HLA DR15 (DR2) and DQB1*0602 typing studies in 188 narcoleptic patients with cataplexy

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HLA DR15 (DR2) and DQB1*0602 typing studies in 188 narcoleptic patients with cataplexy

A.E. Rogers, PhD, RN; J. Meehan, BS; C. Guilleminault, MD; F.C. Grumet, MD; and E. Mignot, MD

Article abstract—Narcolepsy is considered a homogeneous clinical entity when excessive daytime sleepiness and cataplexy are present. Cataplexy is a polymorphic symptom that can be very mild and is thus subjectively defined. The Multiple Sleep Latency Test (MSLT) is widely used as a diagnostic test for narcolepsy. A short mean sleep latency and multiple sleep onset REM periods (SOREMPs) are typically observed in narcoleptic patients. The discovery of a tight association of narcolepsy with HLA class II antigens offers a unique opportunity to explore the respective value of the MSLT or of the presence of clear-cut cataplexy in defining an etiologically homogeneous group of narcoleptic patients. In this study, we carried out HLA typing for DR15 (DR2) and DQB1*0602 in 188 narcoleptic patients with cataplexy in three ethnic groups (24 Asians, 61 Blacks, and 103 Caucasians). These results confirm the importance of DQB1*0602 typing rather than DR15 (DR2) typing in Black narcoleptic patients and demonstrate that the presence of clear-cut cataplexy is a better predictor for DQB1*0602 positivity than the presence of abnormal MSLT results.

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Narcolepsy is a disorder characterized by excessive daytime sleepiness, sudden losses of voluntary muscle tone in response to strong emotion (cataplexy), and other pathologic manifestations of disassociated REM sleep. Although the familial aspects of this disorder have long been recognized, a genetic marker for narcolepsy was only identified in the early 1980s when Honda and his colleagues reported a tight...
association (100%) between human leukocyte antigen (HLA) DR2 and narcolepsy among Japanese patients. These findings were quickly confirmed in Caucasian populations in Australia, Europe, and North America. In these populations, DR2 frequency ranges from 20 to 30% but almost all narcoleptic patients tested were DR2 positive. Some of these earliest reports, which focused on DR2, also mentioned that the frequency of second antigen, HLA-DQ1, was significantly higher in narcoleptic patients than in normal Japanese and Caucasian control subjects. The high frequency of DQ1 in control subjects, 60 to 80%, however, greatly diminished the specificity of DQ1 as a marker for narcolepsy.

The discovery of several cases of DR2-negative narcolepsy during the mid-1980s triggered a flurry of questions. For example, did these patients really have narcolepsy or could these DR2-negative cases be attributed to differences in the criteria used to diagnose narcolepsy? Or, could there be ethnic differences in linkage disequilibrium between DR2 and a putative narcolepsy-susceptibility gene? In one of these early reports, Neely et al. only included Black narcoleptic patients and 67% were DR2 positive. Although Nezu et al. described one Japanese non-DR2 case where the diagnosis of narcolepsy was quite questionable, other DR2-negative patients, mostly Caucasians, had a substantial history that was supportive of the diagnosis of narcolepsy-catalepsy. In 1987, Matsuki et al. reported that DR2 frequencies varied between 92 and 100% depending on the criteria used for diagnosis of narcolepsy (e.g., excessive daily sleepiness (EDS) present for more than 6 months, EDS with cataplexy, EDS with cataplexy plus two sleep-onset REM periods). The conclusion of the Japanese group, based on a large sample of Japanese patients (n = 227), was that presence of cataplexy was the best determinant for DR2 positivity, and that earlier reports on non-DR2 narcoleptic patients were likely the result of differences in diagnostic approaches. This position can be best exemplified as in Honda and Matsuki, “Most of the reports on DR2-negative narcolepsy lack precise clinical definition of cataplexy, and therefore might have included nonnarcoleptic patients owing to a difference in clinical judgment.”

