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An Update on the Genetic Polymorphism of *HLA-B*27* With 213 Alleles Encompassing 160 Subtypes (and Still Counting)

Muhammad A. Khan[1]

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Abstract
Purpose of Review This publication updates an earlier review on the ever increasing knowledge about genetic polymorphism of *HLA-B*27* and discusses its clinical relevance.
Recent Findings As of January 1, 2017, there are 213 known alleles of *HLA-B*27* at nucleotide sequence level, while at the translated protein level, there are 160 known subtypes based on one or more amino acid sequence differences. Some of these subtypes exhibit differential association with ankylosing spondylitis, and there may even be some level of hierarchy in this regard. On the other hand, HLA-B*27 has a protective effect against HCV, and this effect is also influenced by some of the subtypes of HLA-B*27. This may have important implications for designing anti-viral vaccines for global population and also for developing individualized treatments and vaccines.
Summary Disease association and disease protective roles of HLA-B*27 suggest a common ground, i.e., promoting a more pronounced immune/inflammatory response for effective clearance of some pathogens, but that might, on the other hand, lead to autoimmunity and tissue injury in some circumstances.

Keywords HLA-B27 · HLA-B*27 · HLA-B*27:05 · HLA alleles · Subtypes · Polymorphism · Ankylosing spondylitis · Spondyloarthritis · Homozygosity · HCV · HIV

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✉ Muhammad A. Khan
m.asimkhan@gmail.com

[1] Case Western Reserve University, Cleveland, OH, USA

Human leucocyte antigens (HLA) represent a group of highly polymorphic genes that reside in the major histocompatibility complex (MHC) that is located within the 6p21.3 region on the short arm of chromosome 6, and encodes many of the proteins of the immune system [1•]. These include HLA-class I genes that are co-dominantly expressed on the cell surface presenting intracellularly derived peptides to CD8 positive T cells. HLA-B*27 belongs to a family of closely related cell surface proteins encoded in the HLA-B locus. It was discovered as a serological specificity in 1969 and found to be distributed worldwide but with variable prevalence. Four years later it was found to show a remarkable association with ankylosing spondylitis (AS) and related forms of spondyloarthritis (SpA) [2••, 3]. It was later observed that the strength of this association varies not only for different forms of SpA but also among some of the ethnic and racial groups in the world [2••, 3, 4•, 5]. Substantial evidence exists that strongly favors its direct role in genetic susceptibility to AS/SpA, although the underlying molecular basis has yet to be identified [2••, 4•, 6••]. But it is not a prerequisite for occurrence of AS since this disease also affects individuals who lack this gene, and there are now 48 genetic loci known to be associated with increased risk for AS [2••, 4•, 5, 6••, 7••].

*HLA-B*27 gene* shows a high degree of polymorphism as it encompasses an ever increasing number of alleles as well as "subtypes" (i.e., specific HLA proteins). Please note that the name of a gene or allele is written in italics, while normal text is used when using it for mentioning its encoded protein. I hereby provide an update on my last review on this subject [2••]. But before discussing it further, it is imperative to first explain the current HLA nomenclature, especially for those readers who may be unfamiliar or are somewhat confused by this revised nomenclature.

The HLA Nomenclature

The naming of HLA genes, allele sequences, and their quality control is the responsibility of the Word Health Organization (WHO) Nomenclature Committee for Factors of the HLA System. It is now an established procedure for authors to submit their report of new HLA sequences directly to the IPD-IMGT/HLA Database for checking and assignment of an official name prior to publication [1•]. This has resolved the old problems associated with renaming published sequences and the confusion of multiple names for the same sequence.

All HLA alleles are initially identified by a letter(s) indicating its genetic location in the MHC region, such as locus A, B, and C, followed by a number that is assigned in order of discovery, for example HLA-A1, HLA-A2, HLA-A9, HLA-B7, HLA-B8, and HLA-B27. Such HLA nomenclature was used years ago when typing was done by serologic method. HLA-B27 is thus a serologic specificity, but serologic methods resolve only a tiny fraction of all known alleles. Therefore, HLA typing at the DNA level has become the method of choice, and it is also more robust and reproducible. It was decided to insert an asterisk (*) after the letter that assigns the locus and followed by two digit specificity of the molecule in order to indicate that the typing done at the DNA level. So, as an example, HLA-A2, HLA-B7, and HLA-B27 have become HLA-A*02, HLA-B*07, and HLA-B*27, respectively. This is defined as a "low resolution typing."

