

The Genetics of Spondyloarthropathies

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Abstract

Introduction: Spondyloarthropathies are a heterogeneous group of rheumatic disorders that commonly present with axial skeleton or sacroiliac joints involvement. Ocular involvement like uveitis, iritis and conjunctivitis can be present in up to a third of the patients. Genetic factors play a part in the pathogenesis of spondyloarthropathies. Association with the HLA-B27 gene, especially that between ankylosing spondylitis and HLA-B27 antigenic positivity, is one of the strongest association seen between a disease and a Class I antigen. This paper aims to review the frequencies of HLA-B27 gene and its subtypes in different population groups, possible mechanisms leading to the development of joint inflammation and the risk it confers for development of spondyloarthropathies. **Methods:** The MEDLINE database was searched using keywords: HLA-B27, spondyloarthropathy, molecular mimicry, arthritogenic peptides, reactive arthritis and ankylosing arthritis. Related articles for selected papers were also consulted. Books on HLA-B27 and spondyloarthropathy were obtained through the NUS Medical Library's LINC system. **Results:** The genetic subtypes and susceptibility to development of disease vary in different population groups. Other HLA genes and non-HLA genes also play a part in the development of spondyloarthropathies, especially in those who are HLA-B27 negative. HLA-B27-positive relatives of spondyloarthritics have a higher risk of developing a similar condition. The presence of the HLA-B27 gene may serve as an aid to diagnosis or prognosis for clinicians. In juvenile arthritic patients, it is a poor prognostic factor, predicting for disease severity. It is also associated with poor outcomes for patients with anterior uveitis. However screening of asymptomatic individuals for the HLA-B27 gene is not recommended. **Conclusion:** The polygenic nature of the disease needs further elucidation and study.

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Key words: Ankylosing spondylitis, Enthesitis, HLA-B27 gene, Sacroilitis, Uveitis

Introduction

The spondyloarthropathies (SpA) comprise a heterogeneous group of conditions that include ankylosing spondylitis (AS), psoriatic arthritis, reactive arthritis/Reiter's syndrome, arthritis associated with inflammatory bowel disease and pauciarticular, late-onset juvenile chronic arthritis.¹ Undifferentiated forms of the disease are also present.² Enthesitis, sacroilitis and spondylitis are common clinical features and serologically, the salient feature is a lack of rheumatoid factor positivity. Extra-articular involvement e.g. ocular manifestations like uveitis, iritis or conjunctivitis can occur in up to 30% of these patients.³ Possible organ involvement are as outlined in Table I. An interesting feature of this group of conditions is the association with the HLA-B27 gene, a major histocompatibility complex (MHC) Class I gene. The linkage is strongest between HLA-B27 and AS, and is first described independently by 2 research groups in 1973.^{4,5} Over 90% of AS patients are serologically positive for this antigen and this strong association transcend most population groups.⁶

⁹ There are, however, some notable exceptions e.g. in middle-eastern countries like Kuwait, Lebanon, Saudi Arabia and United Arab Emirates.¹⁰⁻¹² To date, there are up to 16 alleles of the HLA-B27 gene reported and their prevalence vary in different population groups. Some of these antigenic subtypes are not associated with susceptibility to development of SpA. Apart from genetic factors, interactions with environmental agents e.g. bacteria are also important for the development of spondyloarthropathies. Studies on transgenic mice have allowed us to understand some of the possible mechanisms e.g. molecular mimicry, arthritogenic peptide, by which the gene-environment interactions can lead to development of disease.

Population Frequencies of HLA-B27 Gene and Prevalence of Spondyloarthropathies

The highly polymorphic HLA-B gene, situated in the Class I region of the major histocompatibility complex, is located on the short arm of chromosome 6 (Fig. 1). The

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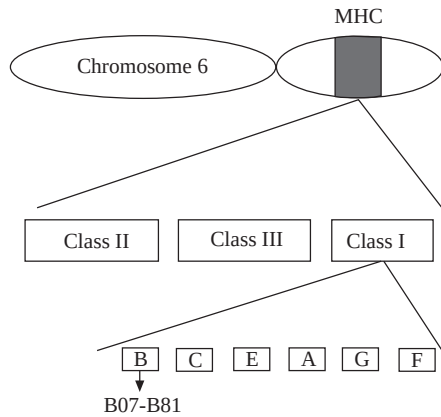


