Full Sequencing and Haplotype Analysis of *MAPT* in Parkinson's Disease and Rapid Eye Movement Sleep Behavior Disorder

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ABSTRACT

Background: *MAPT* haplotypes are associated with PD, but their association with rapid eye movement sleep behavior disorder is unclear.

Objective: To study the role of MAPT variants in rapid eye movement sleep behavior disorder.

Methods: Two cohorts were included: (A) PD (n = 600), rapid eye movement sleep behavior disorder (n = 613) patients, and controls (n = 981); (B) dementia with Lewy bodies patients with rapid eye movement sleep behavior disorder (n = 271) and controls (n = 950). *MAPT*-associated variants and the entire coding sequence of *MAPT* were analyzed. Age-, sex-, and ethnicity-adjusted analyses were performed to examine the association between *MAPT*, PD, and rapid eye movement sleep behavior disorder.

Results: *MAPT*-H2 variants were associated with PD (odds ratios: 0.62-0.65; $P = 0.010$-0.019), but not with rapid eye movement sleep behavior disorder. In PD, the H1 haplotype odds ratio was 1.60 (95% confidence interval: 1.12-2.28; $P = 0.009$), and the H2 odds ratio was 0.68 (95% confidence interval: 0.48-0.96;

$P = 0.03$). The H2/H1 haplotypes were not associated with rapid eye movement sleep behavior disorder.
Conclusions: Our results confirm the protective effect of the *MAPT*-H2 haplotype in PD, and define its components. Furthermore, our results suggest that *MAPT* does not play a major role in rapid eye movement sleep behavior disorder, emphasizing different genetic background than in PD in this locus. © 2018 International Parkinson and Movement Disorder Society
Key Words: REM sleep behavior disorder; Parkinson's disease; genetics; *MAPT*

Rapid eye movement (REM) sleep behavior disorder (RBD) is characterized by loss of muscle atonia and enactment of dreams during REM sleep. RBD will progress, in most cases, to an overt synucleinopathy; either Parkinson's disease (PD), dementia with Lewy bodies (DLB), or, rarely, multiple system atrophy (MSA).[1] Multiple genetic variants have been implicated in PD[2,3] and some in DLB and MSA,[4] yet the potential role of most of them in RBD is still unknown.

Common genetic variation at the *MAPT* locus represent the second strongest genetic association in recent genome-wide association studies in PD,[2] and may also have a minor role in DLB.[5,6] Recent studies in MSA also highlighted the *MAPT* H2 haplotype, although the small sample size precluded a genome-wide significant *P* value.[7,8] Studies in PD focusing on the H1 and H2 *MAPT* haplotypes demonstrated that these haplotypes are associated with increased and decreased risk for PD, respectively,[9-11] and GWAS confirmed that the *MAPT* H2 haplotype was strongly associated with PD risk.[2]

MAPT subhaplotype analysis and a sequencing study recently performed in DLB suggested that a rare subhaplotype, H1G, and a rare coding variant, p.A152T, were associated with DLB.[5,6] However, a previous study in a large DLB cohort showed no evidence of association of the *MAPT* locus with DLB.[12] Overall, it seems that *MAPT* haplotypes play an important role in PD, whereas their role in MSA and DLB is still not clear, and could be minor. Given that RBD patients may convert to either PD or DLB, two studies have been recently performed to determine the association between *MAPT* and RBD.[13,14] Both studies suggested a possible association; however, both studies were small and thus underpowered.

In the current study, we aimed to perform a thorough genetic study of the *MAPT* locus and its association with RBD (idiopathic RBD and RBD in DLB) and PD, using targeted next-generation sequencing (NGS) of the entire coding region of *MAPT*, and in-depth haplotype analysis, in larger cohorts with RBD.

Patients and Methods

Study Population

Two Independent cohorts were included (Supplementary Table 1), and more details on their recruitment and diagnosis is in the Supplementary file: (A) The Montreal Neurological Institute cohort included 600 PD patients, 613 RBD patients, and 981 controls, all unrelated, of European ancestry. (B) The Mayo cohort included 271 patients with clinical DLB who were diagnosed with RBD and 950 controls. All participants in both cohorts signed an informed consent at enrollment to the study, and the respective ethical review boards approved the study protocols.

Genotyping

In cohort A, eight *MAPT* single-nucleotide polymorphisms (SNPs) were genotyped (Table 1), including six *MAPT* locus haplotype-tagging SNPs and two additional *MAPT* SNP, which were previously reported to be associated with PD and RBD.[13,14] In cohort B, the six haplotype-tagging SNPs were previously genotyped and reported. Further details on the genotyping are in the Supplementary file.