An increasing number of HLA alleles are now being discovered, and therefore, the "HLA Extended Allele Nomenclature" system is now used in which a second set of digits (preceded by a colon that is used as a field separator) is added to identify them, such as *HLA-B*27:05* and *HLA-B*27:161*. This second set of digits is assigned in the order in which the DNA sequences have been determined. Such alleles containing the two sets of digits (that are separated by a colon) must have one or more nucleotide substitutions that change the amino acid sequence of their encoded proteins. Therefore, the second of these two sets of digits indicates specific HLA proteins or subtypes. However, a very few of the alleles are not expressed at all (i.e., they do not produce any protein) and are thus called "null" alleles and carry the suffix "N"; for example *HLA-B*27:59 N*.

Alleles that differ only by synonymous nucleotide substitutions (also called "silent" or "non-coding" substitutions) within the coding sequence are distinguished by assigning a third set of two digits. Thus *HLA-B*27:05:32* is one such example where: HLA denotes the human MHC, and it is followed by a hyphen (−) and then the letter B that denotes the HLA-B locus. It is followed by an asterisk (*) that denotes molecular typing, and then the first set of two digits (27) to indicate the antigen (or allele) family. The second and the third sets of digits are separated by colons (that act as field separators); the second set *:05* indicates an allele level "subtype" (i.e., a specific HLA protein), and the third set *:32* indicates a silent or "non-coding" substitution within the coding region.

Those alleles that only differ by sequence differences that are located outside of the coding region are distinguished by adding a fourth set of digits. An example of such an allele is *HLA-B*27:02:01:02* where *:01* indicates a silent nucleotide substitution within the coding region, and the last set *:02* indicates a difference in the non-coding region.

A suffix "S" indicates that the allele specifies a protein which is expressed as a soluble "Secreted" molecule that is not expressed on the cell surface, e.g., *HLA-B*44:02:01:02S*. Another suffix "L" is used to indicate an allele that has "Low" level of expression on cell surface, e.g., *HLA-A*30:14 L*. A "Q" suffix is used when the expression of an allele is "Questionable." A suffix "A" indicates an "Aberrant" expression where there is some doubt as to whether a protein is actually expressed, and a "C" suffix is assigned to alleles that produce proteins that are present in the "Cytoplasm" and not on the cell surface.

*HLA-B*27* Polymorphism

As of January 1, 2017, there are 213 known alleles of *HLA-B*27* that have been defined at the level of nucleotide sequence. This list of alleles is obtained from the IPD-IMGT/HLA Database (The Immuno Polymorphism Database (IPD), International ImMunoGeneTics (IMGT) HLA Database) Release 3.27.0 (2017–01) [1•]. Many of the mutations are located within introns and thus are silent or they occur in exons but do not cause amino acid changes. Therefore, at the translated protein level, there are 160 known subtypes of HLA-B*27 based on one or more amino acid sequence differences. These 160 subtypes can be encompassed by the numbering system HLA-B*27:01 to HLA-B*27:161 because one of the assignments—HLA-B*27:22—was subsequently withdrawn when it was found to be identical to HLA-B*27:06.

I have summarized this long list into a concise table (Table 1). The subtypes of HLA-B*27 are listed in the left column and that listing is continued on to the third column from the left. The second and fourth columns list alleles belonging to some of these subtypes; eg, HLA-B*27:05 encompasses 31 alleles: *HLA-B*27:05:02* to *HLA-B*27:05:32*. because the protein encoded by all of them is identical to the one encoded by *HLA-B*27:05*. It is worth mentioning that *HLA-B*27:05:02* is the most widely distributed *HLA-B*27* allele, and is probably the ancestral allele from which the others evolved. Please note that *HLA-B*27:05:01* is not listed as it was withdrawn when subsequently found to be identical to *HLA-B*27:05*.

