Chapter 5

Genetic difference between relapsing and primary progressive Multiple Sclerosis

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Abstract

HLA-association in Multiple Sclerosis (MS) has repeatedly been confirmed. In this study we used allelic and haplotype association analysis and haplotype sharing analysis to investigate whether differences exist between patients with relapsing-remitting (RR) or secondary progressive (SP) and primary progressive (PP) MS. We studied 194 RR-/SP-MS and 63 PP-MS haplotypes, using 27 microsatellite markers that span 12 Mb on chromosome 6 encompassing the entire HLA region. We found differences both in allele and haplotype frequencies and in length of haplotype sharing between patients with RR-/SP-MS and PP-MS. In the HLA class II region containing HLA-DR and DQ, association and haplotype sharing differences compared with controls were predominant in the RR-/SP-patients. However, in a region telomeric of HLA, we found a difference in association that was almost entirely caused by PP-MS patients. This supports the hypothesis that the different types of MS are part of a spectrum and that disease-modifying genes are located within and close to the HLA region.
5.2 Introduction

Multiple Sclerosis (MS) is a chronic neurologic disease, characterized by inflammation and demyelination in the central nervous system. Most commonly, the disease course is characterized by relapses with worsening of symptoms followed by remissions (relapsing-remitting MS (RR-MS)). On average 10-15 years after disease onset, most RR-MS patients experience progression of symptoms between relapses and they enter the so-called secondary progressive phase (SP-MS). In a smaller number of MS patients the symptoms are progressive from onset without clear-cut relapses. This course of disease is called primary progressive MS (PP-MS). Some patients have an essentially progressive onset, but experience one or more relapses. Their course of disease is called transitional or progressive-relapsing, but often they are considered part of the PP group.

Estimations of the proportion of patients with PP-MS vary from 11% to 37%, probably depending on the criteria used. In the retrospective part of Weinschenker's Canadian study it was 18%, but when patients were seen from their initial presentation it was 7.7%, indicating that part of the patients categorized as having PP-MS may in fact have SP-MS. Whether RR-MS and PP-MS are two ends of a spectrum or two different diseases is still an unsolved question. Apart from their different course in time, RR and PP-MS possibly differ in sex-distribution, age at onset, dissemination across the central nervous system, cognitive profile, radiological characteristics, pathology, immunological characteristics and genetic background as will be discussed.

The association between MS and HLA DR2 (genotype DRB1*1501,DQA1*0102,DQB1*0602) has been found repeatedly. Madigand et al. suggested that the HLA association was different in PP-MS compared with RR-MS. In a French population they found an increase of A1, B8, DR3 in all patients with both primary and secondary progressive MS. Both relapsing and progressive patients showed increased B7, but only the relapsing patients showed increased DR2. HLA-B8 and B35 were associated with PP-MS in males, whereas DR2 was increased among females with RR-MS in a study by Van Lambalgen et al. In a Scottish population, DR2 and DQw1 were more frequent in the relapsing group, whereas DRw6 was overrepresented and DR4 underrepresented in the progressive group (comprising primary and secondary progressive patients). In Swedish RR and SP-MS patients HLA-DRw7, DQw2 has been found to be increased and in PP-MS patients HLA-DR4, DQw8. The same investigators could not confirm this association in a Norwegian cohort, possibly because of small numbers. Other studies found
no differences between RR-MS and PP-MS patients in HLA DR-DQ haplotype distribution\textsuperscript{50} or HLA-DRB\textsubscript{1} phenotype\textsuperscript{51-53}. Some investigators found differences like an increase in DR\textsubscript{4}\textsuperscript{42,54} or DR\textsubscript{3}\textsuperscript{11,49} among PP-MS patients. It has been suggested that these differences may lead to differences in the antigen binding site of the HLA DR\textsubscript{β} chain\textsuperscript{55}.