Fig. 1. Major histocompatibility complex—Class I region.

reported alleles ranged from B*0702 to B*8201. The HLA-B27 gene had 16 alleles¹³ described to date (B*2701 to B*2716). The frequencies of the HLA-B27 gene differ among different population groups. In a survey of 275 genomic DNA samples, obtained from healthy Singaporean Chinese individuals, a gene frequency of 6.2% was found.¹⁴ Table II shows the prevalence rates in some population groups. The prevalence ranged from 0% in central Australian aboriginals to a high of 40% in Siberian Eskimos.^{15,16} The

TABLE I: EXTRA-ARTICULAR INVOLVEMENT IN SPONDYLO-ARTHROPATHIES

Cardiovascular	Aortic insufficiency Conduction defects Myocarditis Pericarditis
Cutaneous	Circinate balanitis Erythema nodosum Keratoderma blennorrhagica
Ocular	Conjunctivitis Iritis Uveitis
Pulmonary	Apical fibrosis

TABLE II: HLA-B27 ANTIGENIC PREVALENCE IN SOME POPULATION GROUPS

Population group	Prevalence
Australian Aborigines	0%
Uzbeks	3%
Micronesians (Guam)	5%
Vietnamese	9%
Tibetans	12%
Northern Scandinavians	16%
Melanesians (Vanuatuans)	23%
Siberian Eskimos	40%

highest prevalence of 50% and 52% were found in the Haida population¹⁷ and an isolated community in the Papua New Guinea,¹⁸ respectively. Prevalence of SpA in a specific population group seems to be correlated with the frequency of the HLA-B27 gene in that population group. In epidemiological studies¹⁹⁻²¹ of 4 indigenous population groups in the Alaskan and Siberian regions, where the gene frequencies ranged from 25% to 40%, the overall prevalence of SpA was high (2% to 3.4%). Further analysis of the HLA-B27 positive individuals showed an even higher overall SpA rate of 4.2%. Among the Haida native Indians, another group with high population frequency of the HLA-B27 gene, they have a reported prevalence of 4% of definite AS among its adult males.²² At the other end of the spectrum, AS was noted to be absent among the central Australian aboriginals of unmixed ancestry and parallels the absence of the HLA-B27 gene among them.¹⁵ A recent study of blood donors of the Berlin population showed a genetic frequency of 9.3% with an estimated SpA prevalence of 1.9%.²³ This further augments the observation of a correlation between the population frequency of the HLA-B27 gene and the prevalence of SpA.

HLA-B27 Subtypes

Frequencies of specific HLA-B27 alleles differ among different population groups. The HLA-B*2705 allele is present in various population groups. They are the predominant allele in the North American natives and African Americans.¹⁶ The 2 commonest alleles found in Chinese, Japanese and Asian Indians were HLA-B*2704 and 2705 allele.²⁴⁻²⁶ Among Asian Indians, it was noted that the HLA-B*2704 was the predominant subtype in AS patients and B*2705 was commonest in the undifferentiated spondyloarthropathies group. Table III summarises the common HLA-B27 alleles in some population groups in the Americas, Africa, Indian subcontinent, Asia and Southeast Asian region. HLA-B*2705 (90.2%) and *2702 (9.8%) were the subtypes detected in a group of Danish blood donors.²⁷ Both were not significantly associated with AS. The allele HLA-B*2703 is present in Gambians from West Africa and is not associated with the development of spondyloarthropathies.²⁸ The HLA-B*2706, found in Indonesian, Singaporean and Thai population groups,²⁹⁻³¹ has been postulated to have a “protective” effect. Indonesians of Chinese descent was noted to have a much higher prevalence of AS than native Indonesians, the difference being HLA-B*2706 occurring as the predominant subtype in the latter group.³² This seems to support the hypothesis that HLA-B*2706 has a “protective” effect. However, a recent study on 2 families of mixed Chinese/Indonesian origin suggests that the allele, though not associated with AS, also does not exert any “protective” effect. Heterozygotes B*2704/B*2706 members develop