Table 1 Remarkable polymorphism of HLA-B*27

Title: Genetic Polymorphism of HLA-B*27

Subtypes	Alleles	Subtypes	Alleles
B*27:01		B*27:23	
B*27:02	B*27:02:01	↓	
	B*27:02:01:02	B*27:50	B*27:50:01
	B*27:02:02		B*27:50:02
	B*27:02:03	B*27:51	
B*27:03		↓	
B*27:04	B*27:04:01	B*27:90	B*27:90:01
	↓		↓
	B*27:04:06		B*27:90:04
B*27:05	B*27:05:02	B*27:91	
	↓	↓	
	B*27:05:32	B*27:96	B*27:96:01
B*27:06			B*27:96:02
B*27:07	B*27:07:01	B*27:97	
	↓	↓	
	B*27:07:05	B*27:161	
B*27:08			
↓			
B*27:21			

This table is derived from the list of HLA-B*27 alleles maintained by the IPD-IMGT/HLA Database Release 3.27.0 (2017–01). The 160 subtypes: HLA-B*27:01 to HLA-B*27:161, are listed in the left column and are continued on to the third column from the left. Please note that there is no HLA-B*27:22 because it was withdrawn when it was found to be identical to HLA-B*27:06. The second and fourth columns list alleles belonging to some of the subtypes; eg, HLA-B*27:05 encompasses 31 alleles: *HLA-B*27:05:02* to *HLA-B*27:05:32*. Please note that *HLA-B*27:05:01* is not listed as it was withdrawn when it was subsequently found to be identical to *HLA-B*27:05. HLA-B*27:13* differs from *HLA-B*27:05:02* only in the leader segment of the gene, which is not part of the expressed product at the cell surface. So the HLA-B*27 molecule encoded by these two alleles is identical [Khan MA, Ball EJ. Genetic aspects of ankylosing spondylitis. Best Pract Res Clin Rheumatol. 2002;16:675–90.]. The "null" alleles are *HLA-B*27:59 N, HLA-B*27:64 N, HLA- B*27:65 N, HLA-B*27:66 N*, and *HLA-B*27:94 N*. Updated, with permission, from: Khan MA: ANKYLOSING SPONDYLITIS-AXIAL SPONDYLOARTHRITIS. PCI (Professional Communications, Inc). West Islip, NY. 2016. pp. 1–333

Differential Association of HLA-B*27 Subtypes With AS

The HLA-B*27 subtypes show an extremely varied racial and ethnic prevalence throughout the world [4•, 5]. HLA-B*27:05 is the most widely distributed subtype and has been the subject of most of the clinical studies dealing with its association with AS. Among the other relatively common disease-associated subtypes are HLA-B*27:02 (Mediterranean populations) and HLA-B*27:04 (Chinese and other Asian populations).

HLA-B*27:06, a subtype prevalent in Southeast Asian populations, has been reported to lack association with AS [8–11]. It differs from the disease associated subtype HLA-B*27:04 only at residues at position 114 (His to Asp) and 116 (Asp to Tyr) that form part of the F pocket at the bottom of the groove where the bound antigenic peptide sits [2••].

Another subtype—HLA-B*27:09—that occurs mostly among Italians that live on the island of Sardinia has also been reported to lack association with AS (12). And, most interestingly, it differs from the most frequent and disease-associated HLA-B*2705 subtype by only a single substitution (His vs. Asp) at position 116 [2••]. Many investigators have been exploring the effects of these sequence variations on peptide-binding specificities of HLA-B*27:06 and HLA-B*27:09 in the hope to uncover the underlying molecular basis of disease association [12, 13, 14•, 15, 16, 17••].

Schittenhelm et al. [17••] have reported 26 peptides that are presented in lower abundance by HLA-B*27:06 and HLA-B*27:09 compared with disease-associated HLA-B*27 subtypes, in their pursuit of the putative "arthritogenic peptide(s)." They indicate that the differences in charge and size that accompany the His-to-Asp substitution at residue 114, and Asp to Tyr substitution at residue 116 (in case of HLA-B*27:06), exclude the acceptance of the sought-after "arthritogenic peptide." Such studies, it is hoped, will also help define which alleles, and therefore which polymorphic positions, predispose to the disease. Dimerization of HLA-B*27 heavy chain during assembly process has been implicated in disease pathogenesis [6••, 18]. Guiliano et al. [19•] have just reported that the above mentioned differences in the residues within the F pocket between the disease-associated and non-disease-associated subtypes of HLA-B*27 influence this assembly process and heavy chain dimerization.

