HLA Class II Genes Associated with REM Sleep Behavior Disorder

Carlos H. Schenck, MD,*† Edgar Garcia-Rill, PhD,§ Miriam Segall, PhD,¶ Harriet Noreen, CHS,** and Mark W. Mahowald, MD*‡

Twenty-five white men with rapid eye movement (REM) sleep behavior disorder, but without narcolepsy, underwent HLA class II antigen typing; 84% (N = 21) were DQw1 (DQB1*05,06) positive (28% [N = 7] were DR2 positive); DQB1*0501 (N = 9) and DQB1*0602 (N = 7) were the most common phenotypes. The 84% DQw1 rate in men with REM sleep behavior disorder was significantly greater ($p = 0.015$) than the 56% DQw1 rate found in a local white comparison group (N = 66), and was greater than the 39 to 66% DQw1 rates published for 12 white groups (N = 40–418/group). Thus, another disorder of REM sleep dysregulation (besides narcolepsy) appears to be strongly associated with specific HLA class II genes.

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Rapid eye movement (REM) sleep behavior disorder (RBD) [1–4] is a parasomnia that mainly affects middle-aged or older men. Clinically, RBD is characterized by complex and violent, dream-enacting behaviors; polysomnographically, RBD is characterized by the loss of electromyographic (EMG) atonia of REM sleep (as indicated by elevated submental EMG tone) or the presence of prominent, excessive phasic EMG twitching during REM sleep. In approximately half of reported patients, RBD is etiologically linked with diverse neurological disorders, especially neurodegenerative disorders and narcolepsy; in the other half of reported patients, RBD is considered to be idiopathic [4].

From the *Minnesota Regional Sleep Disorders Center and Departments of †Psychiatry and ‡Neurology, Hennepin County Medical Center and the University of Minnesota Medical School, Minneapolis; §Department of Anatomy, University of Arkansas for Medical Sciences, Little Rock, AR; ¶Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis; and Immunology/Histocompatibility Laboratory, University of Minnesota Hospital and Clinic, Minneapolis, MN.

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Address correspondence to Dr Schenck, Minnesota Regional Sleep Disorders Center, Hennepin County Medical Center, 701 Park Avenue South, Minneapolis, MN 55415.

Narcolepsy, another prominent disorder of REM sleep dysregulation, has a very strong association with human leukocyte antigen (HLA) class II genes, with the DQB1*0602 (DQw1 group) allele being expressed in nearly all patients [5]. Therefore, in an effort to better understand the biological underpinnings of RBD, we performed HLA class II antigen phenotyping in a group of RBD patients, and now report our findings.

Patients and Methods

All patients had presented clinically to our sleep disorders center on account of a progressively severe disorder of injurious or potentially injurious dream-enacting behaviors. Our extensive clinical and polysomnographic (PSG) evaluations have been described previously [2–4]. Standard PSG recording and scoring methods were utilized [6]. RBD in all patients satisfied standard, recognized diagnostic criteria [1, 3]. Patients with complaints of daytime fatigue or with suspected daytime somnolence underwent a multiple sleep latency test (MSLT) [7] that was conducted the day after an overnight PSG study. Patients also underwent extensive neurological evaluations, as previously described [3, 4].

Of 29 nonnarcoleptic, white men with RBD who were contacted, 25 presented for HLA class II (DR,DQ) phenotyping that was performed using oligonucleotide probes [8] at the University of Minnesota Hospital Immunology/Histocompatibility Laboratory.

After the HLA data for the 25 RBD patients were analyzed and prominent DQw1 findings were identified, a post hoc, local comparison group was selected retrospectively, and consisted of 66 random, healthy, white blood donors who had undergone DNA-based HLA typing for DQ antigens. These random donors represented all normal white control subjects typed in the Immunology/Histocompatibility Laboratory during the previous 2 years.

Statistical analysis, consisting of the χ^2 test with Yates' correction, compared the DQw1 rate in the RBD patients from this study with the published DQw1 rates from 12 healthy, white groups [9–13]. (To our knowledge, the rates from these 12 groups comprise all or nearly all the published DQw1 rates for nonnarcoleptic, healthy whites.) Since these 12 comparisons can be regarded as a set of related tests, the conservative value chosen for declaring a result as being significant was $p < 0.05$ divided by 12, yielding $p < 0.004$.

Results

The clinical and PSG data for the RBD patients were representative of the data for the entire group of RBD patients evaluated at our center [4]. Mean age at RBD onset was 56.7 (±9.4 [standard deviation]) years (N = 22; indeterminate, N = 3). Loss of REM sleep EMG atonia was present in 80% (N = 20) of patients, excessive phasic EMG twitching during REM sleep was present in 88% (N = 22) of patients, and complex or violent behaviors during REM sleep were present in 72% (N = 18) of patients.

HLA Class II (DR, DQ) Antigen Phenotype Data in 25 White Men with REM Sleep Behavior Disorder

HLA Class II Phenotypes	% Patients (N)
DQB1*05,06 (DQw1) group[a]	84.0 (21)
DQB1*0501 (N = 9) or DQB1*0602 (N = 7)	64.0 (16)
DQB1*0503 (N = 4) or DQB1*0603 (N = 4)	32.0 (8)
DQB1*0502 (N = 2) or DQB1*0604 (N = 1)	12.0 (3)
DQB1*03 group	48.0 (12)
DQB1*0201	24.0 (6)
DQB1*0402	8.0 (2)
DR2	28.0 (7)
DRB1*13,14 (DR6) group	36.0 (9)
DRB3*0101,02,0301 group	42.0 (13)
DRB4*01 group	44.0 (11)
DRB5*01,02 group	28.0 (7)

[a]24% (N = 6) of patients had two DQB1*05,06 phenotypes.

