HLA-B27 subtypes may [62], or may not [63], be important in the development of HLA-B27-associated AAU in Japanese patients.

HLA-B27+ SpA expresses its visual features mainly in the form of anterior uveitis and anterior scleritis but posterior scleritis has recently been reported in patients with the B27 haplotype, suggesting a probable association [64].

The long-term prognosis for vision in HLA-B27-associated AAU is favourable, regardless of frequent attacks of severe AAU [65]. Despite more severe
inflammation and hypopyon formation, and a higher rate of recurrence of attacks, the ocular and visual outcomes are similar in HLA-B27+ AU, compared with B27- idiopathic AU, in Korean patients [66]. However, the visual outcome of B27-associated uveitis is worse where there is posterior segment involvement [67]. Hypotonic maculopathy should be considered as a possible cause of vision loss in patients with B27-associated anterior uveitis [68].

Paradoxically, uveitis is milder in patients with HLA-B51+ Behc¸et’s disease who also possess the HLA-B27 haplotype, owing to less posterior segment involvement and complications, and a less chronic course [69].

Herpes simplex virus is the leading cause of infectious corneal blindness in the developed world. HLA-B27 predisposes to recurrence of herpetic eye disease and graft failure following penetrating keratoplasty for herpetic corneal scars, and prophylactic anti-viral therapy should be considered seriously in these patients [70]. HLA-B27 does not influence the risk of AAU following laser in situ keratomileusis (LASIK) [71].

Recurrent AAU has been reported as the initial manifestation of ochronotic arthropathy in a HLA-B27+ man [72]. The occurrence of AAU in a male patient with HLA-B27, after recovery from the systemic features of Q fever, was thought to be a reactive complication triggered by Coxiella burnetii [73].

The pro-inflammatory cytokine TNF-α may participate actively in the pathogenesis of clinical uveitis as patients with HLA-B27+ uveitis have significantly higher concentrations of TNF-α in their aqueous humour than patients without HLA-B27 [74].

Aural Ear involvement is not generally regarded as a complication of SpA. However, studies have shown that sensorineural hearing loss (SNHL), especially at high frequencies, is common in patients with AS [75–78], suggesting that it may be an extra-articular feature of the disease. A reported case of SNHL in a patient with HLA-B27+ sclero-uveitis has hinted at a possible association between HLA-B27 and Cogan’s syndrome [79], an immune-mediated systemic disorder characterized by ocular and audiovestibular inflammation. In a Chinese series of patients with AS, autoantibodies directed against the inner ear were positive in a quarter of cases [75].

Pulmonary Although lung involvement was initially described in 1941, it has been considered as an extra-articular manifestation of AS only since 1965. In a prospective study of patients with AS without respiratory symptoms, non-specific subclinical pulmonary involvement [including altered plain chest radiograph (8%), restrictive pattern on pulmonary function tests (52%) and abnormalities on thoracic high resolution CT (40%)] was common in AS but was not associated with HLA-B27 [80]. Whereas pooled immunogenetic data revealed an association between HLA-B27 and pulmonary sarcoidosis in Czech and Italian populations [81], this has not been confirmed conclusively in clinical practice [82].

Cardiovascular Morbidity and mortality from cardiovascular diseases are increased in inflammatory rheumatic diseases, including SpA [83] and RA [84]. HLA-B27 has been identified as a risk factor for a cardiovascular event in RA and is associated with a decreased lifespan [85]. Although the risk of requiring a permanent cardiac pacemaker has been reported to be substantially increased in men carrying HLA-B27 when compared with other B alleles [86], in an observational study, patients with a permanent pacemaker attending a cardiac clinic were no more likely to be HLA-B27+ than controls [87].

Aortic regurgitation in patients with AS may be due to a combination of inflammation and dilatation of the aorta and fibrosis of the valve itself [88]. While aortitis is usually a feature of long-standing AS, it may also occur early and acutely in young patients with HLA-B27 and SpA [88]. Acute aortitis can lead to abdominal aortic aneurism [89] or non-traumatic dissection of the aorta [90] in HLA-B27+ individuals with AS.

