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Polymorphism of HLA-B27: 105 Subtypes Currently Known

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Abstract HLA-B27 has a high degree of genetic polymorphism, with 105 known subtypes, named HLA-B*27:01 to HLA-B*27:106, encoded by 132 alleles. The most common subtypes associated with ankylosing spondylitis are HLA-B*27:05 (Caucasians), HLA-B*27:04 (Chinese), and HLA-B*27:02 (Mediterranean populations). For Chinese populations, HLA-B*27:04 is associated with a greater ankylosing spondylitis risk than HLA-B*27:05. Two subtypes, HLA-B27*06 and HLA-B27*09, seem to have no disease association. These differential disease associations of HLA-B27 subtypes, and the recent discovery that ERAP1 is associated with ankylosing spondylitis for patients with HLA-B27, have increased attempts to determine the function of HLA-B27 in disease pathogenesis by studying hemodynamic features of its protein structure, alterations of its peptidome, aberrant peptide handling, and associated molecular events. However, after 40 years we still do not fully know how HLA-B27 predisposes to ankylosing spondylitis and related spondyloarthritis.

Keywords Ankylosing spondylitis · Spondyloarthritis · Spondyloarthropathies · HLA-B27 · Subtypes · HLA-B*27 · HLA-B*27:05 · Alleles · HLA-B*27:0502 · Pathogenesis · ERAP1 · Polymorphism · Genetic heterogeneity

Introduction

HLA-B27 is an HLA class I surface protein encoded at the B locus of the major histocompatibility complex (MHC), on the short arm of chromosome 6. It was discovered as a serological specificity in 1969 [1], and four years later its association with ankylosing spondylitis and related forms of spondyloarthritis was discovered [2–4]. It was later observed that the strength of this association varies for different forms of spondyloarthritis and between ethnic and racial groups [5–8].

Polymorphism of HLA-B27 Genes and Molecules

Research has revealed HLA-B27, like many other HLA class I molecules, to have high genetic polymorphism. This polymorphism largely results from nucleotide changes in exons 2 and 3, which encode the alpha 1 and alpha 2 domains of HLA-B27's antigen-binding cleft [9–11]. The number of known subtypes of HLA-B27 is now 105, named HLA-B*27:01 to HLA-B*27:106 by the new nomenclature (Fig. 1) [12]. There is no subtype HLA-B*27:22: this assignment was revoked when it was later found to be based on a sequence error.

The *HLA-B*27* gene has 132 currently-known alleles, defined on the basis of nucleotide sequence difference [12]. As shown in Fig. 1, there are two alleles for the HLA-B*27:02 subtype (*HLA-B*27:0201* and *HLA-B*27:0202*), three alleles for HLA-B*27:04, 21 alleles for HLA-B*27:05, three alleles for HLA-B*27:07, and two alleles for HLA-B*27:90, making 131 alleles altogether [12]. *HLA-B*27:0502* is the most widely distributed allele, and is probably the ancestral allele from which the others evolved [10, 13•, 14].

Some alleles are caused by mutations that are located within introns and are therefore "silent", or are in exons but do not cause amino acid changes. These "null" alleles, with the suffix 'N', are *HLA-B*27:59N*, *HLA-B*27:64N*, *HLA-B*27:65N*, *HLA-B*27:66N*, *HLA-B*27:90N* and *HLA-B*27:94N* [12]. *HLA-B*27:13* differs from *HLA-B*27:0502* only in the leader segment of the gene, which is not part of the expressed product: at the cell surface, the HLA-B27 molecule encoded by these two alleles is identical [10].