Differences among some of the HLA-B*27 subtypes have been reported when it comes to their strength of disease association; and there may even be some level of hierarchy in this regard among some of these subtypes. For example, HLA-B*27:05 and HLA-B*27:02, the relatively common subtypes among Caucasian populations, seem to confer equal susceptibility to AS. On the other hand, among Chinese populations, where HLA-B*27:04 and HLA-B*27:05 are the common subtypes, HLA-B*27:04 confers a greater risk for AS than HLA-B*27:05 [20, 21].

Rare occurrence of AS or related SpA has been observed in individuals with these "disease neutral" subtypes (HLA-B*27:06 and HLA-B*27:09) when, at least some of them, had co-inherited other known disease-predisposing genes (e.g., HLA-B*27:05), or had illnesses (for example inflammatory bowel disease) that can independently predispose such individuals to AS/SpA [2••, 9, 11, 22–28].

Disease association or reports of occurrence of AS/SpA in at least one or more patients possessing any of the first 15 subtypes (from HLA-B*27:01 to HLA-B*27:15), and HLA-B*27:17, HLA-B*27:18, HLA-B*27:19, HLA-B*27:23, HLA-B*27:24, HLA-B*27:25, HLA-B*27:28 and HLA-B*27:49 have been reported [2••, 5, 9, 11, 20, 22–37]. The remaining subtypes are either too rare or are too recently described to have been evaluated for disease presence or association. The available data suggest that HLA-B*27:04, HLA-B*27:05 and HLA-B*27:02 are at top of the disease association hierarchy, while HLA-B*27:09 and more certainly HLA-B*27:06 fall at the bottom of such a list [2••].

Clinical features of AS/SpA may also show some correlation with HLA-B27 polymorphism; e.g., age of onset and occurrence of acute anterior uveitis among AS patients possessing HLA-B*27:04 versus HLA-B*27:05, but there are contradictory reports [34, 38–41]. HLA-B*27:15, a subtype that occurs in Asian populations and differs from B*27:04 by only one amino acid at position 163 (Glu in HLA-B*27:04 to Thr in HLA-B*27:15), seems to be associated with a much younger age of onset than that observed among patients possessing HLA-B*27:04 or HLA-B*27:05 [34, 42].

Few studies have examined the relationship between HLA-B*27 homozygotes and risk for AS and association with clinical manifestations. Khan et al. [43] first reported increased risk for AS, and it was finally confirmed 28 years later [44]. HLA-B*27 homozygosity, however, has no influence on clinical manifestations, radiographic damage and functional disability in AS [43, 45, 46].

Protective Role of HLA-B*27 in HCV and HIV Infections

HLA-B*27 is associated with high rates of spontaneous CD8+ T cell-mediated clearance of hepatitis C virus (HCV) genotype1 infection, and it also has a protective role in human immunodeficiency virus (HIV) infection [47, 48]. These are two of the most highly variable viral pathogens for which effective vaccines are still lacking [49••, 50]. In HIV infection, HLA-B*27 is associated with a low viral load, slow CD4+ decline, and the delayed onset of AIDS [49••, 50].

This efficacy of HLA-B*27 in responding to the HIV infection is associated with its specificity for a highly conserved CD8+ epitope of Gag protein of the virus and which requires a complicated pathway of viral escape to evade this protective response. However, a compensatory mutation of that conserved epitope ultimately leads to viral escape and the onset of AIDS in HLA-B*27+ individuals [49••, 50, 51•].

