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

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nine coronary artery smooth muscle. J Pharmacol Exp Ther 1992;263:123–129.
13. Bax WA, Renzenbrink GJ, Van Heuven-Nolsen D, Thijssen EJM, Bos E, Saxena P. 5-HT receptors mediating contractions of the isolated human coronary artery. Eur J Pharmacol 1993; 239:203–210.
14. Ginsburg R, Bristow MR, Davis K, Dibiase A, Billingham ME. Quantitative pharmacological responses on normal and atherosclerotic isolated human epicardial coronary arteries. Circulation 1984;69:430–440.
15. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalgia 1988;8(suppl 7):19–28.
16. Fowler PA, Lacey LF, Thomas M, Keene ON, Tanner RJN, Baber NS. The clinical pharmacology, pharmacokinetics and metabolism of sumatriptan. Eur Neurol 1991;31:291–294.
17. Muzik O, Beanlands RSB, Hutchins GD, Mangner TJ, Nguyen N, Schwaiger M. Validation of nitrogen-13-ammonia tracer kinetic model for quantification of myocardial blood flow using PET. J Nucl Med 1993;34:83–91.
18. Choi Y, Huang S, Hawkins RA, et al. A simplified method for quantification of myocardial blood flow using nitrogen-13-ammonia and dynamic PET. J Nucl Med 1993;34:488–497.
19. Patlak CS, Blasberg RG. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. J Cereb Blood Flow Metab 1985;5:584–590.
20. Raylman RR, Caraher JM, Hutchins GD. Sampling requirements for dynamic cardiac PET studies using image-derived input functions. J Nucl Med 1993;34:440–447.
21. Andrew PD, Birch HL, Phillpot DA. Determination of sumatriptan succinate in plasma and urine by high-performance liquid chromatography with electrochemical detection. J Pharm Sci 1993;82:73–76.
22. Houghton LA, Foster JM, Whorwell PJ, Morris J, Fowler P. Is chest pain after sumatriptan oesphageal in origin? Lancet 1994;344:985–986.
23. MacIntyre PD, Bhargava B, Hogg KJ, Gemmill JD, Hillis WS. Effect of subcutaneous sumatriptan, a selective $5HT_1$ agonist, on the systemic, pulmonary and coronary circulation. Circulation 1993;87:401–405.
24. MacIntyre PD, Bhargava B, Hogg KJ, Gemmill JD, Hillis WS. The effect of i.v. sumatriptan, a selective 5-HT1-receptor agonist on central haemodynamics and the coronary circulation. Br J Clin Pharmacol 1992;34:541–546.
25. Golino P, Piscione F, Willerson JT, et al. Divergent effects of serotonin on coronary-artery dimensions and blood flow in patients with coronary artherosclerosis and control patients. N Engl J Med 1991;324:641–648.
26. MacLean MR, Smith GCS, Templeton AGB. Adverse reactions associated with sumatriptan. Lancet 1993;341:1092.
27. McFadden EP, Clarke JG, Davies GJ, Kaski JC, Haider AW, Maseri A. Effect of intracoronary serotonin on coronary vessels in patients with stable angina and patients with variant angina. N Engl J Med 1991;324:648–654.
28. Palmer J, Feldman R, Mancini GBJ, Zimmerman M. Glyceryl trinitrate reversal of post-sumatriptan coronary artery narrowing. Lancet 1995;345:1366.
29. Gistri R, Cecchi F, Choudry L, et al. Effect of verapamil on absolute myocardial blood flow in hypertrophic cardiomyopathy. Am J Cardiol 1994;74:363–368.

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

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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,[1-4] a genetic marker for narcolepsy was only identified in the early 1980s when Honda and his colleagues[5,6] reported a tight

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association (100%) between human leukocyte antigen (HLA) DR2 and narcolepsy among Japanese patients. These findings were quickly confirmed in Caucasian populations in Australia,[7] Europe,[8-10] and North America.[11] 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.[7,8,10,12] 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[13-16] 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?[17,18] Or, could there be ethnic differences in linkage disequilibrium between DR2 and a putative narcolepsy-susceptibility gene?[15,16] In one of these early reports, Neely et al.[16] only included Black narcoleptic patients and 67% were DR2 positive. Although Nezu et al.[19] 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-cataplexy.[13-16] In 1987, Matsuki et al.[17] 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,[20] "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.[21] 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.[21] Among those subtypes, DRB1*1501 (DR2) together with DQB1*0602 (DQ1) were identified in all Caucasian and Japanese narcoleptic patients with DR2, DQ1.[22-24] 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,[24] with many patients carrying a new variant of DR15 called DRB1*1503 (19 subjects) and all but one subject being positive for DQB1*0602.[24] 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.[16]