TABLE III: COMMON HLA-B27 ALLELES IN VARIOUS POPULATION GROUPS

Population group	Predominant allele
North American Natives	*2705
African Americans	*2705
West Africans	*2703 *2705
Euro Caucasoids	*2702 *2705
Chinese	*2704 *2705
Northern Indians	*2704 *2705
Japanese	*2704 *2705
Thais	*2704 *2706
Indonesians	*2704 *2705 *2706

spondyloarthropathies despite the supposed “protective” effect of the B*2706 allele.³³ Allele B*2708 is not common among the general population and is not usually associated with development of spondyloarthropathies. In a recent report, it was however shown to be associated with AS in a large family from the Azores.³⁴ A closely related allele, B*2712, was detected in a Caucasian Spanish family and does not seem to confer susceptibility to the development of spondyloarthropathies.³⁵

Influence of other HLA Genes and non-HLA Genes

The HLA-B27 gene, though associated with the development of spondyloarthropathies, is not present in all patients. Table IV summarises the prevalence of HLA-B27 in different patient groups. The strongest association is seen between the gene and AS, and is probably the disease gene in ankylosing spondylitis patients. However, there is still a subset of patients without the HLA-B27 gene and yet manifest the classical features of AS.³⁶ Hence, the presence of the HLA-B27 gene alone cannot explain all cases of spondyloarthropathies, even in clinically definite AS patients. Other genetic factors, either HLA or non-HLA genes, are probably involved, especially in the subset of HLA-B27-negative spondyloarthritic patients. HLA-A9 (A*2402) has been identified as a secondary susceptibility marker for Basque AS patients³⁷ and HLA-B7 was associated with HLA-B27-negative AS in a subgroup of American blacks.³⁸ In Japanese HLA-B27-negative AS and pauciarticular juvenile rheumatoid arthritis patients, the HLA-B39 was found to be significantly more frequent than healthy controls.³⁹ Recent studies showed that HLA-

TABLE IV: SPONDYLOARTHROPATHIES AND HLA-B27 ANTIGENIC PREVALENCE

Condition	HLA-B27 prevalence
Ankylosing spondylitis	>90%
Juvenile chronic arthritis	85%
Reactive arthritis/Reiter's syndrome	75%
Enteropathic arthritis	50%
Psoriatic arthritis	<50%

B27 and B39 recognise overlapping peptide repertoires, indicating that peptides presented by both may play a role in the pathogenesis of SpA.^{40,41} In a family study of a father and son, both of whom have HLA-B27-negative AS, HLA-B40 was identified as the probable allele contributing to increased susceptibility to development of AS.⁴² Among HLA-B27 patients, other HLA alleles may accentuate the risk. Heterozygotes for HLA-B27 and HLA-B60 were noted to have a 3-fold increased risk of developing AS when compared to heterozygotes with HLA-B27 and another HLA-B type.⁴³ However, in HLA-B27-negative Caucasian and Mexican Mestizo AS patients, the HLA-B39 or B60 association was not detected.⁴⁴ The major histocompatibility complex class I-related chain gene (MICA), MICA-002, allele was noted to be present in significantly higher frequency in psoriatic patients with arthritis and is independent of the primary genetic HLA marker (Cw*0602) for psoriasis.⁴⁵ A similar association exists between the MICA gene and Behcet's disease.⁴⁶ However, 2 studies involving AS patients did not demonstrate that the MICA gene exert an independent effect on the pathogenesis of AS.^{47,48} The HLA-C locus antigens, Cw1 and Cw2, demonstrated strong linkage disequilibrium with HLA-B27 but do not confer independent susceptibility for development of AS.⁴⁹ Among the Class II antigens, HLA-DRB1*08 was found to influence the phenotype of spondyloarthritis in Mexican Mestizo but not in Caucasians.⁵⁰ HLA-DR12 was increased in a group of AS-associated anterior uveitis Japanese patients but that is probably due to linkage disequilibrium with HLA-B*2704 allele.⁵¹ In an analysis of 363 white British AS patients for the effect of DR genes, it was concluded that DR genes may have only a weak effect on susceptibility but do not affect disease severity or clinical manifestations.⁵² Associations with the tumour necrosis factor alpha (TNF α) promoter region polymorphisms have been reported. Hohler et al⁵³ found a significant decrease in the variant promoter alleles TNF -238.2 and TNF -308.2 and postulated that these variant alleles may have a protective effect. However, the possibility of linkage disequilibrium cannot be totally ruled out. McGarry and co-workers⁵⁴ recently showed that the TNF -308.1 allele was associated with ankylosing spondylitis independent of HLA-B27. The TAP gene has

also been studied and its polymorphism was not associated with development of AS.⁵⁵ Using more than 200 highly polymorphic microsatellite markers, Brown et al⁵⁶ genome scanned 105 families and provided evidence indicating that apart from 6p, regions in chromosomes 4q and 16q showed linkage with AS. Further studies in these regions will probably yield a better understanding of the contributions of non-HLA genes to the pathogenesis of spondyloarthropathies.