Retroperitoneal Chronic periaortitis (CP) is a rare condition characterized by retroperitoneal periaortico-fibro-inflammatory tissue, which commonly obstructs neighbouring structures [91]. The conditions that it encompasses include idiopathic retroperitoneal fibrosis (RPF) and inflammatory abdominal aortic aneurism [91]. RPF may result from a local immune response to products of aortic atheromatous plaques with subsequent periaortic deposition of fibrous tissue [92]. Extra-articular fibrosis, including apical pulmonary fibrosis and fibrosis of the aortic valve and aorta, is recognized as a feature of AS. In the reported cases of concomitant RPF and SpA, patients developed SpA several years before RPF [92]. Around one-third to a half of reported cases of CP occurring in association with SpA have been HLA-B27+ [91, 93]. HLA-B27 has also occasionally been reported in black American patients with RPF in the absence of SpA, although the antigen has a low prevalence in this population [94]. However, the hypothesis that HLA-B27 might be a genetic risk factor for CP [93] was not supported by a recent immunogenetics study [95].

Haematological A case of myelodysplastic syndrome in a patient with AS prompted further speculation that HLA-B27 might also increase the risk of haematological diseases [96]. Multiple myeloma has occasionally been reported in patients with AS and it has been postulated that persistent reticuloendothelial cell stimulation due to chronic subclinical gastrointestinal infection may lead to activation and proliferation of IgA-producing plasma cells and the subsequent development of IgA myeloma [97].

Female patients with seropositive RA who possess HLA-B27 may be at increased risk of developing drug-induced agranulocytosis, especially if they also
have ANA [98] and HLA-B27 alone may confer an increased risk of this complication in other individuals [98]. Antibody to HLA-B27 has been implicated in a case of neonatal alloimmune thrombocytopenia [99].

Renal
Renal involvement is rare in SpA but includes amyloidosis and GN [100], especially IgA nephropathy [101]. Eighteen per cent of patients with IgA nephropathy carry the HLA-B27 gene [102]. Where IgA nephropathy has been reported in association with SpA, spondyloitis has usually preceded the renal lesion, whereas renal involvement has occurred simultaneously in Reiter’s syndrome [103].

In a study of renal transplant recipients in the USA, HLA-B27 was positively associated with IgA nephropathy-induced end-stage renal disease in African-American and white patients compared with race-matched controls [104]. HLA-B27 is the Class 1 antigen most closely linked with childhood minimal change nephritic syndrome in Egypt [105]. It is also associated with augmented cyclosporine blood availability in renal allograft recipients [106].

Endocrine
A 4-fold increased frequency of HLA-B27 has been found in patients with autoimmune thyroiditis when compared with controls [107]. Possession of HLA-B27 has previously been reported to be associated with an increased risk of developing Icenko–Cushings disease [108] and apparently causes lower levels of glucocorticoid receptors on blood lymphocytes [109].

Osseous
An early [110], but unconfirmed [111], report that one-third of patients with Forrestier’s disease (DISH) possessed HLA-B27 suggested a possible association between the antigen and genes controlling bone formation. This apparent increased frequency of B27 could not be explained by the rare simultaneous occurrence of DISH and AS [112] and no further evidence has been presented linking Forrestier’s disease with HLA-B27.

AS is characterized by both reduced (osteoporosis) and increased (syndesmophytes, joint ankylosis) bone formation. Vertebral osteoporosis is common in patients with AS and appears to be related to disease activity [113]. The spine is a key fracture site in AS, with the reported risk of vertebral fractures varying from 0.4 to 58% [113]. Although vertebral fractures appear to be linked to the duration and severity of the disease rather than to BMD [113], they can also occur in individuals with undiagnosed benign SpA [114]. In a study of family members of a patient with AS and osteogenesis imperfecta (OI), several of whom also had OI and/or possessed HLA-B27, more severe osteoporosis was found in those with HLA-B27 [115]. Recent research involving HLA-B27 transgenic rats has shown an association with bone fragility [116].

Dermatological
As well as its recognized link with psoriasis, through association with PsA, HLA-B27 is a component of several haplotypes associated with vitiligo in Chinese Han patients [117]. In a Turkish study, erythema nodosum (EN) was more common in patients with IBD who were HLA-B27+ than in B27− individuals [118]. This contrasts with earlier data indicating a negative association between EN and HLA-B27 in post-Yersinia ReA [119].

Neurological
Although spinal cord and cauda equina compression may complicate cervical subluxation or lumbar canal stenosis in SpA [100], these neurological manifestations have not been reported to be associated with HLA-B27. While a multiple sclerosis (MS)-like syndrome was recently described in a patient with AS and HLA-B27 [120], MS has also been reported in a patient with HLA-B27−AS [121].