The protective effect against HCV is linked to dominant HLA-B*27 restricted epitopes of the viral protein NS5B. HLA-B*27-restricted CD8+ T cells target three NS5B epitopes; and one of them is NS5B2820. This epitope is immunodominant exclusively in the context of HLA-B*27:02, but not in the context of HLA-B*27:05, the most common subtype worldwide [4•, 52••]. HLA-B*27:02 is mostly prevalent in the Middle East and North Africa, but has only 2 to 10% prevalence among northern European populations [4•, 5, 53, 54]. This differential epitope targeting and immunodominance between these two common HLA-B*27 subtypes has important implications for designing anti-viral vaccines for global population and also for developing individualized treatments and vaccines. In light of these data pertaining to HCV infection, it is possible that a similar differential viral epitope targeting and immunodominance may also exist with regard to HIV infection among some of the HLA-B*27 subtypes, and therefore, it should be further investigated.

Conclusion

As of January 1, 2017, there are 160 known subtypes of HLA-B*27, but an overwhelming majority of them are very rare and have not been studied for disease association. However, a very few of the relatively common subtypes exhibit differential association with AS, and there may even be some level of hierarchy in this regard. It has been hypothesized that the pathogenic role of HLA-B*27 in AS and its protective role in HCV and HIV infections suggest a common ground, i.e., promoting a more pronounced immune/inflammatory response for effective clearance of some pathogens but that can, on the other hand, lead to autoimmunity and tissue injury in some circumstances [49••, 55]. This may involve not only efficient antigen presenting properties of HLA-B*27 but also co-inheritance of other gene variants, thymic selection of CD8+ T-cell precursors, and/or specific T cell receptor repertoires [6••, 7••, 14•, 17••, 19•, 55, 56].

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.• Robinson J, Halliwell JA, Hayhurst JD, et al. The IPD and IMGT/HLA database: allele variant databases. Nucleic Acids Res. 2015;43(Database issue):D423–31. doi:10.1093/nar/gku1161. **This publication explains the Immuno Polymorphism Database (IPD) that was developed in 2003 to provide a centralized system for the study of polymorphism in genes of the immune system. The IPD project was established by the HLA Informatics Group**.

2.•• Khan MA. Polymorphism of HLA-B27: 105 subtypes currently known. Curr Rheumatol Rep. 2013;15:362. doi:10.1007/s11926-013-0362-y. **The author's previous review of the subject that is worth reading for the current update and expansion of this subject**.

3. Brewerton DA. Discovery: HLA and disease. Curr Opin Rheumatol. 2003;15(4):369–73.

4.• Khan MA. Ankylosing spondylitis - axial spondyloarthritis. Professional Communications Inc. (PCI). West Islip, NY. 2016, pp.1–333. ISBN: 978-1-943236-08-4. **The most current book on AS/AxSpA published in September, 2016 that provides additional current information on HLA-B27 and its clinical utility as an aid to disease recognition**.

5. Khan MA. HLA and spondyloarthropathies. Chapter 16. In: Mehra NK, editor. The HLA complex in biology and medicine. A Resource Book. New Delhi: Jaypee Brothers Medical Publishers Ltd; 2010. p. 259–75.

6.•• Bowness P. HLA-B27. Annu Rev Immunol. 2015;33:29–48. **An excellent and comprehensive review covering the role of HLA-B27 in etiopathogenesis of AS/AxSpA**.

7.•• Ellinghaus D, Jostin 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(5):510–8. **The authors report combined assessments of Immunochip genotyping datasets from 52,262 patients with five closely associated diseases (AS, Crohn's disease, psoriasis, primary sclerosing cholangitis and ulcerative colitis; all seronegative inflammatory diseases) and 34,213 healthy controls. They were able to delineate the genetic overlap between these conditions, identify 27 new associations, and highlights disease-specific patterns at shared loci**.

8. Lopez-Larrea C, Sujirachato K, Mehra NK, et al. HLA-B27 subtypes in Asian patients with ankylosing spondylitis: evidence for new associations. Tissue Antigens. 1995;45(3):169–76.

9. Nasution AR, Mardjuadi A, Kunmartini S, et al. HLA-B27 subtypes positively and negatively associated with spondyloarthropathy. J Rheumatol. 1997;24:1111–4.

10. Diaz-Pena R, Lopez-Vazquez A, Lopez-Larrea C. Old and new HLA associations with ankylosing spondylitis. Tissue Antigens. 2012;80:205–13.

11. Van Gaalen FA. Does HLA-B*2706 protect against ankylosing spondylitis? A meta-analysis. Int J Rheum Dis. 2012;15(1):8–12.