Gene-Environmental Agents Interactions

The presence of the susceptible gene does not always lead to development of some form of spondyloarthropathies. Hence, environmental triggers or influences do play significant roles in the pathogenetic process. Taurog et al⁵⁷ reported that a germ-free state prevents development of gut and joint inflammation in HLA-B27 transgenic rats, and this was later confirmed in another study by Rath and co-workers.⁵⁸ The latter study also demonstrated that normal intestinal bacteria which contained *Bacteroides spp* can induce gut inflammation and arthritis in the HLA-B27/human β_2 microglobulin transgenic F344 rats. Pathogenic organisms like *Yersina*, *Salmonella* and *Campylobacter* are well recognised to be associated with reactive arthritis in man. Molecular mimicry between bacterial heat shock protein 60 (hsp60) from *Yersina enterocolita* and self-hsp60 has been postulated as the mechanism for development of reactive arthritis.⁵⁹ In other studies, “arthritogenic” peptides, which may be of unusual length or lacking HLA-B27 canonical residues, have been detected after *Shigella* infection.⁶⁰ These peptides may be important in disease pathogenesis by eliciting an immune response. The HLA-B27 molecule has a B pocket (P2) which is unique in presenting a cysteine-reactive residue (Cys67), and rats with a mutant B27 with a Ser67 substitution of Cys67 have a lower prevalence of arthritis.⁶¹ The exact roles that these factors play in the pathogenesis of spondyloarthropathies are yet to be fully worked out.

Disease Marker or Disease Gene?

Genetic associations can occur because of linkage disequilibrium.⁶² This is the result of close proximity of genetic loci, which can then lead to non-random segregation during chromosomal crossovers. They are not the actual disease susceptibility gene but are close to them. However, the usual finding is the detection of a “weak” to “moderate” association. The strong association between spondyloarthropathies and the HLA-B27 gene indicates that it is probably the major disease gene, at least in the case of AS patients. The contributions of other HLA and non-HLA genes are yet unclear but are significant, especially in HLA-B27-negative patients with SpA. They may also be important as modifiers of disease susceptibility or

clinical manifestations. However, to the clinicians, the important questions are: What is the significance of detecting the presence of the HLA-B27 gene in a patient? What is the risk of developing spondyloarthropathies in these individuals?

Significance of the HLA-B27 Gene's Presence

The presence of the gene predisposes an individual to developing spondyloarthropathies. In a 1984 report, 1.3% of HLA-B27 positive individuals were found to have features of AS. However, if there is a confirmed AS family member, the prevalence rises to 21% among the HLA-B27-positive relatives. This represents a 16-fold increase in the risk of having AS.⁶³ In another study at that time, it was noted that the relative risk of developing spondyloarthropathy was 5.6 for B27-positive relatives of B27-positive patients when compared with relatives of B27-positive healthy subjects.⁶⁴ In a more recent study among blood donors in Berlin, HLA-B27-positive individuals have a 20-fold increased risk of developing SpA.²³ Important as these findings may be, there is no justification for screening of healthy, asymptomatic individuals for the HLA-B27 gene. It is useful as an adjunct to the diagnosis of AS especially in those who understand the principles of probability.⁶⁵ Otherwise it may represent a waste of resources. In an Auckland study, it was shown that 43% of the HLA-B27 tests were positive when ordered by rheumatologists, compared to only a 12% positivity rate for those ordered by other doctors. The authors concluded that non-rheumatologists ordered an excessive number of tests in patients with a low probability of HLA-B27 associated disease.⁶⁶ Apart from its usefulness as an adjunct to diagnosis, it does have prognostic implications in some patients. In patients with juvenile chronic arthritis, it was noted that those with the HLA-B27 gene have more active disease, develop secondary amyloidosis about 6 years earlier and underwent arthroplasty on average 3 years earlier than their B27-negative counterparts.⁶⁷ The HLA-B27 gene seems to be a predictor for more severe disease in juvenile arthritics. The HLA-B27 gene also seems to confer a worse outcome in patients with anterior uveitis. There were more complications and the percentage of legally blind patients was significantly higher in HLA-B27-positive patients with or without associated systemic disease.⁶⁸