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.[25-27] To date, however, there is no evidence for a direct involvement of the immune system in this sleep disorder.[27] 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.[26-30] Pathologic studies have also shown that the CNS of human patients with narcolepsy does not contain sites of lymphocytic infiltrations.[31] HLA DR15 or DQB1*0602 may thus be only linkage markers and not the actual susceptibility genes for narcolepsy.[20,29,32] 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.[33] 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.[34,35] 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,[22-24] with only 0.02 to 0.16% affected with narcolepsy-cataplexy.[36] DQB1*0602 sequence is identical in control and narcoleptic subjects.[24,35,37,38] A few patients with typical narcolepsy-cataplexy are negative for DQB1*0602[34,35,39] and family members frequently share the same HLA haplotype with the proband and never develop narcolepsy.[10,12,20] 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.[40,41] Overall, the data suggest that narcolepsy-cataplexy, like many other HLA-associated disorders, is a complex disorder that involves both genetic predisposition and environmental triggering factors.

Increasingly sophisticated techniques are being developed for identifying the genetic causes of disease, but without careful subject selection, valuable

Table 1 *Clinical subgroups of patients with narcolepsy*

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

EDS = excessive daily sleepiness; MSLT = Multiple Sleep Latency Test; SOREMP = sleep-onset REM period.

time and resources may be wasted. It is thus more critical than ever to standardize the criteria used for the diagnosis of narcolepsy. In the past, diagnosis was based on a clinical history and often included sleepy patients who had apnea, upper airway resistance syndrome (UARS), and idiopathic hypersomnia. Current American Sleep Disorders Association (ASDA) criteria[42] require that the diagnosis be based on polysomnographic studies (a nocturnal study to rule out other sleep disorders and the MSLT that measures the speed at which subject falls asleep as well as the presence or absence of REM sleep). Cataplexy is not required for the diagnosis of narcolepsy if other criteria are met. Yet, in other countries such as Japan, the diagnosis of narcolepsy is not made unless the patient reports experiencing cataplexy.[17,18,20] In many cases, however, cataplexy is very mild and its presence is subjectively determined. Thus, we are back to the question originally posed by Matsuki et al.[17]: Do the different criteria used for the definition of cataplexy and narcolepsy alter the frequency with which the markers associated with narcolepsy are found?

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 homogeneous group of patients displaying the highest possible HLA association.

Methods. *Subjects.* A total of 188 subjects was obtained 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-cataplexy or were diagnosed at the Stanford Sleep Disorder Clinic; (2) parents or relatives of random narcoleptic patients for haplotype relative risk studies or HLA haplotype segregation analysis (n = 93 relatives); (3) relatives and narcoleptic patients of multiplex families (n = 342 subjects in 48 families)[43,44]; (4) narcoleptic subjects recruited because they were found to be non-DR2 positive at another sleep center (n = 41)[34,35]; (5) subjects and parents with essential hypersomnia (n = 4); (6) posttraumatic narcolepsy cases (n = 6).

In this study, only available "random" narcoleptic subjects with a complete clinical file and an established diagnosis of narcolepsy-cataplexy were included in the analysis. Subjects recruited because of DR2 negativity, posttraumatic 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 polygraphic studies (e.g., MSLT and nocturnal polysomnography), 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 diagnosis/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 categorized 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-cataplexy 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 background, e.g., Asian-Caucasian, black-Caucasian were also excluded due to their small number (n = 9). Our final

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

Variable	Patients positive for DRB1*15	Percent positive for DRB1*15	*df*	Chi-square statistic	*p* Value	Patients positive for DQB1*0602	Percent positive for DQB1*0602	*df*	Chi-square statistic	*p* Value
Gender										
Female	84/105	80.0	1	0.68	0.41	91/104	87.5	1	0.00	1.000
Male	68/82	82.9				70/80	87.5			
Ethnicity										
Asian	23/24	95.8	2	11.4	0.003	21/23	91.3	2	0.53	0.765
Black	41/61	67.2				54/61	88.5			
Caucasian	87/103	84.5				87/102	86.1			
Cataplexy										
Clear-cut	144/174	82.8	1	8.80	0.003	154/171	90.1	1	12.88	0.001
Atypical/doubtful	7/14	50.0				8/14	57.1			
MSLT findings										
Positive	113/144	78.5	2	2.38	0.30	125/143	87.4	2	0.97	0.617
Ambiguous	22/27	81.5				21/25	84.0			
Never performed	16/17	94.1				16/17	94.1			

MSLT = Multiple Sleep Latency Test.