We reported earlier on the results of an HLA screen in a population of Dutch MS patients\textsuperscript{56} using 22 microsatellite markers that spanned a 12 Mb interval comprising the HLA region. Three methods of analysis were used: allelic association analysis, a Transmission/ Disequilibrium test (TDT)\textsuperscript{57} and the Haplotype Sharing Statistic (HSS)\textsuperscript{58}. We found strong indications for the presence of an MS susceptibility gene in the HLA-region situated most likely in the interval between marker loci G511525 and D6S1666.

In order to investigate whether in our population a genetic difference exists between RR- and SP- versus PP-MS, we compared these two patients’ subgroups with respect to haplotype sharing, allelic and haplotypic association. We added five markers to the telomeric end of the studied region in order to investigate whether or not we could strengthen the allelic association, haplotype sharing and transmission distortion that we had previously found in that region.
5.3 Subjects and methods

Subjects
DNA of 129 MS patients with ancestry within the three northeast provinces of the Netherlands was collected as reported previously\(^5\). All patients were diagnosed with MS according to standard criteria\(^5\). Both patients with relapse-onset MS and patients with primary progressive MS were included. Relatives of patients were asked to participate as well to form trios. DNA of the available relatives was used to determine linkage phase between the loci. Furthermore, each trio yielded a control genotype either by haplotypes that were not transmitted from the parents to the affected child (these haplotypes were either directly available or derived from sibs, \(n=82\)) or by the haplotypes of the spouse (either directly available or derived from children, \(n=37\)). Families consisting of one parent and one child \((n=3)\) yielded only one control haplotype and not a complete genotype. If a relative of the proband was also affected, his or her haplotypes were considered patient haplotypes. This resulted in a total of 261 patient haplotypes and 252 control haplotypes. Missing alleles caused by PCR failures or non-fitting segregation reduced the resulting numbers per locus for analysis. Patients were categorized into RR-MS, SP-MS and PP-MS according to the definitions of Lublin and Reingold\(^4\). In our sample, 96 patients were categorized as having RR- or SP-MS and 31 as having PP-MS (two patients could not be categorized due to lack of information).

The Ethical Committees of the University Hospital Groningen and the Martini Hospital in Groningen approved the study. All participants gave their informed consent; children under 18 were excluded.

Methods
We determined haplotypes on a set of 27 microsatellite markers covering the HLA-region. Twenty-two of these had been used previously\(^5\) and five markers were added towards the telomeric end because we previously found results suggestive for a disease susceptibility gene in this region (Table 1). The data were analyzed by association methods comparing the frequencies of the alleles by means of chi-square tests and comparing haplotype frequencies (estimated by an Expectation Maximization (EM)-algorithm) using a likelihood ratio test. Odds ratios (ORs) and 95% confidence intervals (CI) were determined using the raw data without adjusting for confounding variables. Furthermore, we used the Haplotype Sharing Statistic (HSS)\(^5\) and the CROSS test. The latter test hypothesizes that a patient and a control ha-
Plotype will on average show less haplotype sharing than two patient or two control haplotypes, which is tested by means of a randomization test that permutes the affection status over all haplotypes.