Conclusion

The genetics of spondyloarthropathies is relatively complex even though the HLA-B27 gene plays a prominent role in this group of disorders. Many genes are involved. The mechanism of how the HLA-B27 gene causes spondyloarthropathies is not yet fully elucidated but environmental factors like bacterial agents do play an

important part, e.g. in patients with reactive arthritis. The interaction between the gene and the environment is an interesting one and will definitely be the subject of further study by various research groups. Genome scanning studies, especially of SpA patients from various ethnic groups, can also help us to understand more about the contributions of non-HLA genes. Finally, with better understanding of the polygene effects, clinicians will be able to prognosticate and undertake genetic counselling more accurately.

REFERENCES

- Khan M A. Seronegative spondyloarthropathies. In: Howe H S, Feng P H, editors. *Textbook of Clinical Rheumatology*. Singapore: National Arthritis Foundation, 1998:125-47.
- Zeidler H, Mau W, Khan M A. Undifferentiated spondyloarthropathies. *Rheum Dis Clin North Am* 1992; 18:187-202.
- Rosebaum J T. Characterisation of uveitis associated with spondyloarthropathies. *J Rheumatol* 1989; 16:792-6.
- Brewerton D A, Caffrey H, Hart F D, James D C O, Nicholls A, Sturrock R D. Ankylosing spondylitis and HLA-B27. *Lancet* 1973; 1:904-7.
- Schlosstein T, Terasaki P I, Bluestone R, Pearson C M. High association of a HLA antigen w27, with ankylosing spondylitis. *N Engl J Med* 1973; 288:704-6.
- Khan M A. Ankylosing spondylitis: Clinical features. In: Klippel J H, Dieppe P A, editors. *Rheumatology*. 2nd ed. London: Mosby, 1998:6.16.1-10.
- Chan S H, Satkunananthan K, Wee G B, Sirinivan N, Chacha P. HLA-B27 and Chinese ankylosing spondylitis. *Singapore Med J* 1980; 21:710-2.
- Prakash S, Mehra N K, Bhargava S, Vaidya M C, Malaviya A N. Ankylosing spondylitis in North India: a clinical and immunogenetic study. *Ann Rheum Dis* 1984; 43:381-5.
- Deesomchok U, Tumrasvin T. Clinical study of Thai patients with ankylosing spondylitis. *Clin Rheumatol* 1985; 4:76-82.
- Alharbi S A, Mahmoud F F, Al Awadi A, Al Jumma R A, Khodakhast F, Alsulaiman S M. Association of MHC Class I with spondyloarthropathies in Kuwait. *Eur J Immunogenet* 1996; 23:67-70.
- Awadia H, Baddoura R, Naman R, Klayme S, Mansour I, Tamouza R, et al. Weak association between HLA-B27 and the spondyloarthropathies in Lebanon. *Arthritis Rheum* 1997; 40:388-9.
- Al-Arfaj A. Profile of ankylosing spondylitis in Saudi Arabia. *Clin Rheumatol* 1996; 15:287-9.
- <http://www.anthonynolan.com/HIG/seq/nuc/text/b.nt.txt>.
- Norkamar A A, Chan L, Tin S K, Fong K Y and the Singapore Lupus Research Group. Prevalence of HLA-B27 antigen in systemic lupus erythematosus and correlation with clinical manifestations [abstract]. 5th Annual Scientific Meeting, Tan Tock Seng Hospital Abstract Book 1997:33.
- Cleland L G, Hay J AR, Milazzo SC. Absence of HLA-B27 and of ankylosing spondylitis in central Australian aboriginals [abstract]. *Scand J Rheumatol* 1975; 8(suppl):30.
- Khan M A. Prevalence of HLA-B27 in world populations. In: Lopez-Larrea C, editor. *HLA-B27 in the Development of Spondyloarthropathies*. Heidelberg: Springer-Verlag, 1997:93-112.
- Gofton J P. Epidemiology, tissue type antigen and Betchterew's syndrome (ankylosing spondylitis) in various ethnical populations. *Scand J Rheumatol* 1980; 9(Suppl 32):166-8.