Since these earlier reports, HLA class II typing techniques have become increasingly sophisticated. This first led to the subtyping of DR2 into DR15 and DR16 subtypes, with all narcoleptic patients found to be DR15-positive. As DR15 is the most common subtype of DR2 in most ethnic groups, this serologic splitting of DR2 did not improve the value of HLA typing for diagnostic purposes. More recently, subtyping was made possible at the genomic level, thus leading to the identification of more than 15 subtypes of DR2 and 30 subtypes of DQ1. Among those subtypes, DRB1*1501 (DR2) together with DQB1*0602 (DQ1) were identified in all Caucasian and Japanese narcoleptic patients with DR2, DQ1. In black Americans, genomic typing in 28 patients with cataplexy and abnormal Multiple Sleep Latency Test (MSLT) revealed the presence of DRB1*1501 in only three subjects, with many patients carrying a new variant of DR15 called DRB1*1503 (19 subjects) and all but one subject being positive for DQB1*0602. DQB1*0602 is thus now considered as the best HLA marker across all ethnic groups and this result likely explains the substantially lower DR2 frequency previously reported in black Americans.

Most of the known HLA DR- or DQ-associated disorders (e.g., multiple sclerosis, insulin-dependent diabetes mellitus) are autoimmune in nature and several investigators have suggested a similar pathologic mechanism for narcolepsy. To date, however, there is no evidence for a direct involvement of the immune system in this sleep disorder. Human narcolepsy is not associated with any detectable circulating autoantibodies, CSF oligoclonal bands, increased sedimentation rate, C-reactive protein at the onset of the disease, or changes in CD4/CD8 lymphocytes subsets usually found in other autoimmune disorders. Pathologic studies have also shown that the CNS of human patients with narcolepsy does not contain sites of lymphocytic infiltrations. Most HLA DR15 or DQB1*0602 may thus be only linkage markers and not the actual susceptibility genes for narcolepsy. Recent studies do not, however, favor the linkage marker hypothesis. First, the onset of narcolepsy is associated with increased microglial class II expression in a canine model of the disorder. Second, detailed HLA haplotyping studies in human narcoleptic patients indicate that susceptibility to narcolepsy narrowly maps to the coding region of the DQB1*0602 and associated DQA1*0102 genes and not in the region flanking these alleles. These results suggest that the HLA DQ molecules themselves are involved in disease predisposition.

Whether or not narcolepsy is autoimmune, DQB1*0602 is neither necessary nor sufficient for the development of the disorder. This DQB1 allele is present in 12 to 38% of the general population in various ethnic groups, with only 0.02 to 0.16% affected with narcolepsy-catalepsy. DQB1*0602 sequence is identical in control and narcoleptic subjects. A few patients with typical narcolepsy-catalepsy are negative for DQB1*0602 and family members frequently share the same HLA haplotype with the proband and never develop narcolepsy. Even monozygotic twins can be discordant for the development of narcolepsy; only 25 to 31% of the monozygotic twins reported to date are concordant for narcolepsy. Overall, the data suggest that narcolepsy-catalepsy, like many other HLA-associated disorders, is a complex disorder that involves both genetic predisposition and environmental triggering factors.
was based on a clinical history and often included
tance syndrome (UARS), and idiopathic hypersom-
the diagnosis of narcolepsy. In the past, diagnosis
was critical than ever to standardize the criteria used for
current American Sleep Disorders Association
sleepy patients who had apnea, upper airway resis-
ture to rule out other sleep disorders and the MSLT
be found to be non-DR2 positive at another sleep center (n = 41) or due to
subjects and parents with essential hypersomnia (n = 4); (6) posttraumatic nar-
colepsy cases (n = 6).

In this study, only available “random” narcoleptic subjects
with a complete clinical file and an established diag-
nosis of narcolepsy-cataplexy were included in the analy-
sis. Subjects recruited because of DR2 negativity,
potraceatonic narcolepsy, or as part of recruitment effort
aiming at gathering multiplex family study were thus not
included in the analysis. A clinical file was established for
every subject. The file contained photocopies of clinical
notes obtained from the medical file(s) of the patient, notes
made by direct interview of the patient by the Center For
Narcolepsy staff (mostly by phone), and results of poly-
ographic studies. (e.g., MSLT and nocturnal polysomnogra-
phy), if any. The Stanford Center for Narcolepsy Sleep
Inventory, a 146-item questionnaire requesting details and
specific examples for all narcolepsy symptoms experienced,
with special emphasis on cataplexy, was also completed
and included in the file (108 of 188 patients). Final diagno-
sis/categorization was made by one of us (C.G.) after a
review of the clinical data file and without any knowledge
of the HLA testing, name of the patient, or the patient’s
geographic origin. Table 1 shows how subjects were catego-
rized based on their clinical history and polysomnographic
studies.