Infections
A wider understanding has been gained about the role of HLA-B27 in host defence against infections and how it exerts its protective effect. Virus-specific CD8+ T cell responses play an important role in the natural course of infection. Cytotoxic T lymphocyte responses, activated by HLA antigen presentation, especially HLA-B27, are implicated in the control of HIV replication, thereby retarding the progression to AIDS and conferring a better prognosis [122].

HLA-B27 also promotes spontaneous CD8+ T cell-mediated viral clearance of HCV [123] and is associated with a more favourable course in certain other virus infections as well, including influenza virus, EBV and HSV-2 infections [122].

The frequency of HLA-B27 is lowest (0%) in the equatorial region and highest (40%) in the arctic and most northerly populations [30]. Its geographic spread broadly follows a latitude-related gradient which is inverse to that of endemic malaria [124]. In Western India, Plasmodium falciparum is more likely to infect HLA-B27− individuals [125]. If it confers greater susceptibility to more severe forms of malaria, the B27 gene will be negatively selected in endemic regions, thereby explaining the observed inverse relationship.

In a study of Indian patients with juvenile SpA, tuberculosis was diagnosed in 14.3% of cases of whom 60% possessed HLA-B27, suggesting that B27 positivity may also predispose to tuberculosis [56]. An association has also been reported between HLA-B27 and tuberculosis in Tuvinian nationals in the Republic of Tyva in Central Asia [126].

The musculoskeletal system is involved in 30–85% of patients with brucellosis, with peripheral arthritis and sacroiliitis being the commonest articular manifestations [127]. An early report from Hungary suggested that patients with chronic brucellosis who possessed the HLA-B27 antigen had a considerably increased risk of SpA [128]. However, while brucellosis may be an
occasional triggering infection for ReA in HLA-B27+ individuals [129], no association was found between HLA-B27 and brucellosis-associated SpA, including ReA and spondylitis, in Peruvian and Spanish patients when compared with healthy individuals [130, 131].

Likewise, although the frequency of HLA-B27 was found to be higher in Turkish patients with brucellosis complicated by osteoarticular involvement, particularly spondylitis, when compared with patients without osteoarticular involvement or healthy controls, the difference was not statistically significant [132]. Yersinia enterocolitica pneumonia is rare but has been reported in a patient with diabetes mellitus and HLA-B27+ SpA [133], raising the question of whether HLA-B27 may have played a role in the infection.

Miscellaneous

HLA-B27 positivity may contribute to an increased frequency of sacroiliitis in patients with FMF [134]. The reported associations between HLA-B27 and diseases of different organs and systems are summarized in Table 1.

### Conclusion

The exact role of HLA-B27 in pathogenesis remains unclear but features that distinguish it from other genes and differences between its many subtypes have provided the basis for several putative explanations as to how it might predispose to and mediate disease. Most hypotheses seeking to explain the association between HLA-B27 and AS take into account the existence of differentially associated B27 alleles, on the grounds that the small differences between healthy and disease-associated subtypes may help to characterize the peptides that are involved in the pathogenesis of SpA. However, none of the current hypotheses, including those based on the peptide binding properties of HLA-B27 or the aberrant folding of its heavy chain, fully explains its immunobiological activity or the variation in the strength of association of the different B27 subtypes with AS. Whereas research has hitherto focused predominantly on the HLA-B27 molecule itself, recent discoveries have highlighted the role of networks of interacting genes in mediating and modulating disease expression. Haplotype linkages could transpire to be more important than subtle differences in the B27 subtypes.

While its relationship is strongest with SpA, associations have also been reported between HLA-B27 and many other diseases or particular clinical features. Some are indisputable, whereas, for others, time will tell whether they are true associations or merely chance occurrences. Other genes, or gene combinations, are likely to be identified that influence the penetrance and phenotypic expression of HLA-B27. These and other factors may also clarify our understanding of how HLA-B27 protects

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### Table 1: Associations between extra-articular organ disease and HLA-B27

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<td>Immune system</td>
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against certain infections, while possibly increasing susceptibility to others. Additionally, they may provide pointers for the development of specifically targeted therapies. Although HLA-B27 still harbours many secrets, this fascinating and versatile molecule continues to give an intriguing insight into the connection between heredity and disease.

**Rheumatology key messages**

- HLA-B27 affects clinical expression in SpA and other diseases.
- HLA-B27 mitigates the virulent effects of certain viruses, including HIV and HCV, but may increase susceptibility to malaria.

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