- Clunie G P, Koki G, Prasad M L, Richens J E, Bhatia K, Keat A. HLA-B27, arthritis and spondylitis in an isolated community in Papua New Guinea. *Br J Rheumatol* 1990; 29:97-100.
- Erdesz S, Shubin S V, Shoch B P, Krylov M Y, Mylov N M, Chekalina N A, et al. Spondyloarthropathies in circumpolar populations of Chukotka (Eskimos and Chukchi): Epidemiology and clinical characteristics. *J Rheumatol* 1994; 21:1101-4.
- Boyer G S, Templin D W, Cornoni-Huntley J C, Everett D F, Lawrence R C, Heyse S F, et al. Prevalence of spondyloarthropathies in Alaskan Eskimos. *J Rheumatol* 1994; 21:2292-7.
- Alexeeva L, Krylov M, Vturin V, Mylov N, Erdesz S, Benevolenskaya L. Prevalence of spondyloarthropathies and HLA-B27 in the native population of Chukotka, Russia. *J Rheumatol* 1994; 21:2298-300.
- Gofton J P, Chalmers A, Price G E, Reeve C E. HLA-B27 and ankylosing spondylitis in B.C. Indians. *J Rheumatol* 1975; 2:314-8.
- Braun J, Bollow M, Remlingar G, Eggens U, Rudwaleit M, Distler A, et al. Prevalence of spondyloarthropathies in HLA-B27 positive and negative blood donors. *Arthritis Rheum* 1998; 41:58-67.
- Lin J, Lu H, Feng C. Ankylosing spondylitis and heterogeneity of HLA-B27 in Chinese. *Chin Med J (Engl)* 1996; 109:313-6.
- Tamaguchi A, Ogawa A, Tsuchiya N, Shiota M, Mitsui H, Tokunaga K, et al. HLA-B27 subtypes in Japanese with seronegative spondyloarthropathies and healthy controls. *J Rheumatol* 1996; 23:1189-93.
- Kanga U, Mehra N K, Larrea C L, Lardy N M, Kumar A, Feltkamp T E. Seronegative spondyloarthropathies and HLA-B27 subtypes : a study in Asian Indians. *Clin Rheumatol* 1996; 15(Suppl):13-8.
- Baech J, Schmidt-Olsen S, Steffensen R, Varming K, Grunnet N, Jersild C. Frequency of HLA-B27 subtypes in an Asian population and in Danish patients with ankylosing spondylitis. *Tissue Antigens* 1997; 49:499-502.
- Hill A V, Allsopp C E, Kwiatkowski D, Anstey N M, Greenwood B M, McMichael A J. HLA Class I typing by PCR: HLA-B27 and an African B27 subtype. *Lancet* 1991; 337:640-2.
- Nasution A R, Mardjuadi A, Kunmartini S, Suryadhana N G, Setyohadi B, Sudarsono D, et al. HLA-B27 subtypes positively and negatively associated with spondyloarthropathy. *J Rheumatol* 1997; 24:1111-4.
- Ren E C, Koh W H, Sim D, Boey M L, Wee G B, Chan S H. Possible protective role of HLA-B*2706 for ankylosing spondylitis. *Tissue Antigens* 1997; 49:67-9.
- Lopez-Larrea C, Sujirachato K, Mehra N K, Chiewsilp P, Isarangkura D, Kanga U, et al. HLA-B27 subtypes in Asian patients with ankylosing spondylitis : evidence for new associations. *Tissue Antigens* 1995; 45:169-76.
- Nasution A R, Mardjuadi A, Suryadhana N G, Daud R, Muslichan S. Higher relative risk of spondyloarthropathies among B27 positive Indonesian Chinese than native Indonesians. *J Rheumatol* 1993; 20:988-90.
- Sudarsono D, Hadi S, Mardjuadi A, Nasution A R, Dekker-Sacys A J, Breur-Vriesendorp B S, et al. Evidence that HLA-B*2706 is not protective against spondyloarthropathy. *J Rheumatol* 1999; 26:1534-6.
- Armas J B, Gonzalez S, Martinez-Borra J, Laranjeira F, Ribeiro E, Correia J, et al. Susceptibility to ankylosing spondylitis is independent of the Bw4 and Bw6 epitopes of HLA-B27 alleles. *Tissue Antigens* 1999; 53:237-43.
- Balas A, Santos S, Garcia-Sanchez F, Lillo R, Merino J L, Vicario J L. Complete coding sequence of HLA-B*2712: a serologic B27-negative antigen associated to Bw6. *Tissue Antigens* 1998; 51:394-7.
- Khan M A, Kusher I, Braun W E. Comparison of clinical features in HLA-B27 positive and negative patients with ankylosing spondylitis.