In this study, we HLA-typed narcoleptic patients
with cataplexy in three ethnic groups. Patients were
stratified by gender, ethnicity, presence of clear-cut
cataplexy (brief episodes of weakness in the knees,
jaw, face, or neck triggered by laughter, amusement,
happiness, game playing, or anger) versus atypical
or extremely mild cataplexy (doubtful cataplexy) and
abnormal versus atypical MSLT. Our aim was to
study the respective value of abnormal MSLT results
and of clear-cut cataplexy for defining a homoge-
neous group of patients displaying the highest possi-
ble HLA association.

Methods. Subjects. A total of 188 subjects was ob-
tained from a database of 777 narcoleptic subjects and
relatives whose HLA typing has been done at Stanford
University. Subjects in the database were recruited using
six possible protocols: (1) “random” narcoleptic patients
from various ethnic groups (n = 291); these subjects were
referred to the center because they had narcolepsy-
catataplexy or were diagnosed at the Stanford Sleep Disor-
der Clinic; (2) parents or relatives of random narcoleptic
patients for haplotype relative risk studies or HLA haplo-
type segregation analysis (n = 90 relatives); (3) relatives
and narcoleptic patients of multiplex families (n = 342
subjects in 48 families) or narcoleptic subjects rec-
ruited because they were found to be non-DR2 positive at
another sleep center (n = 41); (4) narcoleptic subjects re-
cruited by direct interview of the patient by the Center For
Narcolepsy staff (mostly by phone), and results of poly-
graphic studies (e.g., MSLT and nocturnal polysomnogra-
phy), if any. The Stanford Center for Narcolepsy Sleep
Inventory, a 146-item questionnaire requesting details and
specific examples for all narcolepsy symptoms experienced,
with special emphasis on cataplexy, was also completed
and included in the file (108 of 188 patients). Final diagno-
sis/categorization was made by one of us (C.G.) after a
review of the clinical data file and without any knowledge
of the HLA testing, name of the patient, or the patient’s
geographic origin. Table 1 shows how subjects were catego-
rized based on their clinical history and polysomnographic
studies.

Ninety-four of the 291 “random” subjects were excluded
either because the patient’s diagnosis of narcolepsy-
catataplexy could not be confirmed or because the clinical file
was not complete at the time of the submission of this
manuscript. Subjects reporting a mixed ethnic back-
ground, e.g., Asian-Caucasian, black-Caucasian were also
excluded due to their small number (n = 9). Our final

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (n = 132)</td>
<td>Clear-cut cataplexy and EDS, MSLT with mean sleep latency ≤ 8 min and only one SOREM observed</td>
</tr>
<tr>
<td>B (n = 6)</td>
<td>Clear-cut cataplexy and EDS, MSLT with mean sleep latency of ≤ 8 min and only one SOREM observed</td>
</tr>
<tr>
<td>C (n = 10)</td>
<td>Clear-cut cataplexy and EDS, polygraphic test other than MSLT (or MSLT without preceding nocturnal polysomnogram) showing EDS and SOREMPs</td>
</tr>
<tr>
<td>D (n = 6)</td>
<td>Clear-cut cataplexy and EDS, MSLT with mean sleep latency ≤ 8 min without any SOREMPs or mean sleep latency &gt; 8 min with two or more SOREMPs</td>
</tr>
<tr>
<td>E (n = 3)</td>
<td>Clear-cut cataplexy, MSLT with mean sleep latency &gt; 8 min and one or no SOREMPs; patients with clear-cut cataplexy but no complaints of EDS</td>
</tr>
<tr>
<td>F (n = 17)</td>
<td>Clear-cut cataplexy and EDS, but no polygraphic tests performed</td>
</tr>
<tr>
<td>G (n = 14)</td>
<td>Atypical cataplexy with positive polygraphic tests (G1) Doubtful cataplexy with positive polygraphic tests (G2) Atypical or doubtful cataplexy with inconclusive polygraphic tests (G3)</td>
</tr>
</tbody>
</table>

EDS = excessive daily sleepiness; MSLT = Multiple Sleep Latency Test; SOREM = sleep-onset REM period.
sample included 107 females and 80 males (1 unknown) recruited from Asia (n = 14), Europe (n = 3), and North America (n = 171). Twenty-four subjects (12.8%) were Asian, 61 (32.4%) were black, and 103 (54.8%) were Caucasian. Four (2.1%) of the 188 subjects recruited as "random" were later found to have another family member with documented narcolepsy-cataplexy.