12. D'Amato M, Fiorillo MT, Carcassi C, et al. Relevance of residue 116 of HLA-B27 in determining susceptibility to ankylosing spondylitis. Eur J Immunol. 1995;25:3199–201.

13. Khan MA, Mathieu A, Sorrentino R, Akkoc N. The pathogenetic role of HLA-B27 and its subtypes. Autoimmun Rev. 2007;6(3):183–9.

14.• Jeanty C, Sourisce A, Noteuil A, et al. HLA–B27 subtype oligomerization and intracellular accumulation patterns correlate with predisposition to spondyloarthritis. Arthritis Rheumatol. 2014;66(8):2113–23. **This paper enhances our understanding of the pathogenic role of HLA-B27**.

15. Cheng X, Mei Y, Ji X, et al. Molecular mechanism of the susceptibility difference between HLA-B*27:02/04/05 and HLA-B*27:06/09 to ankylosing spondylitis: substitution analysis, MD simulation, QSAR modelling, and in vitro assay. SAR QSAR Environ Res. 2016;27(5):409–25.

16. Mou YK, Zhang PP, Li QX, et al. Changes of serum levels of MMP-3, sRANKL, and OPG in juvenile-onset ankylosing spondylitis patients carrying different HLA-B27 subtypes. Clin Rheumatol. 2015;34(6):1085–9.

17.•• Schittenhelm RB, Sivaneswaran S, Lim Kam Sian TC, et al. Human leukocyte antigen (HLA) B27 allotype-specific binding and candidate arthritogenic peptides revealed through heuristic clustering of Data-independent Acquisition Mass Spectrometry (DIA-MS) data. Mol Cell Proteomics. 2016;15(6):1867–76. **The authors have identified 26 peptides, which are presented in**

lower abundance by HLA-B*27:06 and HLA-B*27:09 compared with disease-associated HLA-B27 subtypes. They point out that "although these differences were observed to be very subtle, these 26 peptides might encompass the sought-after arthritogenic peptide(s)".

