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A common HLA phenotype in slipped capital femoral epiphysis?

Accepted: 12 January 2000

Abstract Studies from three different countries have linked the HLA B12 and DR4 antigens with slipped capital femoral epiphysis (SCFE). We questioned whether our patients shared in common either of these antigens. HLA phenotype was determined in 7 patients with SCFE, two of whom were brothers with almost identical haplotypes. The B12 antigen was found in none of our patients and the DR4 in only 3. Neither of the 2 brothers held the DR4 antigen. The commonest antigens (also shared by the 2 brothers) were B35, present in 5 and DR52 in 4 of 7 patients. We conclude that neither the previously described B12 nor the DR4 antigen can reliably serve as genetic markers for SCFE in our region.

Résumé Des études provenant de trois autres pays ont impliqué que la survenue de l'éphysiolyse fémorale supérieure est liée à la présence des antigènes HLA B12 et DR4. Nous avons mis en question si nos patients aussi possèdent les mêmes allèles. À ce propos, on a déterminé les groupes HLA chez six garçons et une fille, dont deux frères ayant des antigènes presque identiques. L'antigène B12 de classe I est absent chez tous nos sujets et le DR4 de classe II présent en seulement trois. Aucun des deux frères ne possède l'allèle DR4. Les antigènes les plus communs parmi nos patients et également présents chez les deux frères sont B35, se trouvant en cinq de nos 7 sujets, et le DR52 en 4. Ces faits nous amènent à conclure que ni le HLA B12 ni le DR4 ne peuvent servir comme gènes marqueurs pour l'éphysiolyse fémorale supérieure dans notre région.

Introduction

The relationship between HLA phenotype and certain rheumatic diseases is well established. Notable examples are of the class I antigen HLA B27 with ankylosing spondylitis and of class II antigen HLA DR4 with rheumatoid arthritis [5,7]. These HLA genotypes serve as genetic markers by virtue of their strong associations with these diseases. Three investigations have advocated that a similar marker may exist for slipped capital femoral epiphysis (SCFE). The first two from the UK and New Zealand implicated the B12 locus, while the third from Turkey put forward the DR4 locus [1,3,4]. We sought to determine whether a common HLA phenotype existed for our patients and if it did, whether it would match either of those reported from the three previous different geographical regions.

Materials and methods

Seven patients who had pinning of SCFE at our institution were randomly recalled for determination of their HLA genotypes. There were 6 boys and 1 girl, aged 11–13 years at time of slip. Their HLA phenotypes were determined by a complement-dependent micro-lymphocytotoxic technique (Biotest Diagnostics, Germany).

Table 1 lists the phenotypes of our patients. The first two listed patients are brothers who presented with SCFE at the same age, but 10 years apart. Both have almost identical haplotypes, except that the younger brother does not have class I antigen BW6 and has CW4 instead of CW2 antigen.

Discussion

Human leukocyte antigens (HLA) are produced by genes located in a segment on the short arm of chromosome 6, called the major histocompatibility complex. The entire complex, spanning approximately 1,000 kilobase, is divided into three regions, class I, II and III loci. Several rheumatic diseases have been associated with class I and class II alleles. Examples of those associated with class I antigen include ankylosing spondylitis and Reiter's syn-

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Table 1 HLA phenotype by study

Patients/study	Country	Sex	Age at slip	HLA Class I phenotype	HLA Class II phenotype
1	Bahrain	M	12	A10 A32(19) B22 B35	CW1 CW4 DR16(2) DR12(5) DR52 DR51 DQ1 DQ7(3)
2		M	12	A10 A32(19) B22 B35 BW6	CW1 CW2 DR16(2) DR12(5) DR52 DR51 DQ1 DQ7(3)
3		F	11	A2 A33 B71(70) B35 BW6	CW3 CW4 DR1 DR17(3) DR52 DQ5(1) DQ2
4		M	13	A24(9) A43 B60(40) B35 BW6	CW4 DR7 DR10 DR53 DQ5(1) DQ2
5		M	13	A2 B51(5) BW4	CW3 DR4 DR8 DR53 DQ8(3)
6		M	13	A34(10) A28 B51(5) B71(70) BW4 BW6	CW3 CW4 DR18(13) DR4 DR52 DR53 DQ8(3)
7	New Zealand	M	11	A2 B50(21) B35 BW4 BW6	CW6 CW4 DR4 DR8 DR53 DQ8(3) DQ7(3)
Twins (Allen and Calvert)		M	15	A2 B12	
Twins (Gajraj)	UK	F	11	A11 B12(44)	
Twins (Bednarz and Stanitski)	USA	M	12	A2 A26 B51 B60 BW4 BW6	
		M	12	A2 A24 B51 B60 BW4 BW6	
Gunal and Ates	Turkey	M	16	A3 A9 B7 B14	DR4Dw52
		M	13	A10 A19 B16 B14	DR4DR3
		M	14	A28 A19 B15 B22	DR4DR7
		F	14	A2 A10 B5 B22	DR4Dw52
		F	13	A1 A3 B15 BW6	DR4DRw11
		M	14	A9 B7 B12	DR4 DR2

drome. Ninety per cent of patients with ankylosing spondylitis are HLAB27 positive as opposed to only 8% of the normal population. However, the absolute risk of the disease developing in patients with this haplotype is small, varying from 1 to 10% [5]. Class II antigens have been linked with rheumatoid arthritis, Sjögren's syndrome, juvenile rheumatoid arthritis and systemic lupus erythematosus. Sixty to 80% of patients with rheumatoid arthritis are serologically type HLA-DR4 compared with approximately 20% of the general population [7].

Gajraj [3] in 1986 first determined the HLA phenotype in patients with SCFE. He identified the class I antigens, A11, B12(44) in identical 11-year-old British twin girls and suggested that further phenotyping could lead to isolation of a genetic marker for the condition. In 1990, Allen and Calvert [1] from New Zealand reported the phenotypes of identical 15-year-old twin boys with SCFE to be A2, B12. They drew attention to the B12 antigen that both sets of twins shared in common. Bednarz and Stanitski in 1998 remarked that, while their 12-year-old male twin patients shared the A2 allele in common with the New Zealand twins, their phenotypes did not match any of the British twins' antigens [2]. None of the foregoing three reports stated the class II antigens of their patients. In 1997, Günel and Ates [4] from Turkey described a common HLA-DR4 genotype in all their 6 patients, 4 boys and 2 girls. The B12 antigen was absent in all their patients except one.

Interestingly, our study includes two brothers with almost identical phenotypes who presented at the same age with SCFE, 10 years apart. The B12 antigen, previously noted in the 2 sets of identical twins from Britain and New Zealand, is not present in either brother or any of our other patients. The DR4 antigen observed in all 6

Turkish patients is found in only 3 of our 7 patients and in neither of the brothers. The commonest class I and II antigens that are also held by the two brothers are B35, present in 5 of 7 patients (71%) and DR52 in 4 patients (57%), respectively. None of the Turkish patients held either the B35 or DR52 antigens.

Associations between diseases and HLA phenotype are known to vary when studied in different populations. Despite taking this fact into account, no clear relationship emerged in our small number of patients between SCFE and either a class I or class II antigen. Rarity of the condition in our region [6] and cost of laboratory tests preclude further extensive investigation for the moment. We can only conclude that neither the DR4 nor B12 locus can reliably be used as genetic markers in our area. Worldwide determination of HLA phenotype in patients with SCFE may shed further light on the existence of any real association.

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