- Arthritis Rheum 1977; 20:909-12.
37. De Juan M D, Reta A, Cancio J, Belzunequi J, Cuadrado E. HLA-A*9, a probable secondary susceptibility marker to ankylosing spondylitis in Basque patients. *Tissue Antigens* 1999; 53:161-6.
 38. Khan M A, Kusher I, Braun W E. A subgroup of ankylosing spondylitis associated with HLA-B7 in American blacks. *Arthritis Rheum* 1978; 21:528-30.
 39. Yamaguchi A, Tsuchiya N, Mitsui H, Shiota M, Ogawa A, Tokunaga K, et al. Association of HLA-B39 with HLA-B27-negative ankylosing spondylitis and pauciarticular juvenile rheumatoid arthritis in Japanese patients. Evidence for a role of the peptide-anchoring B pocket. *Arthritis Rheum* 1995; 38:1672-7.
 40. Sobao Y, Tsuchiya N, Takiguchi M, Tokunaga K. Overlapping peptide-binding specificities of HLA-B27 and B39: evidence for a role of peptide supermotif in the pathogenesis of spondyloarthropathies. *Arthritis Rheum* 1999; 42:175-81.
 41. Yague J, Ramos M, Vazquez J, Marina A, Albar J P, Lopez de Castro J A. The South American allotypes HLA-B*3909 has the largest known similarity in peptide specificity and common natural ligands with HLA-B27. *Tissue Antigens* 1999; 53:227-36.
 42. Skomsvoll J F, Ostensen M, Romberg O, Anda S. HLA-B27 negative ankylosing spondylitis in a father and son. *Scand J Rheumatol* 1995; 24:321-2.
 43. Feltkamp T E. Non-HLA-B27 genetic factors in HLA-B27 associated disease. *Clin Rheumatol* 1996; 15(Suppl 1):40-3.
 44. Maksymowych W P, Tao S, Vaile J, Suarez-Almazor M, Ramos-Remus C, Russell A S. LMP2 polymorphism is associated with extraspinal disease in HLA-B27 negative Caucasian and Mexican Mestizo patients with ankylosing spondylitis. *J Rheumatol* 2000; 27:183-9.
 45. Gonzalez S, Martinez-Borra J, Torre-Alonso J C, Gonzalez-Roces S, del Rio S, Rodriguez Perez A, et al. The MIC-A9 triplet repeat polymorphism in the transmembrane region confers additional susceptibility to develop psoriatic arthritis, and is independent of the associations of Cw*0602 in psoriasis. *Arthritis Rheum* 1999; 42:1010-6.
 46. Mizuki N, Ota M, Limura M, Ohno S, Ando H, Katsuyama Y, et al. Triplet repeat polymorphism in the transmembrane region of the MICA gene: A strong association of six GCT repetitions with Behcet's disease. *Proc Natl Acad Sci U S A* 1997; 94:1298-303.
 47. Tsuchiya N, Shiota M, Moriyama S, Ogawa A, KomatsuWakui M, Mitsui H, et al. MICA allele typing of HLA-B27 positive Japanese patients with seronegative spondyloarthropathies and healthy individuals: differential linkage disequilibrium with HLA-B27 subtypes. *Arthritis Rheum* 1998; 41:68-73.
 48. Yabuki K, Ota M, Goto K, Kimura T, Nomura E, Ohno S, et al. Triplet repeat polymorphisms in the MICA gene in HLA-B27 positive and negative Caucasian patients with ankylosing spondylitis. *Hum Immunol* 1999; 60:83-6.
 49. Arnett F C, Hochberg M C, Bias W B. HLA-C locus antigens in HLA-B27 associated arthritis. *Arthritis Rheum* 1978; 21:885-8.
 50. Maksymowych W P, Gorodezky C, Olivo A, Alaez C, Wong C, Burgos-Vargas R, et al. HLA-DRB1*08 influences the development of disease in Mexican Mestizo with spondyloarthropathy. *J Rheumatol* 1997; 24:904-7.
 51. Konno Y, Numaga J, Tsuchiya N, Ogawa A, Islam S M, Mochizuk M, et al. HLA-B27 subtypes and HLA-Class II alleles in Japanese patients with anterior uveitis. *Invest Ophthalmol Vis Sci* 1999; 40:1838-44.
