

## SHORT REPORT

# HLA antigens in multiple sclerosis of Northern Spanish population

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## Abstract

HLA-A, -B, -C, -DR, -DQ antigens were studied in 43 multiple sclerosis (MS) patients with clinically definite remittent sclerosis from Asturias (North Spain). The prevalence of HLA-B7, B7 and B27 were significantly increased in MS. HLA-B35 was under-represented in these patients. DR2 was increased but not significantly. No association with DQw1 was discovered. The existence of several susceptibility factors in the more common B7/DR2/DQw1 haplotype is discussed.

Several studies have found an association between susceptibility to multiple sclerosis (MS) and HLA-A3, -B7 antigens.<sup>1</sup> This association seems to be secondary to a stronger DR2 and DQw1 in different white populations.<sup>2</sup> The strength of A3-B7-DR2-DQw1 associations decreases from Northern to Southern Europe and correlates with the known MS latitude prevalence distribution.<sup>3</sup> However, a few controversial studies from Mediterranean populations have been reported.<sup>4,5</sup>

The objective of this work has been to map susceptibility genes within the HLA in a sample of Northern Spanish MS patients. Furthermore, a correlation has been made with the different haplotypic A3-B7-DR2-DQw1 associations which appear in Spanish and other North European populations.

## Patients and methods

### Population sample

HLA class I and class II antigens were studied in 43 unrelated patients from Northern Spain (Asturias region) with clinically definite remittent MS. This area has medium frequency of MS (prevalence of 20/100 000). The diagnostic criteria used was established by Poser *et al.*<sup>6</sup> Healthy volunteers from a sample of the Spanish population (100) were used for the HLA control.

### HLA typing

HLA-A, -B, -C, -DR typing was performed on defibrinated blood as previously described.<sup>7</sup> Local and Ninth HLA Workshop antisera were used.

### Statistical analysis

Analysis was carried out using a computer programme. When the frequency antigens deviated significantly from those of normal

individuals, the corresponding p values were multiplied by the number of antigens which were considered only in a series with more than 20 alleles. The chi-square test with Yates's correction was used to compare the frequencies of HLA antigens. Relative risk (RR) was calculated according to Svejgaard *et al.*<sup>8</sup>

## Results

The HLA antigen frequencies of 43 patients with MS and the HLA control are listed in the table. Significant association was found with B7 ( $p < 0.01$ ) and B27 ( $p < 0.05$ ). B35 was significantly under-represented in the patients ( $p < 0.01$ ). DR5 was also decreased in MS (5.7% versus 20.7;  $p < 0.05$ ).

HLA-DR2 was increased but not significantly (37.7% versus 23.9) as expected by the results found in other ethnic groups. The HLA-DR2 increment was probably secondary to the observed B7-DR2 association. However, the frequency of DR2 in the Northern Spanish region was comparable to that reported in other white populations (not shown). The association B7-DR2 was also increased in MS (27.9% versus 6.1%;  $p < 0.01$ ) but the B7-DR2 risk did not differ significantly from the B7 relative risk (4.2 versus 3.4). DQw1 was not found associated with MS as might have been expected because of the well established linkage disequilibrium DR2/DQw1.

## Discussion

Several studies have shown an association between susceptibility to MS disease and the HLA antigens. HLA-DR2 has been described as a related antigen in different ethnic groups.<sup>5</sup> The common A3/B7/DR2 haplotype was found to be increased in Northern Europeans.<sup>1</sup> It is clear that DR2 itself does not cause susceptibility in MS. In this context, DQw1 showed a strong association as expected because of the well established linkage DQw1-DR2.<sup>2</sup> Genomic HLA-class II typing with DQalpha and DRbeta cDNA probes has confirmed these results.<sup>9</sup> In

Table HLA antigen frequencies (%) in Northern Spanish patients with multiple sclerosis and normal controls

Antigen	MS patients (n = 43)	Controls (n = 100)	Relative risk	$\chi^2$
B35†	7.5	27.2	0.22	8.1
B44	25.0	11.3	0.38	3.9
B27*	2.2	9.4	4.68	3.8
B7†	34.0	13.0	3.42	8.9
DR2	37.7	23.9	1.92	3.1
B7-DR2†	27.9	6.1	4.20	8.0
B7-non DR2	7.0	6.9	0.84	0.1
DR5*	5.7	20.7	0.23	5.8

\* $p < 0.05$ ; † $p < 0.01$ .

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contrast these HLA associations were not evident in Orientals.<sup>10</sup> There has been controversy over the relationship of ethnic groups of Mediterranean origin.<sup>1-3</sup> Populations in South Europe have not been sufficiently investigated. Our results suggest that B7 is closely associated to the disease in Northern Spanish MS patients. DR2 and DQw1 are not significantly increased and play a secondary role as susceptibility factors. The negative association of B35 and DR5 is thought to have a protective role against the development of the disease. It was observed that the more frequent B7/DR2 haplotype in white populations is weakly maintained in the Spanish population.<sup>7</sup> The strength of the B7/DR2 haplotype decreases from Northern to Southern Europe and it is independent of the similar frequency of B7 and DR2 found in Spanish and other reported Northern European populations.<sup>1,3,7</sup> This correlates with the difference in prevalence of MS at different MS latitudes.<sup>3</sup> It supports the idea that B7 and DR2 could act as independent genetic factors of susceptibility. It is likely that a dysequilibrium between HLA-class I and HLA-class II play a role in the pathogenesis of MS. These findings are consistent as several closely linked MS susceptibility factors may exist within the A3/B7/DR2/DQw1

haplotype. The presence of some of these genetic factors could be necessary for the development of MS in different populations.

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