**Table 2 Chi-square analysis of DRB1*15 and DQB1*0602 by patient characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients positive for DRB1*15</th>
<th>Percent positive for DRB1*15</th>
<th>df</th>
<th>Chi-square statistic</th>
<th>Patients positive for DQB1*0602</th>
<th>Percent positive for DQB1*0602</th>
<th>df</th>
<th>Chi-square statistic</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>84/105</td>
<td>80.0</td>
<td>1</td>
<td>0.68</td>
<td>91/104</td>
<td>87.5</td>
<td>1</td>
<td>0.00</td>
<td>1.000</td>
</tr>
<tr>
<td>Male</td>
<td>68/82</td>
<td>82.9</td>
<td></td>
<td></td>
<td>70/80</td>
<td>87.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>23/24</td>
<td>95.8</td>
<td>2</td>
<td>11.4</td>
<td>21/23</td>
<td>91.3</td>
<td>2</td>
<td>0.53</td>
<td>0.765</td>
</tr>
<tr>
<td>Black</td>
<td>41/61</td>
<td>67.2</td>
<td></td>
<td></td>
<td>54/61</td>
<td>88.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>87/103</td>
<td>84.5</td>
<td></td>
<td></td>
<td>87/102</td>
<td>86.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cataplexy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear-cut</td>
<td>144/174</td>
<td>82.8</td>
<td>1</td>
<td>8.80</td>
<td>154/171</td>
<td>90.1</td>
<td>1</td>
<td>12.88</td>
<td>0.001</td>
</tr>
<tr>
<td>Atypical/doubtful</td>
<td>7/14</td>
<td>50.0</td>
<td></td>
<td></td>
<td>8/14</td>
<td>57.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSLT findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>113/144</td>
<td>78.5</td>
<td>2</td>
<td>2.38</td>
<td>125/143</td>
<td>87.4</td>
<td>2</td>
<td>0.97</td>
<td>0.617</td>
</tr>
<tr>
<td>Ambiguous</td>
<td>22/27</td>
<td>81.5</td>
<td></td>
<td></td>
<td>21/25</td>
<td>84.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never performed</td>
<td>16/17</td>
<td>94.1</td>
<td></td>
<td></td>
<td>16/17</td>
<td>94.1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MSLT = Multiple Sleep Latency Test.

Statistical analysis. Four variables were used to describe the population: gender, ethnicity (Asian, black, Caucasian), history of cataplexy (clear-cut, atypical/doubtful), and MSLT findings (abnormal, ambiguous, not performed). These variables were examined singly and in combination both for descriptive purposes and to evaluate their interrelationships. First, each variable was examined for its relationship with being positive for DRB1*15, and only those variables with a p value of less than 0.10 were included in the multiple logistic regression modeling. Tests of association between each categorical predictor variable and DRB1*15 positivity were based on chi-square tests. Variables deemed to be significant, statistically and/or medically, were included in final model. The association between being positive for DQB1*0602 and the predictor variables gender, ethnicity, history of cataplexy, and MSLT results was tested in the same way.

