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*.

<table>
<thead>
<tr>
<th>HLA-B*2709+</th>
<th>AS Patients n=37</th>
<th>Controls n=121</th>
</tr>
</thead>
<tbody>
<tr>
<td>X^2 = 1.25</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>P = 0.26</td>
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*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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REFERENCES


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