18. Colbert RA, Tran TM, Layh-Schmitt G. HLA-B27 misfolding and ankylosing spondylitis. Mol Immunol. 2014;57(1):44–51. doi:10.1016/j.molimm.2013.07.013.
19.• Guiliano DB, North H, Panayoitou E, et al. Polymorphisms in the F pocket of HLA-B*27 subtypes strongly impact on assembly, chaperone interactions and heavy chain misfolding. Arthritis Rheumatol. 2016. doi:10.1002/art.39948. **This paper enhances our understanding of the pathogenic role of HLA-B27**.
20. Liu X, Hu LH, Li YR, Chen FH, Ning Y, Yao QF. The association of HLA-B*27 subtypes with ankylosing spondylitis in Wuhan population of China. Rheumatol Int. 2010;30(5):587–90.
21. Liu Y, Jiang L, Cai Q, Danoy P, Barnardo MC, Brown MA, et al. Predominant association of HLA-B*2704 with ankylosing spondylitis in Chinese Han patients. Tissue Antigens. 2010;75(1):61–4.
22. Hou TY, Chen HC, Chen CH, Chang DM, Liu FC, Lai JH. Usefulness of human leucocyte antigen-B27 subtypes in predicting ankylosing spondylitis: Taiwan experience. Intern Med J. 2007;37(11):749–52.
23. Zou HY, Yu WZ, Wang Z, He J, Jiao M. Human leukocyte antigen-B27 alleles in Xinjiang Uygur patients with ankylosing spondylitis. Genet Mol Res. 2015;14(2):5652–7.
24. Cauli A, Vacca A, Mameli A, Passiu G, Fiorillo MT, Sorrentino R, et al. A Sardinian patient with ankylosing spondylitis and HLA-B*2709 co-occurring with HLA-B*1403. Arthritis Rheum. 2007;56(8):2807–9.
25. Olivieri I, D'Angelo S, Scarano E, Santospirito V, Padula A. The HLA-B*2709 subtype in a woman with early ankylosing spondylitis. Arthritis Rheum. 2007;56(8):2804–7.
26. Cauli A, Vacca A, Dessole G, Fiorillo MT, Porru G, Ibba V, et al. HLA-B*2709 and lack of susceptibility to sacroiliitis: further support from the clinic. Clin Exp Rheumatol. 2008;26(6):1111–2.
27. Siala M, Mahfoudh N, Gdoura R, et al. Distribution of HLA-B27 and its alleles in patients with reactive arthritis and with ankylosing spondylitis in Tunisia. Rheumatol Int. 2009;29(10):1193–6.
28. Ben Radhia K, Ayed-Jendoubi S, Sfar I, et al. Distribution of HLA-B*27 subtypes in Tunisians and their association with ankylosing spondylitis. Joint Bone Spine. 2008;75(2):172–5.
29. Birinci A, Bilgici A, Kuru O, Durupinar B. HLA-B27 polymorphism in Turkish patients with ankylosing spondylitis. Rheumatol Int. 2006;26(4):285–7.
30. Zhou HY, Yu WZ, Wang Z, et al. Human leukocyte antigen-B27 alleles in Xinjiang Uygur patients with ankylosing spondylitis. Genet Mol Res. 2015;14(2):5652–7.
31. Shankarkumar U, Ghosh K, Mohanty D. HLA B27 polymorphism in Western India. B*2714 was observed in a patient with ankylosing spondylitis. Tissue Antigens. 2002;60(1):98–101.
32. García-Fernández S, Gonzalez S, Miña Blanco A, et al. New insights regarding HLA-B27 diversity in the Asian population. Tissue Antigens. 2001;58(4):259–62.
33. Diyarbakir E, Eyerci N, Melikoglu M, Topcu A, Pirim I. HLA B27 subtype distribution among patients with ankylosing spondylitis in eastern Turkey. Genet Test Mol Biomarkers. 2012;16(5):456–8.
34. Mou Y, Wu Z, Gu J, Liao Z, Lin Z, Wei Q, et al. HLA-B27 polymorphism in patients with juvenile and adult-onset ankylosing spondylitis in Southern China. Tissue Antigens. 2010;75(1):56–60.
35. Stanevicha V, Eglite J, Zavadska D. HLA B27 allele types in homogeneous groups of juvenile idiopathic arthritis patients in Latvia. Pediatr Rheumatol Online J. 2010;8:26. doi:10.1186/1546-0096-8-26.
36. Ma HJ, Hu FP. Diversity of human leukocyte antigen-B27 alleles in Han population of Hunan province, southern China. Tissue Antigens. 2006;68(2):163–6.
37. Grubić Z, Kerhin-Brkljacić V, Perić P, Cecuk E, Kastelan A. Variation in HLA-B27 gene subtypes and susceptibility of ankylosing spondylitis in the Croatian population. Reumatizam. 2001;48(1):7–11.
38. Chavan H, Samant R, Deshpande A, Mankeshwar R. Correlation of HLA B27 subtypes with clinical features of ankylosing spondylitis. Int J Rheum Dis. 2011;14(4):369–74. doi:10.1111/j.1756-185X.2011.01635.x.
39. Qi J, Li Q, Lin Z, Liao Z, Wei Q, et al. Higher risk of uveitis and dactylitis and older age of onset among ankylosing spondylitis patients with HLA-B*2705 than patients with HLA-B*2704 in the Chinese population. Tissue Antigens. 2013;82(6):380–6. doi:10.1111/tan.12254.
40. Li H, Li Q, Ji C, Gu J. Ankylosing spondylitis patients with HLA-B*2704 have more uveitis than patients with HLA-B*2705 in a North Chinese population. Ocul Immunol Inflamm. 2016;18:1–5.
41. Wu Z, Lin Z, Wei Q, Gu J. Clinical features of ankylosing spondylitis may correlate with HLA-B27 polymorphism. Rheumatol Int. 2009;29(4):389–92.
42. Mou Y, Zhang P, Li Q, et al. Clinical features in juvenile-onset ankylosing spondylitis patients carrying different B27 subtypes. Biomed Res Int. 2015;2015:594878. doi:10.1155/2015/594878.].
43. Khan MA, Kushner I, Braun WE, Zachary AA, Steinberg AG. HLA– B27 homozygosity in ankylosing spondylitis: relationship to risk and severity. Tissue Antigens. 1978;11:434–8.
44. Jaakkola E, Herzberg I, Laiho K, Barnardo MC, Pointon JJ, Kauppi M, et al. Finnish HLA studies confirm the increased risk conferred by HLA-B27 homozygosity in ankylosing spondylitis. Ann Rheum Dis. 2006;65(6):775–80.
45. Kim TJ, Na KS, Lee HJ, Lee B, Kim TH. HLA-B27 Homozygosity has no influence on clinical manifestations and functional disability in Ankylosing Spondylitis. Clin Exp Rheumatol. 2009;27(4):574–9.
46. Kim TJ, Sung IH, Lee S, et al. HLA-B27 homozygosity has no influence on radiographic damage in ankylosing spondylitis: observation study of Korean Spondyloarthropathy Registry (OSKAR) data. Joint Bone Spine. 2013;80(5):488–91.
47. Goulder PJ, Watkins DI. Impact of MHC class I diversity on immune control of immunodeficiency virus replication. Nat Rev Immunol. 2008;8:619–30.
48. McKiernan SM, Hagan R, Curry M, McDonald GS, Kelly A, Nolan N, et al. Distinct MHC class I and II alleles are associated with hepatitis C viral clearance, originating from a single source. Hepatology. 2004;40:108–14.
49.•• Neumann-Haefelin C. HLA-B27-mediated protection in HIV and hepatitis C virus infection and pathogenesis in spondyloarthritis: two sides of the same coin? Curr Opin Rheumatol. 2013;25(4):426–33. **The author reviews the multiple virological and immunological mechanisms that have been suggested to contribute to HLA-B27-mediated protection in HIV and HCV infection. It is suggested that some of these mechanisms may also be involved in HLA-B27-associated pathogenesis in AS and associated forms of spondyloarthritis**.
50. Neumann-Haefelin C, Oniangue-Ndza C, Kuntzen T, et al. HLA-B27 selects for rare escape mutations that significantly impair Hepatitis C virus replication and require compensatory mutations. Hepatology. 2011;54(4):1157–66.
51.• Hecht L, Dormer A. The evolutionary significance of certain amino acid substitutions and their consequences for HIV-1 immunogenicity toward HLA's A*0201 and B*27. Bioinformation. 2013;9(6):315–