Results. DRB1*15 as a marker for narcolepsy. Of the total sample, 19.7% (n = 37) of the subjects were negative for DR15 (DR2), and 80.3% (n = 151) of the subjects were positive. Univariate testing revealed that being positive for DR15 was not associated with gender or MSLT results (table 2). Therefore, only two covariates (history of cataplexy and ethnicity) were included in the final models tested (table 3). Two indicator variables were used to analyze the effect of ethnicity; Caucasian, which refers to a comparison of Caucasian and black subjects, and Asian, which compares Asian and black subjects. Additional statistical testing revealed that blacks were significantly dif-
Table 3 Summary of model results for DRB1*15 and DQB1*0602

<table>
<thead>
<tr>
<th>Model</th>
<th>Variable</th>
<th>Coefficient</th>
<th>Standard error</th>
<th>Wald chi-square</th>
<th>p value</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRB1*15 #1</td>
<td>Constant</td>
<td>$8.47 \times 10^{-16}$</td>
<td>0.5345</td>
<td>0.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cataplex</td>
<td>1.5686</td>
<td>0.5710</td>
<td>7.55</td>
<td>0.006</td>
<td>4.80</td>
</tr>
<tr>
<td>DRB1*15 #2</td>
<td>Constant</td>
<td>$-0.4675$</td>
<td>0.5833</td>
<td>0.64</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cataplex</td>
<td>1.3596</td>
<td>0.5881</td>
<td>5.34</td>
<td>0.02</td>
<td>3.90</td>
</tr>
<tr>
<td></td>
<td>Caucasian*</td>
<td>0.9350</td>
<td>0.3930</td>
<td>5.66</td>
<td>0.02</td>
<td>2.55</td>
</tr>
<tr>
<td></td>
<td>Asian†</td>
<td>2.2434</td>
<td>1.0618</td>
<td>4.46</td>
<td>0.03</td>
<td>9.45</td>
</tr>
<tr>
<td>DQB1*0602</td>
<td>Constant</td>
<td>0.2877</td>
<td>0.5401</td>
<td>0.28</td>
<td>0.59</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cataplex</td>
<td>1.9161</td>
<td>0.5975</td>
<td>10.28</td>
<td>0.001</td>
<td>6.79</td>
</tr>
</tbody>
</table>

* Caucasians compared with blacks.
† Asians compared with blacks.

Different from Asians ($\chi^2 = 7.584, p = 0.005$) and Caucasians ($\chi^2 = 6.656, p = 0.009$), but there was no significant difference in Asians and Caucasians ($\chi^2 = 2.169, p = 0.140$). Although the first model tested (DRB1*15 #1, see table 3), using cataplexy alone, was significant ($p = 0.007$, and $p = 0.003$), it was neither sensitive nor specific. When cataplexy and ethnicity were combined in the second model (DRB1*15 #2, see table 3), both sensitivity and specificity were improved. Subjects with atypical/doubtful cataplexy were 3.9 times more likely than subjects with clear-cut cataplexy to be DR15-negative in this model. Black patients are 2.5 and 9.4 times more likely than Asian or Caucasian patients to be DR15-negative in this model.

DQB1*0602 as a marker for narcolepsy. Most subjects were positive for DQB1*0602 ($n = 162, 87.6\%$), only 23 subjects were negative (15 of whom had 146-item narcolepsy sleep inventory completed on file). Although it appeared that more Asians (91.3\%) were positive than blacks (88.5\%) and Caucasians (86.1\%), these differences were not statistically significant ($\chi^2 = 0.536, p = 0.765$). Since chi-square testing revealed that ethnicity, gender, and MSLT results were not associated with being positive for DQB1*0602 (see table 2), only a history of cataplexy was included in the logistic regression model (see table 3). Although this model was highly significant ($p = 0.0026$, and $p = 0.0003$), it is not particularly sensitive or specific. The addition of other covariates, e.g., ethnicity or MSLT results, did not improve the sensitivity or specificity of the model. Subjects with doubtful/atypical cataplexy were 6.8 times more likely than subjects with clear-cut cataplexy to be DQB1*0602 negative in this model.

Discussion. Our finding that ethnicity influences the frequency of DRB1*15 among narcoleptic patients confirms previous studies\textsuperscript{13,22-24} that used much smaller sample sizes. Only 41 of our 61 (67.2\%) black narcoleptic subjects were positive for this marker, compared with 84.5\% ($n = 87$) of our Caucasian subjects and 95.8\% ($n = 23$) of our Asian subjects (see table 2). In contrast, DQB1*0602 positivity was roughly equivalent in all ethnic groups, with values ranging from 86.1 to 91.3\% (table 2). Typing for DQB1*0602, rather than for DRB1*15, thus increased diagnostic specificity in blacks but has little or no influence in Asians or Caucasians. In this last ethnic group, however, a recent study\textsuperscript{34,35} has shown that a small but significant portion (10\%) of non-DR15 patients may carry rare DQB1*0602-positive haplotypes without DR15. Typing for DQB1*0602 should thus ideally be performed in all patients instead of typing for DR2 or DR15.

