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MAPT ASSOCIATION WITH REM SLEEP BEHAVIOR DISORDER

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Idiopathic REM sleep behavior disorder (IRBD) is a REM sleep parasomnia comprising unpleasant dreams, dream-enacting behaviors, and loss of muscle atonia during REM sleep. Longitudinal studies have demonstrated that because most patients with IRBD develop with time Parkinson disease (PD) and other synucleinopathies including dementia with Lewy bodies (DLB) or multiple system atrophy (MSA), IRBD represents a prodromal stage of these diseases.[1] In PD, 5%–10% of cases are caused by nonfrequent mendelian mutations segregating with disease in pedigrees, but the vast majority of cases are sporadic. Unbiased genome-wide association studies in sporadic PD (sPD) have shown that single nucleotide polymorphisms (SNPs) in the α-synuclein (*SNCA*) and microtubule-associated protein tau (*MAPT*) genes modulate disease susceptibility.[2] Given that IRBD often antedates sPD and that, akin to PD, familial clustering of IRBD is rare, we hypothesized that genetically shared variation at *SNCA* and *MAPT* may influence disease susceptibility to both conditions. Accordingly, we genotyped PD-associated genetic variants in *SNCA* and *MAPT* in a cohort of Spanish patients with IRBD.

Methods. The SNPs rs356219 (A/G) in *SNCA* and rs1800547 (H1/H2) in *MAPT* have been consistently associated with sPD in the Spanish population.[3,4] Here, we genotyped these markers in a Spanish Caucasian sample of 121 patients with IRBD and 175 healthy controls. This population was studied in a previous report.[5] The IRBD group was recruited at the Multidisciplinary Sleep Unit of the Hospital Clínic de Barcelona, had a polysomnography-confirmed diagnosis, and consisted of 21/100 women/men (17.4/82.6%), with age at IRBD onset of 68.3 ± 6.2 years and age at sample collection of 71.2 ± 6.4 years. Patients fulfilled the diagnosis of IRBD and were free of parkinsonism, mild cognitive impairment, and dementia at the time of sample collection. After 6.8 ± 4.1 years of follow-up from IRBD diagnosis, 38 patients (31.4%) were clinically diagnosed with a synucleinopathy (DLB in 19 patients, PD in 18, and MSA in 1). Sex-, age-, and demographic-matched controls were recruited at the Multidisciplinary Sleep Unit of the Hospital Clínic de Barcelona (n = 45) and the Clínica Universitaria de Navarra (n = 129), and consisted of 21/154 women/men (13.6/86.4%) with age at sample collection of 71.7 ± 6.4 years. DNA was extracted from the peripheral blood using standard procedures. Genotyping was performed using the predesigned TaqMan assays C-1020193-10 (*SNCA* rs356219) and C-7563692-10 (*MAPT* rs1800547) in a StepOnePlus Real-time PCR System (Applied Biosystems, Foster City, CA). Allelic and genotypic frequencies were compared using SNPstats software (bioinfo.iconcologia.net/SNPstats).

Standard protocol approvals, registrations, and patient consents. Samples were collected after patient's signed consent, and the local ethics committee approved the study.

Results. We found no allelic or genotypic distribution differences of the *SNCA* marker rs356219 in patients with IRBD and in controls. However, we found an association of the *MAPT* polymorphism rs1800547 with IRBD. More specifically, we found that the frequency of the *MAPT* H2/H2 genotype which is protective for PD[3,4] was underrepresented in our patients with IRBD. This association held statistically significant after adjusting for sex and age as covariates (odds ratio = 0.16; 95% confidence interval = 0.04–0.69; $p = 0.002$; table). Moreover, we observed that *MAPT* genotypes in patients with IRBD, but not in controls, were not in the Hardy-Weinberg equilibrium ($p = 0.049$), a finding which is consistent with previous observations for disease-linked loci in disease-affected individuals.[6]

Discussion. We found that the *MAPT* marker rs1800547 is associated with IRBD. Consistently, we detected that the H2 variant which is protective for PD was underrepresented in our patients with IRBD. On the contrary, we did not find an association of the *SNCA* polymorphism rs356219 with IRBD. Altogether, these results are in agreement with another IRBD study reporting association for *MAPT* but not for *SNCA* polymorphisms.[7] Yet, markers in both studies were different. These data raise the question whether IRBD shares with PD the same genetic

Table Distribution of genotypic frequencies of *SNCA* and *MAPT* polymorphisms in patients with IRBD (n = 121) and sex- and age-matched healthy controls (n = 175)

Marker	Frequency in IRBD	Frequency in controls	OR (95% CI)	Adjusted *p* value
***MAPT* rs1800547**				
H1/H1	0.537 (n = 65)	0.474 (n = 83)	0.16 (0.04–0.69)	0.002
H1/H2	0.438 (n = 53)	0.423 (n = 74)		
H2/H2	0.025 (n = 3)	0.103 (n = 18)		
***SNCA* rs356219**				
A/A	0.562 (n = 68)	0.497 (n = 87)	0.45 (0.31–1.69)	0.45
A/G	0.364 (n = 44)	0.400 (n = 70)		
G/G	0.074 (n = 9)	0.103 (n = 18)		

Abbreviations: CI = confidence interval; IRBD = idiopathic REM sleep behavior disorder; OR = odds ratio.
p Values were calculated using the Student *t* test, adjusting for sex and age as covariates, and comparing the *MAPT* PD-protective genotype H2/H2 vs H1/H1 + H1/H2 and the *SNCA* PD-risk *SNCA* genotype G/G vs G/A + A/A.

risk factors or whether, alternatively, IRBD represents a specific endophenotype of PD with only certain genetic risk factors shared in common by both conditions. The later might be a plausible explanation because, although IRBD is considered a prodrome of sPD, not all patients with sPD develop RBD prior to parkinsonism. Supporting this view, we have recently reported that pathogenic mutations in the leucine-rich repeat kinase 2 gene (*LRRK2*), which are the most frequent genetic cause of PD, are absent in our IRBD cohort.[5] One limitation of our study is the reduced number of patients with IRBD. Thus, future studies in larger cohorts are warranted to validate the association of *MAPT* with IRBD and also to further elucidate whether or not *SNCA* polymorphisms play a role in disease. We found that one polymorphism in *MAPT* which is associated with PD also modulates the propensity to IRBD. These results point toward an at least in part overlapping genetic susceptibility to both conditions in our Spanish population.

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