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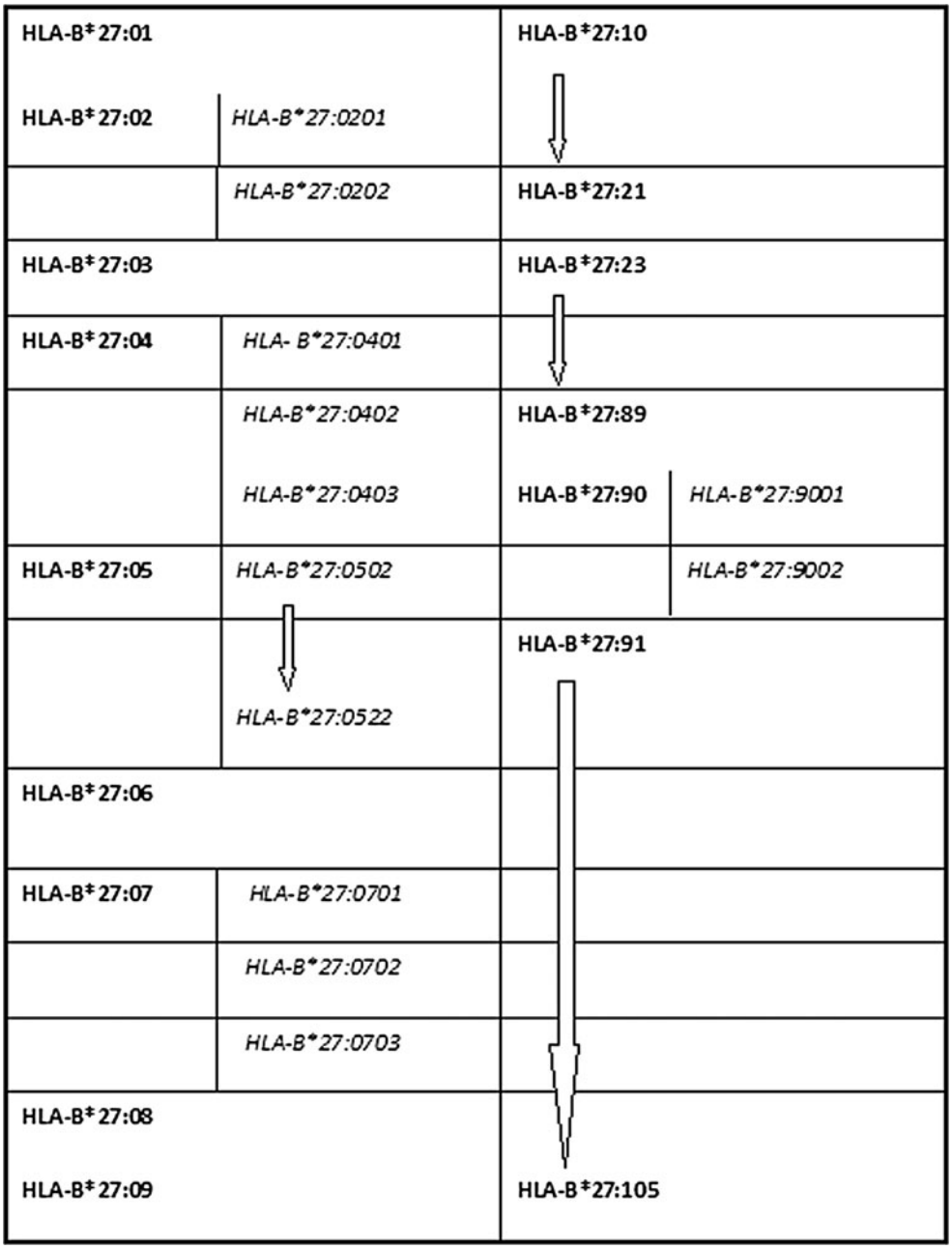

Fig. 1 List of 105 subtypes (B*27:01 to B*27:106); note that one designation (HLA-B*27:22) was withdrawn when subsequent studies revealed it to be identical with HLA-B*27:06. HLA-B*27:06 and HLA-B*27:09 are not associated with ankylosing spondylitis. There are two alleles for HLA-B*27:02: *HLA-B*27:0201* and *HLA-B*27:0202*. Also shown are three alleles of HLA-B*27:04, 21 alleles of HLA-B*27:05, three alleles of HLA-B*27:07, and two alleles of HLA-B*27:90. As of April 2013, 131 alleles are known. Note: HLA-B*27:105 in Fig. 1 should be HLA-B*27:106*

Differential Disease Associations of HLA-B27 Subtypes

The common disease-associated subtypes are HLA-B*27:05 (Caucasians), HLA-B*27:02 (Mediterranean populations) and HLA-B*27:04 (Chinese) [13•]: for Chinese populations, HLA-B*27:04 carries a greater risk of ankylosing spondylitis than HLA-B*27:05 [15, 16•]. Definite disease association or disease occurrence for at least one patient has been observed for subjects born with subtypes HLA-B*27:01, HLA-B*27:02, HLA-B*27:03, HLA-B*27:04, HLA-B*27:05, HLA-B*27:07, HLA-B*27:08, HLA-B*27:10, HLA-B*27:13, HLA-B*27:14, HLA-B*27:15, HLA-B*27:19, HLA-B*27:23, HLA-B*27:24, HLA-B*27:25, and HLA-B*27:49 [11, 13•, 14, 15, 16•, 17–20]. Most other subtypes are either too rare or too recently described to have been evaluated for disease presence or association.