Although the percentage of blacks and Asians positive for these markers is similar to those reported in earlier studies,\textsuperscript{13,22-24} the percentage of Caucasian subjects positive for either DR15 (DR2) or DQB1*0602 is slightly lower than usually reported (i.e., 91–100\%).\textsuperscript{6,12,22-24} We are aware of only two other studies reporting such a low percentage of Caucasian subjects with cataplexy who are positive for DRB1*15.\textsuperscript{23,46} The method of diagnosis and recruitment used in our study may explain the relatively lower HLA association observed. First, we included all our patients without any prior knowledge of HLA typing results. In many other studies, diagnosis was not performed blind of HLA typing results and we believe this is likely to have a significant influence, especially in the context of the 100\% association initially reported in Japan. Second, we included patients based on the report of “cataplexy” by a referring clinician and not by direct clinical interviews, and some of these patients had questionable or atypical cataplexy (Category G, doubtful cataplexy in table 1) after review of their clinical files at Stanford University.

In favor of this last hypothesis, the presence of “clear-cut” versus “possible” cataplexy was identified as a critical factor in predicting both DR15 and DQB1*0602 positivity. This contrasted with the poor predictive value of the MSLT findings in this group of patients with cataplexy (see table 2). Significantly more subjects with clear-cut cataplexy were positive for DRB1*15 than subjects whose symptoms were considered atypical or possible cataplexy (82.3\% versus 50.0\%, $\chi^2 = 8.80, p = 0.003$). Only 57.1\% of subjects with possible cataplexy were positive for DQB1*0602 compared with 90.1\% of those with clear-cut cataplexy. Cataplexy was a significant covariate in both models. Patients with history of cataplexy were more likely to be positive for DR15 and DQB1*0602 than patients with a possible history of
cataplexy. Clearly clinically defining cataplexy might thus be more important than the MSLT for the diagnosis of narcolepsy.

Even in patients with clear-cut cataplexy, HLA DQB1*0602 is neither sufficient nor necessary for the diagnosis of narcolepsy. Approximately 10% of patients with definite cataplexy (with or without MSLT findings) were DQB1*0602 negative in this large series. Genetic epidemiologic data also suggest that HLA-related genetic factors constitute only a small fraction of genetic predisposition to narcolepsy. Twelve to thirty-eight percent of the normal general population in various ethnic groups carry the HLA DQB1*0602 allele and only 0.02 to 0.06% of the population has narcolepsy-cataplexy. The gene has been sequenced in many control and narcoleptic subjects and found to be normal in all cases. Even if DQB1*0602 is the actual HLA narcolepsy susceptibility gene, it is thus a very low penetrance factor since more than 99.9% of individuals with the gene do not have narcolepsy. Family and twin studies also suggest the importance of environmental and non HLA genetic factors.

In spite of these limitations, HLA typing can be a useful diagnostic tool, especially in cases where cataplexy is doubtful, atypical, or not present. Samples described in the literature contain varying portions of “narcoleptic” subjects without cataplexy (8–42%), suggesting that this less-studied clinical subgroup might actually represent a substantial number of patients. The absence of DQB1*0602 in subjects without or with atypical cataplexy should help the clinician to explore more thoroughly other possible causes for excessive daytime sleepiness (e.g., abnormal breathing or movements during sleep) and this may have therapeutic consequences. MSLT testing might also be more useful in this group of patients with “possible narcolepsy” than in patients with cataplexy. In our study, of the 157 patients with clear-cut cataplexy who had undergone an MSLT, only 132 (84%) had typical MSLT results (sleep latency ≤8 min and ≥2 SOREMPs). Thus, many genuinely narcoleptic patients would be excluded if positive MSLT findings were required for the diagnosis. In contrast, MSLT can be very useful to demonstrate sleepiness in patients with ill-defined fatigue, tiredness, or sleepiness, with or without sleep paralysis or other symptoms of abnormal REM sleep.

References

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