### Table 1: Markers and primer sequences

<table>
<thead>
<tr>
<th>Locus</th>
<th>Marker</th>
<th>Forward primer</th>
<th>Reverse primer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>D6S1560</td>
<td>CTCCAGTCCCCCCTGC</td>
<td>CCCAAGGCCACATAGC</td>
</tr>
<tr>
<td>2</td>
<td>RING3CA</td>
<td>TGCTTAGGGAGACTACCG</td>
<td>GATGGGAAGTTTCCAGAGT</td>
</tr>
<tr>
<td>3</td>
<td>D6S2445</td>
<td>AATATGATGGAAGAAGTAACCG</td>
<td>GGATTACAGGTTAAAGCACAG</td>
</tr>
<tr>
<td>4</td>
<td>TAP1</td>
<td>GCTTTGATCTTCCTCCCTCT</td>
<td>GGAAATATTTTGTCCTCAGG</td>
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<tr>
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<td>D6S2444</td>
<td>GAGCCAAGAACCCACACCT</td>
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<tr>
<td>6</td>
<td>G511525</td>
<td>GGTTAAGCTCTGAGTCCTGCC</td>
<td>GACAGCCTCTCTAACTG</td>
</tr>
<tr>
<td>7</td>
<td>D6S1666</td>
<td>CTGAGTTGGGAGCAATTTG</td>
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</tr>
<tr>
<td>8</td>
<td>D6S273</td>
<td>GCCAATCTTCTGACTTCAATCA</td>
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<tr>
<td>9</td>
<td>TNFa</td>
<td>GCCCTCTAGATTTCACCCAGGACA</td>
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<td>D6S265</td>
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<td>TTTNTAGTAGAAGACAGGAGGTTT</td>
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<td>D6S306</td>
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<td>TGAGATTTCATGAGCC</td>
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<tr>
<td>14</td>
<td>D6S464</td>
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<td>D6S558</td>
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<td>D6S928</td>
<td>GATGCGACCTTTTAAAATCC</td>
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<td>20</td>
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<td>TGCTCATGATCTCTGACTGCT</td>
</tr>
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<td>D6S1691</td>
<td>TTTAGACATGCTGCGAGTC</td>
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<tr>
<td>22</td>
<td>MS03</td>
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<td>MS02</td>
<td>TTGGTTGATTAAGGAGGATGCTC</td>
<td>AAATGTTTAAATTTGCAAGG</td>
</tr>
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<td>MS01</td>
<td>AATGCTTATCTGGCAAGGAAAAA</td>
<td>AGGACAAATATCTCAACATC</td>
</tr>
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<td>25</td>
<td>D6S461</td>
<td>GACTCTGAGGTTTACGGGAGT</td>
<td>GGGTCTCTGCTCAAAGGAA</td>
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<tr>
<td>26</td>
<td>MS05</td>
<td>AGGAACCTGCTCTGTGAGAAGAA</td>
<td>CTGTTTCAGAAGGCAAGAAG</td>
</tr>
<tr>
<td>27</td>
<td>MS06</td>
<td>AGGCAGCATTGATTTGATTAG</td>
<td>AGCATGTTCAGCAGATTGAG</td>
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Genetic difference between relapsing and primary progressive MS
5.4 Results

Association analysis

Figure 1 shows the results of single locus association analysis. For RR-/SP-MS patients compared to controls, marker D6S1666 shows the strongest association (p=3.0×10⁻⁵). In the sample of all MS patients maximum single locus association was observed at marker G511525 (p=2.9×10⁻⁵). For PP-MS patients compared to controls, association did not reach significance. Direct comparison of allele frequencies between RR-/SP-MS patients and PP-MS patients did not yield significant results either (not shown).

Figure 1. Results of single locus association analysis in RR- and SP-MS patients (n=194, dotted line), PP-MS patients (n=63, striped line) and in all MS patients (n=261, solid line). The distributions of alleles in patients and in controls are compared using a χ² test. The results are presented as the value of the significance on a logarithmic scale.
In Figure 2, the results of three-locus haplotype association analysis are shown. For RR- and SP-MS patients, the strongest association is found for haplotypes containing markers G511525 and D6S1666. For PP-MS patients the most significant difference ($p=6.9 \times 10^{-5}$) is found at locus MS01. For RR-/SP-MS patients, the frequency differences in this region do not reach significance ($p=0.02$) despite the fact that the sample of RR-/SP-MS patients is twice as large as the sample of PP-MS patients. Direct comparison of the haplotype frequencies between RR-/SP-MS patients and PP-MS patients did not show significant results (not shown).