It has been known for a while that subtypes HLA-B*27:06 and HLA-B*27:09 have no disease association [13•, 17, 21–25]. If ranking subtypes by their associated disease risk, the Southeast Asian subtype HLA-B*27:06 ranks last because it seems to be "disease neutral", neither predisposing to ankylosing spondylitis nor preventing its occurrence [21–23]. This may also be the case for HLA-B*27:09, a subtype mostly restricted to the Italian island of Sardinia [24, 25]. However,

ankylosing spondylitis may be observed in individuals with these "disease neutral" subtypes when they have co-inherited a disease-associated subtype (for example HLA-B*27:05), or have other known disease-predisposing genes or a co-morbidity (for example colitis) that can independently predispose patients to ankylosing spondylitis. A few such cases have been reported [21, 26–28].

HLA-B*27:09 differs from disease-associated subtype HLA-B*27:05 by a substitution at residue 114 only, where aspartic acid is replaced by histidine (Fig. 2) [10, 13•, 29]. HLA-B*27:06 differs from HLA-B*27:04, the disease-associated Asian subtype, by amino acid substitutions at residues 114 and 116: histidine at position 114 is replaced by aspartic acid, and aspartic acid at position 116 by tyrosine (Fig. 2) [10, 13•, 29]. These substitution sites, which seem to be associated with altered disease risk, are in pockets D/E of the antigen-binding cleft (Fig. 3) [29], and affect antigen-binding specificity.

Inheritance of a disease-associated subtype from both parents, i.e. HLA-B27 homozygosity, triples the risk of disease [30, 31], but does not affect clinical manifestation of ankylosing spondylitis [32].

Disease Association With Other HLA Class I alleles

The genetic heterogeneity of ankylosing spondylitis was indicated by studies of HLA-B27-negative patients, which revealed other HLA class 1 alleles to be associated with the disease [33–42]. This conclusion was strongly supported by genetic studies conducted by the International Genetics of Ankylosing Spondylitis Consortium [43••]. Of particular interest is HLA-B60, a split of HLA-B40 that is part of the HLA-B7 cross-reacting antigens group (B7-CREG) [39, 44]

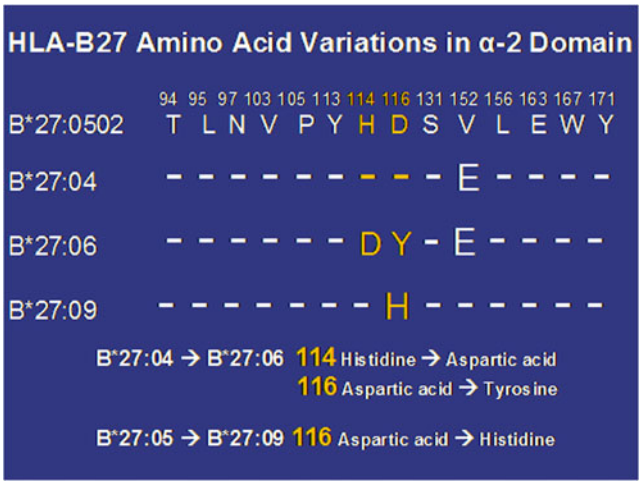

Fig. 2 Amino acid variations in alpha-2 domains of disease-associated subtypes HLA-B*27:04 and HLA-B*27:05, compared with HLA-B*27:06 and HLA-B*27:09 subtypes that seem to have no association with ankylosing spondylitis

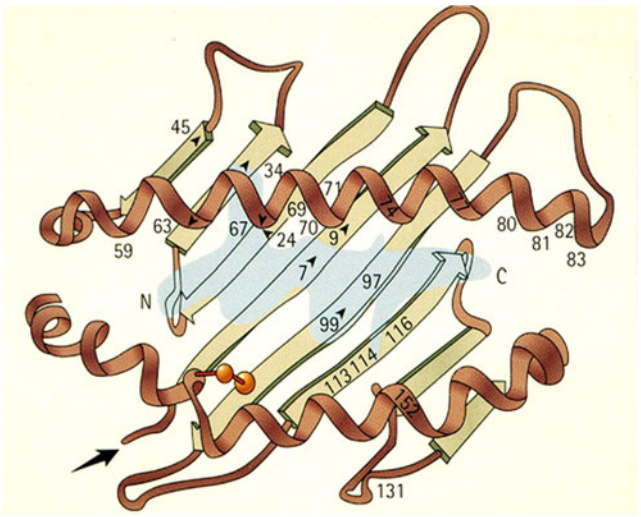

Fig. 3 Schematic ribbon diagram of the HLA-B27 molecule's peptide-binding cleft with a bound peptide (*light blue*); the letters *N* and *C* indicate, respectively, the amino and carboxy termini of the bound peptide. HLA-B*27:06, one of the two subtypes that seem to have no association with ankylosing spondylitis, and the disease-associated subtype HLA-B*27:04, differ from each other by two residues at positions 114 and 116, see reference [13] for more detailed legend for this figure. (Reprinted from Khan [27]; copyright 2005; with permission from Springer.)