 52. Brown M A, Kennedy L G, Darke C, Gibson K, Pile K D, Shatford J L, et al. The effect of HLA-DR genes on susceptibility to and severity of ankylosing spondylitis. *Arthritis Rheum* 1998; 41:460-5.
 53. Hohler T, Schaper T, Schneider P M, Meyer zum Buschenfelde K H, Marker-Hermann E. Association of different tumor necrosis factor alpha promoter allele frequencies with ankylosing spondylitis in HLA-B27 positive individuals. *Arthritis Rheum* 1998; 41:1489-92.
 54. McGarry F, Walker R, Sturrock R, Field M. The -308.1 polymorphism in the promoter region of the tumor necrosis factor gene is associated with ankylosing spondylitis independent of HLA-B27. *J Rheumatol* 1999; 26:1110-6.
 55. Konno Y, Numaga J, Mochizuki M, Mitsui H, Hirata R, Macda H. TAP polymorphism is not associated with ankylosing spondylitis and complications with acute anterior uveitis in HLA-B27-positive Japanese. *Tissue Antigens* 1998; 52:478-83.
 56. Brown M A, Pile K D, Kennedy L G, Campbell D, Andrew L, March R, et al. A genome-wide screen for susceptibility loci in ankylosing spondylitis. *Arthritis Rheum* 1998; 41:588-95.
 57. Taurog J D, Richardson J A, Croft J T, Simmons W A, Zhou M, Fernandez-Sueiro E, et al. The germfree state prevents development of gut and joint inflammatory disease in HLA-B27 transgenic rats. *J Exp Med* 1994; 180:2359-64.
 58. Rath H C, Herfarth H H, Ikeda J S, Grenther W B, Hamm T E, Balish E, et al. Normal luminal bacteria *Bacteroides* species, mediate chronic colitis, gastritis, and arthritis in HLA-B27/Human beta₂ microglobulin transgenic rats. *J Clin Invest* 1996; 98:945-53.
 59. Mertz A K H, Ugrinovic S, Lauster R, Wu P, Grolms M, Botther U, et al. Characterisation of the synovial T cell response to various recombinant *Yersinia* antigens in *Yersinia enterocolitica*-triggered reactive arthritis. *Arthritis Rheum* 1998; 41:315-26.
 60. Boisgerault F, Mounier J, Tieng V, Stolzengerg M C, Khalil-Daher I, Schmid M, et al. Alteration of HLA-B27 peptide presentation after infection of transfected murine L cells by *Shigella Flexneri*. *Infect Immun* 1998; 66:4484-90.
 61. Taurog J D, Maika S D, Satumtira N, Dorris M L, McLaen I L, Yanagisaw S A, et al. Inflammatory disease in HLA-B27 transgenic rats. *Immunol Rev* 1999; 169:209-23.
 62. Fong K Y. Genes and rheumatic diseases. In: Howe H S, Feng P H, editors. *Textbook of Clinical Rheumatology*. Singapore: National Arthritis Foundation, 1998:10-6.
 63. Van der Linden S M, Valkenburg H A, de Jongh B M, Cats A. The risk of developing ankylosing spondylitis in HLA-B27 positive individuals. A comparison of relatives of spondylitis patients with the general population. *Arthritis Rheum* 1984; 27:241-9.
 64. Calin A, Marder A, Becks E, Burns T. Genetic differences between B27 positive patients with ankylosing spondylitis and B27 positive healthy controls. *Arthritis Rheum* 1983; 26:1460-4.
 65. Ferraz M B, Sesso R, Atra E. Usefulness of HLA-B27 in the diagnosis of ankylosing spondylitis: positive and negative predictive value and the probability ratio of disease. *Rev Paul Med* 1990; 108:153-6.
 66. Thomas M G, Hart H H, Grigor R R, Gow P J, Moore T E. Use of HLA B27 test in Auckland. *N Z Med J* 1984; 97:686-8.
 67. Savolainen H A, Lehtimäki M, Kautiainen H, Aho K, Anttila P. HLA-B27: a prognostic factor in juvenile chronic srthritis. *Clin Rheumatol* 1998; 17:121-4.
 68. Power W J, Rodriguez A, Pedroza-Seres M, Foster C S. Outcomes in anterior uveitis associated with the HLA-B27 haplotype. *Ophthalmology* 1998; 105:1646-51.