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" narcoleptic patients were later found to have another family member with documented narcolepsy-cataplexy.

HLA typing. The presence or absence of DQB1*0602 and DRB1*15 was determined either using polymerase chain reaction sequence specific oligonucleotide (PCR-SSO) as previously described[24,39] or using Innotype reverse dot blot kits according to manufacturer recommendation (Robbins Scientific, Sunnyvale, CA). All non-DR15 and/or non-DQB1*0602-positive subjects were fully HLA DR and DQ high resolution PCR SSO typed as described in Kimura et al.[45] to confirm the presence or absence of DR15 and DQB1*0602.

Subject categorizations. Group assignments (A–G) were then used to categorize subjects by their history of cataplexy and MSLT results. Subjects who reported recurrent brief episodes of weakness in the knees, jaw, face, or neck triggered by laughter, amusement, happiness, game playing, or anger were considered to have clear-cut history of cataplexy (Groups A–F). Subjects who reported atypical symptoms (e.g., unilateral weakness in one arm or cataplexy mostly induced by stress or by other less typical emotions, unusually long episodes, etc.) or extremely mild symptoms (e.g., feeling of weakness that does not result in detectable changes in body position or report of a single or a few attacks in the past) were considered to have a "possible" history of cataplexy (Group G).

MSLT data were then analyzed on all subjects. When subjects had a mean sleep latency of ≤8 minutes and at least two sleep onset REM periods (SOREMPs) their MSLT findings were considered positive (Groups A, G1, G2). Polygraphic results were considered ambiguous when the mean sleep latency was either >8 minutes, or when there were less than two SOREMPs during the MSLT (Groups B, D, G3) or when polygraphic tests other than MSLTs were performed and suggested a possible abnormality (Group C). A third category, no sleep studies performed, was created for subjects who had well-documented history of EDS and clear-cut cataplexy but who had never undergone any diagnostic studies (Group F). Ethnicity and gender were determined from information provided by the subjects.

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*

Model	Variable	Coefficient	Standard error	Wald chi-square	*p* value	Odds ratio
DRB1*15 #1	Constant	8.47×10^{-16}	0.5345	0.00	1.00	
	Cataplexy	1.5686	0.5710	7.55	0.006	4.80
DRB1*15 #2	Constant	−0.4675	0.5833	0.64	0.42	
	Cataplexy	1.3596	0.5881	5.34	0.02	3.90
	Caucasian*	0.9350	0.3930	5.66	0.02	2.55
	Asian†	2.2434	1.0618	4.46	0.03	9.45
DQB1*0602	Constant	0.2877	0.5401	0.28	0.59	
	Cataplexy	1.9161	.5975	10.28	0.001	6.79

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

ferent 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[16,24] 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[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,[16,22-24] the percentage of Caucasian subjects positive for either DR15 (DR2) or DQB1*0602 is slightly lower than usually reported (i.e., 91–100%).[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.[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[22-24] and only 0.02 to 0.06% of the population has narcolepsy-cataplexy.[36] The gene has been sequenced in many control and narcoleptic subjects and found to be normal in all cases.[24,35,38] 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.[36,43,44,47]

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%),[16,17,20,46,48] 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 lead 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 $\leq$8 min and $\geq$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