Figure 2: Three-locus haplotype association analysis in RR-/SP-MS patients ($n=192$, dotted line), PP-MS patients ($n=62$, striped line) and all patients ($n=258$, solid line). The distributions of haplotype frequencies estimated by an EM-algorithm are compared between subgroups of patients and controls are compared using a likelihood-ratio test.
Tables 2 and 3 show the frequencies and ORs of the most strongly associated alleles, allele carriers (Table 2), haplotypes and haplotype carriers (Table 3) in the HLA-DR/DQ region and the more telomeric region. In the HLA-DR/DQ region at markers G511525 and D6S1666 significant associations are observed for the RR-/SP-MS patients compared with controls. For PP-MS patients, no significant differences are observed. However, the frequencies are only slightly lower than those in RR-/SP-MS patients, suggesting that the absence of significance may be caused by the smaller sample size.

Individuals carrying either one of the alleles 217 or 223 at G511525 or one of the alleles 132 or 136 at D6S1666 are at 1.6 to 3.6 times increased risk for RR-/SP-MS. This risk is particularly increased in individuals carrying two risk haplotypes (homozygotes for haplotype 217-136: OR=18.1, 95% CI 1.0-324; homozygotes for haplotype 223-132: OR=18.4, 95% CI 2.3-150). For compound heterozygotes (carrying haplotypes 223-132 and 217-136) the risk is increased as well (OR 14.8, 95% CI 1.9-116 for RR-/SP-MS and OR 6.7, 95% CI 0.6-76.4 for PP-MS) (not shown). We found this effect previously for the entire patient sample60. For the PP-MS patients, the risk seems to be restricted to homozygotes for the haplotype 223-132: OR=13.4 (95% CI 1.2-147), since no homozygotes for the haplotype 217-136 were observed.

At the more telomeric markers MS02, MS01, D6S461, MS05 and MS06 associated alleles and haplotypes consisting of these alleles as well as carriers of these alleles and haplotypes are more frequent among PP-MS patients than among controls and among RR-/SP-MS patients (Tables 2 and 3). Individuals who have one or more of these alleles have a significantly increased risk for PP-MS compared with controls (Table 2). When they carry haplotypes of these alleles, however, the risk increases, even up to 15 times. Haplotypes of the associated alleles at all five markers were almost exclusively found among PP-MS patients (5.7%; RR-/SP-MS 0.7%; controls 0.0%). In particular, the carrier frequency is much higher among PP-MS patients (13.6%) than among RR-/SP-MS patients (1.3%) and controls (0.0%). In contrast, the same alleles and haplotypes caused only an about two times increased risk for RR-/SP-MS.
Table 2: Allele and allele carrier frequencies at the strongest associated loci

<table>
<thead>
<tr>
<th>Locus</th>
<th>allele</th>
<th>freq PP (n=63 alleles; 31 carriers)</th>
<th>freq OR</th>
<th>freq carriers PP (n=194 alleles; 96 carriers)</th>
<th>freq OR</th>
<th>freq carriers controls (n=255 alleles; 105 carriers)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>alleles</td>
<td>carriers</td>
<td>alleles</td>
<td>carriers</td>
<td>alleles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>freq</td>
<td>OR</td>
<td>freq</td>
<td>OR</td>
<td>freq</td>
</tr>
<tr>
<td>G511525</td>
<td>217</td>
<td>16.9%</td>
<td>1.8</td>
<td>34.5%</td>
<td>2.3</td>
<td>22.0%</td>
</tr>
<tr>
<td></td>
<td>223</td>
<td>44.1%</td>
<td>1.5</td>
<td>69.0%</td>
<td>1.5</td>
<td>45.7%</td>
</tr>
<tr>
<td></td>
<td>132</td>
<td>30.5%</td>
<td>1.7</td>
<td>51.7%</td>
<td>2.0</td>
<td>37.6%</td>
</tr>
<tr>
<td></td>
<td>136</td>
<td>15.3%</td>
<td>1.9</td>
<td>31.0%</td>
<td>2.3</td>
<td>20.4%</td>
</tr>
<tr>
<td>D6S1666</td>
<td>132</td>
<td>31.7%</td>
<td>2.0</td>
<td>53.3%</td>
<td>2.3*</td>
<td>20.7%</td>
</tr>
<tr>
<td></td>
<td>136</td>
<td>54.1%</td>
<td>2.5*</td>
<td>83.3%</td>
<td>3.5*</td>
<td>37.8%</td>
</tr>
<tr>
<td>MS02</td>
<td>305</td>
<td>32.8%</td>
<td>1.4</td>
<td>56.7%</td>
<td>2.1</td>
<td>27.9%</td>
</tr>
<tr>
<td></td>
<td>137</td>
<td>17.6%</td>
<td>2.3</td>
<td>32.0%</td>
<td>2.9*</td>
<td>13.3%</td>
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</table>