and that increases ankylosing spondylitis risk two to threefold for white patients, irrespective of HLA-B27 status [40, 45]. In a very recent study, 18.2 % of ankylosing spondylitis patients had both HLA-B27 and HLA-B60 (B*40:01), whereas this combination was observed in only 0.4 % of controls [45]. Thus, individuals with a genotype that includes both HLA-B27 and HLA-B60 have a very high risk of ankylosing spondylitis, indicating a strong epistatic interaction between these two HLA class I risk antigens in this disease [45].

HLA-B27 and ERAP1

Endoplasmic reticulum aminopeptidase 1 (ERAP1) has a strong genetic association with ankylosing spondylitis, but only for patients who have HLA-B27 [46•, 47•]. This restriction to HLA-B27-positive patients, and ERAP1's known function of trimming peptides before they bind to major histocompatibility complex (MHC) class I molecules including HLA-B27, support the hypothesis that aberrant peptide processing in ankylosing spondylitis may have secondary pathogenic effects on adaptive and/or innate immune response [48]. Ongoing genetic studies have identified two ankylosing spondylitis-associated regions encoding four aminopeptidases involved in processing peptides before MHC class I presentation [43••]. These discoveries, and the differential associations of HLA-B27 subtypes with ankylosing spondylitis, have speeded up studies of the hemodynamic features of their protein structure, aberrant peptide processing, alterations of their peptidome, and related molecular events to elucidate the

role of HLA-B27 in disease pathogenesis [43••, 48, 49]. *ERAP1* alleles associated with reduced peptidase activity seem to be protective against ankylosing spondylitis, suggesting ERAP1 inhibition may be a possible therapeutic strategy [48].

Conclusions

There are now 105 known subtypes of HLA-B27, HLA-B*27:01 to HLA-B*27:106, which are encoded by 132 alleles. The differential disease associations of some of these subtypes, and the discovery of the association of ERAP1 with ankylosing spondylitis for HLA-B27-positive patients, have increased the pace of studies to determine their role in disease pathogenesis.

However, after 40 years we still do not fully know how HLA-B27 predisposes to ankylosing spondylitis and related spondyloarthritis. It is possible that this is because studies have been looking for one mechanism to explain every case, when HLA-B27 may cause disease via several mechanisms. For example, studies by Paul Bowness and colleagues have revealed that HLA-B27 can also be expressed at the cell surface of antigen-presenting cells as a free heavy chain (without beta-2 microglobulin) and as disulfide-bonded heavy chain homodimers, and that cellular expression of these non-classical forms of HLA-B27 may be involved in disease pathogenesis [50, 51•].

Misfolding of HLA-B27 in the endoplasmic reticulum, with a subsequent unfolded protein response (UPR), has been reported to cause inflammation in ankylosing spondylitis, but this was not supported by a very recent study [52]. Misfolding of HLA-B27 has been observed by studying intestinal mucosal biopsies of ankylosing spondylitis patients with subclinical gut inflammation [53, 54•], but this misfolding is accompanied by activation of autophagy rather than by a UPR [53]. This autophagy seems to be associated with intestinal modulation of IL-23 in ankylosing spondylitis [46•, 53, 54•].

There is increasing interest in the gut microbiome—the symbiotic microorganisms in the human gastrointestinal system and their collective interacting genomes—and its interactions with the host in health and disease [55–57]. It is now generally acknowledged that persistent pathogens, especially that associated with *Chlamydia* infection, are present in the arthritic joints of some of the patients with HLA-B27-associated reactive arthritis, but the relationship with the disease is still not fully understood [58•]. Thus, a complex interaction of genetic predisposition and microbial infection, resulting in disturbed innate and adaptive immune response, contributes to ankylosing spondylitis and to associated diseases including colitis and uveitis [54•, 57, 58•, 59–63, 64••, 65].

Compliance with Ethics Guidelines

Conflict of Interest Muhammad Asim Khan declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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- •• Of major importance

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