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SHORT COMMUNICATION

FREQUENCY OF THE NEW HLA-B*2709 ALLELE IN ANKYLOSING SPONDYLITIS PATIENTS AND HEALTHY INDIVIDUALS

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We have recently described a new HLA-B27 subtype, named HLA-B*2709 (Del Porto *et al.* 1994). This allele is identical to the subtype most frequently found in Caucasoids, HLA-B*2705, except for a single amino acid substitution (Asp to His) in position 116. This residue, that is part of the F pocket of the molecule, has been shown to be relevant in determining which C-terminal amino acid of HLA-class I-binding peptides can be accomodated into the groove (Elliott, 1993). In nonamer peptides, this aminoacid corresponds to a primary anchor position (P9; Madden *et al.*, 1992). Accordingly, we have previously shown that B2709 molecule hardly accepts nonamer peptides with an Arg or Tyr in P9, while the same amino acids represent good anchors for B2705 molecules (Fiorillo *et al.*, 1995).

Special attention is focused on HLA-B27 subtypes because of the strong association of B27 with ankylosing spondylitis (AS). More than 90% of AS patients are B27-positive and, conversely, about 4% of B27-positive individuals in the population are affected. This represents a relative risk over 100, that is the highest in HLA-disease associations. However, little is known on the pathogenic mechanisms of the disease. Following the hypothesis that an antigenic B27-binding peptide is involved in the disease (the so-called "arthritogenic peptide"), differential association with the different B27 subtypes may give a clue on the nature of such peptide. If two subtypes of partially overlapping peptide binding specificity are found to be both AS-associated, this would restrict the search for peptides that can be bound by both allelic products. Conversely, if a B27 subtype is found to be non AS-associated, this would be even more helpful in eliminating an array of peptides as possible candidates.

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Table 1. Distribution of the HLA-B*2709 allele in Ankylosing Spondylitis patients and healthy individuals from an Italian population*.

	AS Patients n=37	Controls n=121
HLA-B*2709+	0	4

$X^2 = 1.25$ $P = 0.26$

*Patients and controls were collected in Northern-Central Italian regions.

With the aim of testing whether or not HLA-B*2709 is AS-associated, genomic typing was performed as previously described (Del Porto *et al.*, 1994) on a panel of healthy as well as AS-affected individuals, selected as B27-positives on the basis of serological HLA-class I typing. The results are shown in Table 1.

HLA-B*2709 accounts for only a small proportion of B27 alleles in Italy (3,3%). Since the allele frequency of HLA-B27 as a whole is 2.2% (Imanishi *et al.*, 1992), the estimated allele frequency of HLA-B*2709 in the entire Italian population is extremely low (0.08%). Among the 37 AS patients tested none was found to carry B*2709.

These data suggest the possibility that B*2709, unlike B*2705, does not confer susceptibility to AS. However, it is difficult and sometimes impossible, for this as well as for other B27 subtypes with similarly low frequencies, to collect a number of patients sufficient to reach statistical significance. Concerning the other rare Caucasoid subtypes, B*2701 is considered to be probably AS-associated, since at least one positive AS patient has been reported (MacLean 1992) and B*2702 to be certainly associated since several positive AS patients are known (Breur-Vriesendorp *et al.*, 1987). In the same way, B*2709 can be stated to be probably AS-non associated; certainly, there is no suggestion of preferential association of AS with this allele since, so far, no patient with B*2709 has been found. A better assessment can be sought in two ways: either expanding the number of AS patients tested in the Italian population (but at least 115 patients with no single instance of B*2709 positivity would be needed to reach $P = 0.05$), or looking for other populations where the frequency of B*2709 is higher, so that statistically significant differences between AS patients and controls can be more easily tested. The latter may be a more effective choice and we are currently pursuing it.

If the non association of B*2709 with AS will be confirmed this will indicate a critical role of the P9 anchor residue of the "arthritogenic peptide" involved in the disease pathogenesis.

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