*significant: 95% confidence interval did not contain 1
### Table 3: Haplotype and haplotype carrier frequencies at the strongest associated loci

<table>
<thead>
<tr>
<th>Loci</th>
<th>PP (n=62 haplotypes;31 carriers)</th>
<th>RP or SP (n=192 haplotype; 96 carriers)</th>
<th>controls (n=210 haplotypes;105 carriers)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>haplotype</td>
<td>haplotypes carriers</td>
<td>haplotypes carriers</td>
</tr>
<tr>
<td></td>
<td>freq  OR</td>
<td>freq OR</td>
<td>freq OR</td>
</tr>
<tr>
<td>G511525-D6S1666</td>
<td>217-136</td>
<td>15.5% 1.9</td>
<td>19.7% 2.5*</td>
</tr>
<tr>
<td></td>
<td>215-136</td>
<td>29.3% 2.6*</td>
<td>34.5% 3.2*</td>
</tr>
<tr>
<td>MS01-MS01-D6S461</td>
<td>305-164-241</td>
<td>13.9% 15.0*</td>
<td>3.9% 1.5</td>
</tr>
<tr>
<td>MS01-D6S461-MS05</td>
<td>301-241-137</td>
<td>21.6% 3.1*</td>
<td>9.8% 1.5</td>
</tr>
<tr>
<td>D6S461-MS05-MS06</td>
<td>241-137-262</td>
<td>10.0% 10.8</td>
<td>3.0% 3.1</td>
</tr>
<tr>
<td>MS02-MS01-MS02-MS01-MS05</td>
<td>305-151-241-137</td>
<td>5.5% n.a.</td>
<td>0.7% n.a.</td>
</tr>
</tbody>
</table>

*significant: 95% confidence interval did not contain 1
Haplotype sharing analyses

The differences in haplotype sharing between RR-/SP-MS and PP-MS patients as tested by the HSS and the CROSS-test are shown in Figure 3. The maximum difference observed by the HSS between the two patient subgroups is found at D6S1666 (p=1.8 $10^{-3}$). The CROSS-test shows the largest difference at the same locus. The HSS and the CROSS-test are statistically independent tests. In the region where the three-locus association analysis showed a significant result, HSS and the CROSS-test did not show an increase in haplotype sharing. Marker MS03 has been eliminated after showing false positive results, probably related to the large number of phase-unknown alleles.

Figure 3: Difference in length of haplotype sharing as tested by the HSS (solid line) and CROSS-test (dotted line) between RR- and SP-MS patients (n=194) and PP-MS patients (n=63).
5.5 Discussion

Whether RR-/SP-MS and PP-MS are two ends of a spectrum or two different diseases is still an unsolved question. The distinction is made based on the course of disease, but there appear to be clinical and laboratory differences as well. Our study investigated whether there are also genetic differences in and close to the HLA region.

In a former study we examined a population of MS patients from the northern part of the Netherlands. We found increased haplotype sharing among patients compared with controls in the HLA class II region with a maximum in the interval between markers G511525 and D6S1666, an interval of 51 kb in which DQB1 is situated. The involvement of this interval in susceptibility to MS was supported by association analysis and TDT.