Narcolepsy was not diagnosed in any patient. No patient reported a history of cataplexy, hypnagogic hallucinations, or sleep paralysis. Each of the 18 patients undergoing an MSLT had a mean sleep latency of longer than 5 minutes; the group mean sleep latency on the MSLT was 13.2 ± 5.3 minutes; REM sleep did not occur during any of the 82 MSLT nap opportunities.

There was a modest overrepresentation of idiopathic RBD (68%, N = 17). In contrast 32% (N = 8) of patients were diagnosed with "symptomatic RBD," in which the onset of RBD was etiologically linked with the onset of a neurological disorder: Parkinson's disease (N = 5), stroke (N = 2), or spinocerebellar degeneration (N = 1).

RBD developed in 1 (DQw1-positive) patient shortly after the onset of rheumatoid arthritis at the age of 63 years. In another patient, a malignancy developed more than 10 years after the onset of RBD. No other patient had a history of autoimmune disease or malignancy.

The Table contains the HLA data. The main finding was that 84.0% (N = 21) of patients were DQw1 positive; 76.5% (13/17) of the idiopathic RBD subgroup and 100% (8/8) of the symptomatic RBD subgroup were DQw1 (DQB1*05 and/or DQB1*06) positive. Also, 28% of patients were DR2 positive.

In the comparison group, 56.1% (N = 37) of the 66 subjects (mean age, 35.2 ± 9.2 years; N = 44 women) were DQw1 positive, which was significantly less than the 84% rate found in the 25 RBD patients ($p = 0.015$, Fisher's exact test).

The published DQw1 prevalence rates for the 12 white comparison groups were always lower than that found in our RBD group, and were significantly lower in eight of these groups: 39% (156/400) of healthy North Americans ($p < 0.001$) [9]; 39% (39/99) of healthy Swedes ($p < 0.001$) [10]; 34.5 to 50.6% of five different southern European groups (N = 84–187/group) ($p < 0.001$ in four of five groups) [11]; 44% (58/131) ($p < 0.001$) and 45% (24/54) ($p = 0.002$) of healthy Danes [10]; 55% (22/40) of healthy Norwegians [10]; 54.5% (60/110) of French nonnarcoleptic "normal" subjects [12]; and 65.8% (275/418) of German nonnarcoleptic "normal" subjects [13].

Discussion

Our initial data on 25 white men with RBD appear to indicate a strong association between (nonnarcoleptic) RBD and the HLA DQw1 (DQB1*05 and DQB1*06) alleles. In narcolepsy, the DQB1*0602 allele is present in nearly all patients, and is presumed to represent, or be closely linked to, the narcolepsy susceptibility allele [5]. The DR2 haplotype (DR15 subtype; specifically, DRB1-1501) is also present in nearly all patients with narcolepsy, and is very closely linked to the DQB1*0602 allele [5]. In contrast to the nearly 100% DQw1-DR2 linkage in narcolepsy, only 28% of RBD patients in this report were DR2 positive. The strong *dissociation* between DQw1 and DR2 in RBD can be contrasted with the very strong DQw1-DR2 *association* in narcolepsy. To summarize, these two major disorders of REM sleep appear to have strikingly convergent (DQw1) and divergent (DR2) HLA findings.

The 56% DQw1 rate in our comparison group (N = 66) is concordant with the 39 to 66% DQw1 rates found in the 12 comparison groups [9–13]. Also, the 28% DR2 rate in our RBD group is concordant with the range of DR2 rates found in the same 12 comparative groups.

Controlled studies are needed to confirm the present findings and to determine the correlation, if any, between DQw1 phenotypes and various RBD subgroups, including narcoleptic [14, 15] and nonnarcoleptic [3, 4] RBD subgroups.

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Bell's Palsy–associated Blepharospasm Relieved by Aiding Eyelid Closure

John C. Chuke, MD,* Robert S. Baker, MD,*† and John D. Porter, PhD*‡

The efficacy of the blink reflex is maintained by adaptive control mechanisms. We describe a 39-year-old woman with the rare complication of blepharospasm-like symptoms appearing contralateral to an eyelid weakened by facial nerve palsy. The hyperexcitable blink reflex may be a maladaptive consequence of adaptive systems but was not accompanied by an expected increase in main sequence slope. Eyelid spasms were eliminated by the implantation of a gold weight to assist closure of the paretic eyelid. We suggest that aiding closure of the weak eyelid in this case caused a reduction in blink system excitability via the same compensatory mechanisms that initially produced the eyelid spasm. Data also suggest that blink-adaptive systems act via changes in reflex excitability and/or main sequence relationships, and that these may be regulated either synergistically or independent of one another.

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The blink reflex is a reproducible and easily quantifiable behavior. For any motor control system, adaptive gain mechanisms must be operative to ensure that there is a precise match between the intended and actual movement. The comparison of an internal copy of the motor command (efference copy or corollary discharge), an index of the intended movement, with multimodal sensory feedback (e.g., visual, somatosensory), potentially a source of information regarding the actual movement, allows precise adaptive adjustments in motor output. While the operation of gain control mechanisms is a key principle of the ocular motor system, there is accumulating evidence that compensatory mechanisms operate to maintain the efficacy of the protective blink reflex as well [1–4].

In our prior study of Bell's palsy [4], we found that

From the Departments of *Ophthalmology, †Neurology, and ‡Anatomy and Neurobiology, University of Kentucky Medical Center, Lexington, KY.

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Address correspondence to Dr Baker, Department of Ophthalmology, E304 Kentucky Clinic, University of Kentucky Medical Center, Lexington, KY 40536-0284.