1. Westfall C. Eigenthümliche mit Einschläfen verbundene Anfälle. Arch Psychiat 1877;7:631–635.
2. Baraitser M, Parkes J. Genetic study of the narcolepsy syndrome. J Med Genet 1978;15:254–259.
3. Yoss R, Daly D. Hereditary aspects of narcolepsy. Trans Am Neurol Assoc 1960;85:239–240.
4. Kessler S, Guilleminault C, Dement WC. A family study of 50 REM narcoleptics. Acta Neurol Scand 1979;50:503–512.
5. Honda Y, Asaka A, Tanaka Y, Juji T. Discrimination of narcolepsy by using genetic markers and HLA [abstract]. Sleep Research 1983;12:254.
6. Juji T, Satake M, Honda Y, Doi Y. HLA antigens in Japanese patients with narcolepsy—all the patients were DR2 positive. Tissue Antigens 1984;24:316–319.
7. Doran T, Rouse S, Hakos G, Honeyman M. FT31 may demonstrate a DQw1 variant in narcoleptic patients. In: Aizawa M, ed. HLA in Asia-Oceania 1986. Sapporo, Japan: Hokkaido University Press; 1986:783–786.
8. Langdon N, Welch KI, Van Dam M, Vaugham R, Parkes J. Genetic markers in narcolepsy. Lancet 1984;2:1178–1180.
9. Billiard M, Seignalet J. Extraordinary association between HLA-DR2 and narcolepsy. Lancet 1985;1:226–227.
10. Mueller-Eckhardt G, Meier-Ewert KA, Schendel DJ, Reinecker FB, Mueller-Eckhardt C. HLA and narcolepsy in a German population. Tissue Antigens 1986;28:163–169.
11. Poirier G, Montplaisir J, Decary F, Momege D, Lebrun A. HLA antigens in narcolepsy and idiopathic central nervous system hypersomnolence. Sleep 1986;9:153–158.
12. Meier-Ewert K, Mueller-Eckhardt G, Schendel DJ. Narcolepsy and HLA in the Federal Republic of Germany: population and family data. In: Honda Y, Juji T, eds. HLA in narcolepsy. Berlin: Springer-Verlag, 1985:114–120.
13. Guilleminault C, Grumet C. HLA-DR2 and narcolepsy: not all narcoleptic-cataplectic patients are DR2. Hum Immunol 1986; 17:1–2.
14. Andreas-Zietz A, Keller E, Scholz S, et al. DR2 negative narcolepsy. Lancet 1986;2:685–686.
15. Confavreux C, Gebuhrer L, Betuel H, et al. HLA-DR2 negative narcolepsy. J Neurol Psychiatr 1987;50:635–643.
16. Neely S, Rosenberg R, Spire JP, Antel J, Arnason BEW. HLA antigens in narcolepsy. Neurology 1987;37:1178–1180.
17. Matsuki K, Honda Y, Juji T. Diagnostic criteria for narcolepsy and HLA-DR2 frequencies. Tissue Antigens 1987;30:155–160.
18. Honda Y. Introduction. In: Honda Y, Juju T, eds. HLA in narcolepsy. Berlin: Springer-Verlag, 1988:1–7.
19. Nezu S, Noji K, Tsutsumi Y, et al. An interim report about correlation of HLA antigens with narcolepsy. J Psychiatr Soc Kanagawa Prefecture 1985;35:81–86.
20. Honda Y, Matsuki K. Genetic aspects of narcolepsy. In: Thorpy MJ, ed. Handbook of sleep disorders. New York: Marcel Dekker, 1990:217–234.
21. Marsh GE. Nomenclature for factors of the HLA system, update February 1996. Tissue Antigens 1996;47:360.
22. Lin L, Kuwata S, Tokunaga K, Sasaki T, Honda Y, Juji T. In: Tsuji K, Aizawa M, Sasazuki T, eds. HLA 1991, Proceedings of the 11th International Histocompatibility Workshop and Conference (November 1991, Yokohama, Japan). Vol. 2. Oxford: Oxford University Press, 1992:333–335.
23. Kuwata S, Juji T, Sasaki T, et al. In: Tsuji K, Aizawa M, Sasazuki T, eds. HLA 1991, Proceedings of the 11th International Histocompatibility Workshop and Conference (November 1991, Yokohama, Japan). Vol. 2. Oxford: Oxford University Press, 1992:730–732.
24. Mignot E, Lin X, Arrigoni J, et al. DQB1*0602 and DQA1*0102 (DQ1) are better markers than DR2 for narcolepsy in Caucasian and black Americans. Sleep 1994;17:S60–S67.
25. Parkes JD, Langdon N, Lock C. Narcolepsy and immunity. BMJ 1986;292:359–360.
26. Carlander B, Eliaou JF, Billiard M. Autoimmune hypothesis in narcolepsy. Neurophysiol Clin 1993;23:15–22.
27. Mignot E, Tafti M, Dement WC, Grumet FC. Narcolepsy and immunity. Adv Neuroimmunol 1995;5:23–37.
28. Fredrikson S, Carlander B, Billiard M, Link H. CSF Immune variable in patients with narcolepsy. Acta Neurol Scand 1990; 81:253–254.
29. Matsuki K, Juji T, Honda Y. Immunological features in Japan. In: Honda Y, Juji T, eds. HLA in narcolepsy. Berlin: Springer-Verlag, 1988:58–76.
30. Rubin RL, Hajdukovitch RM, Mitler MM. HLA DR2 association with excessive somnolence in narcolepsy does not generalize to sleep apnea and is not accompanied by systemic autoimmune abnormalities. Clin Immunol Immunopathol 1988;49: 149–158.
31. Erlich SS, Itabashi HH. Narcolepsy: a neuropathological study. Sleep 1986;9:126–132.
32. Montplaisir J, Poirier G. HLA and narcolepsy in Canada. In: Honda Y, Juji T, eds. HLA in narcolepsy. Berlin: Springer-Verlag, 1988:97–113.
33. Tafti M, Nishino S, Aldrich MS, Dement WC, Mignot E. Nar-