20. **This study shows that the vaccines based upon the envelope glycoprotein of HIV are unlikely to be effective in eliciting an immune response in vivo in HLA-B*27+ individuals because the predominant 9-mers IRIGPGQAF of gp120 are significantly less immunogenic toward HLA-B*27 than to HLA-A*02**.

52.•• Nitschke K, Barriga A, Schmidt J, et al. HLA-B*27 subtype specificity determines targeting and viral evolution of a hepatitis C virus-specific CD8+ T cell epitope. J Hepatol. 2014;60(1):22–9. **This important study shows that a hepatitis C virus-specific CD8+ T cell epitope NS5B2820 is immunodominant in the context of HLA-B*27:02 (that is frequent in the Mediterranean populations), but is not restricted by HLA-B*27:05 (the most common subtype worldwide). These findings may have important implications for the selection of epitopes for global vaccines**.

53. Johnsen SS, Bakland G, Nossent JC. The distribution of HLA-B27 subtype in patients with ankylosing spondylitis in Northern Norway. Scand J Rheumatol. 2014;43(4):296–300.

54. Baech J, Schmidt-Olsen S, Steffensen R, et al. Frequency of HLA-B27 subtypes in a Danish patient population and in Danish patients with ankylosing spondylitis. Tissue Antigens. 1997;49(5):499–502.

55. Mathieu A, Paladini F, Vacca A, et al. The interplay between the geographic distribution of HLA-B27 alleles and their role in infectious and autoimmune diseases: a unifying hypothesis. Autoimmun Rev. 2009;8(5):420–5.

56. Rana MK, Luthra-Guptasarma M. Differences in conformational stability of the two alpha domains of the disease associated and non-disease-associated subtypes of HLA-B27. Int J Biol Macromol. 2017;95(Part A):233-45. doi:10.1016/j.ijbiomac.2016.08.066.