In order to investigate whether in our population a difference exists between RR-/SP-MS and PP-MS patients in this region, we analyzed their data separately by association analysis and haplotype sharing analysis using HSS and the Cross-test. Furthermore, five more microsatellite marker loci towards the telomeric side of the region were investigated. In our previous study, a slight increase in association and haplotype sharing in that region raised the need for further investigation.

For the HLA DR-DQ-region, in which we found in our previous study association in all patients versus controls, differences in allele and haplotype frequencies were predominantly observed in RR-/SP-MS patients. For PP-MS patients these results were not significant, possibly because of small numbers. Remarkably, however, the association in the sample of all patients is hardly increased compared with the sample of all RR-/SP-MS patients, despite the fact that the number of haplotypes is increased by almost 50%. This implies that PP-MS patients likely do not contribute to the association found at marker loci G511525 and D6S1666 in the sample of all patients. This is in contrast with the results of Bohringer et al., who presented evidence that HLA-DRB1 was more important in predisposing to MS in their sample of PP-MS patients than in the sample of all patients. It should be noted that we did not observe significant differences in allele or haplotype frequencies at markers G511525 and D6S1666 between RR-/SP-MS and PP-MS patients.

Remarkable, however, is that homozygotes for the previously identified risk haplotype 217-136 were not found among PP-MS patients, while we know that in particular homozygotes for this haplotype are at highly increased risk. For the other previously identified risk haplotype 223-132 we found rather similar increased risks among homozygotes for RR-/SP-MS (OR = 18.1) and for PP-MS (OR = 13.4) (not shown).
The difference in haplotype sharing between PP- and RR-/SP-MS patients is maximal at D6S1666. Haplotype inspection showed that RR- and SP-MS patients more often share two haplotypes in this region than PP-MS patients do. This implies that for the region of markers G511525 and D6S1666, where HLA-DQ and DR are situated, RR-/SP-MS patients are genetically more similar than PP patients are. This suggests that the HLA-DR-DQ-region is more important in susceptibility to RR-/SP-MS than to PP-MS, which, again is in contrast with the results of Bohringer et al. Towards the telomeric end of the studied region, however, haplotype sharing is increased in PP- compared with RR-/SP-MS patients. In the interval between markers D6S1691 and MS06, only one hypothetical gene is situated according to current knowledge (NCBI, build 35 version 1). A possible explanation is that the region contains regulatory sequences, influencing expression and function of other regions. Marrosu et al. found association telomeric from HLA-DR at marker D6S183. This marker is used in our screen too, but shows no association or increased haplotype sharing.

The risk haplotypes that we observed in RR-/SP-MS patients were overrepresented too in PP-MS patients compared with controls, and the other way around. This confirms also the similarities between both types of MS, supporting the hypothesis that the different types of MS are likely to be part of a spectrum. Genetically this means that some underlying susceptibility genes are likely to be identical in patients with different types of MS, but modifying loci may be different. In addition, there may be epistatic effects. The contribution of HLA alleles or genotype to susceptibility may be different in patients with RR-/SP- and PP-MS, which would be in accordance with our results.

Other diseases that share important characteristics with MS, such as neuromyelitis optica (Devic), may also share susceptibility genes. This is supported on a pathological level by the patterns described by Lucchinetti et al. and on an immunological level by Eikelenboom et al. who found that the opticospinal type of MS shares characteristics with neuromyelitis optica rather than with prototypic MS.

Summarizing, we found differences in both haplotype sharing and frequencies between patients with RR-/SP-MS and PP-MS. In RR-/SP-MS patients, association and haplotype sharing tests show more significant results in the region containing HLA-DR and DQ, whereas in PP-MS patients three-locus association is stronger in a region telomeric of HLA. Both RR-/SP-MS and PP-MS patients, however, have predisposing haplotypes in common.
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55. Greer JM, Pender MP. The presence of glutamic acid at positions 71 or 74 in pocket 4 of the HLA-DRbeta1 chain is associated with the clinical course of multiple sclerosis. J Neurol Neurosurg Psychiatry 2005; 76(5):656-662.