colepsy is associated with increased microglia expression of MHC class II molecules. J Neurosci 1996;16:4588–4595.
34. Mignot E, Kimura A, Lattermann A, et al. HLA class II studies in non DRB1*1501 patients with narcolepsy-cataplexy. In: Charon D, Fauchet R, eds. HLA 1996, Proceedings of the 12th International Histocompatibility Workshop and Conference: Genetic diversity of HLA: Functional and medical implications (June 1996, St. Malo, France). Vol. 1. Paris: EDK Press, 1996.
35. Mignot E, Kimura A, Lattermann A, et al. Extensive HLA Class II studies in 58 non DRB1*15 (DR2) narcoleptic patients with cataplexy maps susceptibility to the coding region of DQA1*0102 and DQB1*0602. Tissue Antigens (in press).
36. Hublin C, Partinen M, Kaprio J, Koskenvuo M, Guilleminault C. Epidemiology of narcolepsy. Sleep 1994;17:S7–12.
37. Lock CB, So AKL, Welch KI, Parkes JD, Trowsdale J. MHC class II sequences of an HLA-DR2 narcoleptic. Immunogenetics 1988;27:449–455.
38. Uryu N, Maeda M, Nagata Y, et al. No difference in the nucleotide sequence of the DQbeta betal domain between narcoleptic and healthy individuals with DR2, Dw2. Hum Immunol 1989;24:175–181.
39. Mignot E, Lin X, Kalil J, et al. DQB1-0602 (DQw1) is not present in most nonDR2 Caucasian narcoleptics. Sleep 1992; 15:415–422.
40. Partinen M, Hublin C, Kaprio J, Koskenvuo M, Guilleminault C. Twin studies in narcolepsy. Sleep 1994;17:S13–S16.
41. Hyduk R, Flodman P, Spence A, Erman MK, Mitler MM. Monozygotic twins with narcolepsy: preliminary report [abstract]. Sleep Research 1996;25:252.
42. Diagnostic Classification Steering Committee. International classification of sleep disorders: diagnostic and coding manual. Rochester, MN: American Sleep Disorders Association, 1990.
43. Guilleminault C, Mignot E, Grumet C. Family study of narcolepsy. Lancet 1989;2:1376–1379.
44. Mignot E, Meehan J, Grumet FC, et al. HLA Class II and narcolepsy in thirty-three multiplex families [abstract]. Sleep Research 1996;25:303.
45. Kimura A, Dong RP, Harada H, Sasazuki T. DNA typing of HLA class II genes in B-lymphoblastoid cell lines homozygous for HLA. Tissue Antigens 1992;40:5–12.
46. Acton R, Shettar S, Wise M, et al. A comparison of HLA-DR2 (DRB1-1501) and DQ6 (DQB1-0602) associations with narcolepsy and diagnostic features in Caucasian Americans and African Americans [abstract]. Sleep Research 1995;24:184.
47. Singh SM, George CFP, Kryger MH. Genetic heterogeneity in narcolepsy. Lancet 1990;335:726–727.
48. Aldrich MS. The clinical spectrum of narcolepsy and idiopathic hypersomnia. Neurology 1996;46:393–401.