Targeted NGS

A subset of cohort A, including samples from 525 PD patients, 342 RBD patients, and 825 controls was sequenced using targeted NGS. The coding sequences of 51 PD-related genes (Supplementary Table 2), including *MAPT*, were captured using molecular inversion probes, as was previously described.[15] Further details on alignment, filtering, and analysis are in the Supplementary file.

Statistical Analysis

Full details on the statistical analysis can be found in the Supplementary file. To account for potential bias that may have occurred in cohort A, attributed to the different populations in patients and controls (despite all being of European origin), a principal component analysis (PCA) was performed. Goodness-of-fit chi-square test with one degree of freedom was performed to examine deviation from Hardy-Weinberg equilibrium (HWE) in the controls for each variant. Adjusted and unadjusted regression models were performed to examine the association between the tested SNPs and haplotypes in the *MAPT* locus and PD or RBD. Burden analysis was done as described in the Supplementary file. All analyses were performed with PLINK 1.9 or R.

Results

Association of *MAPT* SNPs With PD and RBD

Data on population stratification and adjustment is in the Supplementary file. Genotyping success rate of

TABLE 1. Allele frequencies of *MAPT* variants genotyped with TaqMan assays or identified in targeted NGS

	Minor Allele Frequency			PD vs. Control		RBD vs. Control	
	PD (n = 600)	RBD (n = 613)	Controls (n = 981)	OR (95% CI)[a]	*P* Value[a]	OR (95% CI)[a]	*P* Value[a]
SNPs genotyped using TaqMan assays							
rs12185268	0.213	0.237	0.252	**0.64 (0.45-0.92)**	**0.015**	0.90 (0.60-1.35)	0.603
rs1467967	0.347	0.300	0.328	1.15 (0.90-1.46)	0.267	0.96 (0.72-1.28)	0.771
rs242557	0.336	0.345	0.335	1.10 (0.86-1.40)	0.455	1.01 (0.76-1.34)	0.936
rs1800547	0.213	0.237	0.249	**0.65 (0.46-0.93)**	**0.018**	0.97 (0.66-1.43)	0.883
rs3785883	0.158	0.179	0.155	0.93 (0.69-1.26)	0.627	0.93 (0.66-1.32)	0.692
rs2471738	0.222	0.194	0.203	1.31 (1.00-1.73)	0.053	1.21 (0.87-1.67)	0.262
rs8070723	0.219	0.240	0.253	**0.65 (0.46-0.93)**	**0.018**	0.86 (0.57-1.30)	0.471
rs7521	0.468	0.466	0.454	0.95 (0.75-1.20)	0.666	0.93 (0.70-1.23)	0.595
Variants identified in targeted NGS							
rs63750417	0.207	0.232	0.244	0.72 (0.44-1.16)	0.176	1.14 (0.69-1.88)	0.605
rs63750072	0.053	0.058	0.053	0.96 (0.44-2.06)	0.910	1.23 (0.61-2.44)	0.566
rs62063786	0.216	0.232	0.247	**0.63 (0.43-0.90)**	**0.012**	0.90 (0.59-1.36)	0.613
rs62063787	0.216	0.232	0.246	**0.64 (0.44-0.91)**	**0.015**	0.91 (0.60-1.38)	0.666
rs17651549	0.216	0.232	0.248	**0.65 (0.45-0.93)**	**0.019**	0.94 (0.62-1.42)	0.757
rs2258689	0.184	0.207	0.200	0.91 (0.68-1.21)	0.513	0.97 (0.69-1.35)	0.852
rs10445337	0.216	0.232	0.247	**0.62 (0.43-0.89)**	**0.010**	0.90 (0.59-1.35)	0.596

[a]Adjusted for age, sex, and the two major components in the population stratification PCA.
Bold values indicate statistically significant associations, $P < 0.05$.

the eight selected *MAPT* SNPs was 100% in both cohorts, and all variants were in HWE in the control group. An additional seven common variants with allele frequencies >0.05 were identified in the subset of samples from cohort A (525 PD patients, 342 RBD patients, and 825 controls) that underwent targeted NGS of *MAPT*. Logistic regression models, with and without adjustment for age, sex, and population principal components, were performed (Table 1).

Of the 15 common variants (Table 1), seven H2-haplotype variants were in almost full linkage disequilibrium (rs12185268, rs8070723, rs1800547, rs62063786, rs62063787, rs17651549, and rs10445337), all associated with a reduced risk for PD (odds ratios [ORs]: 0.62-0.65; $P = 0.010$-0.019, age, sex, and ethnicity adjusted). The two other H2-haplotye SNPs that were previously reported to be associated with RBD, rs12185268 and rs1800547,[13,14] were not associated with RBD in the current study, nor were any of the other *MAPT* SNPs. In cohort B, rs7521 was nominally associated with DLB-RBD (OR, 1.24; 95% confidence interval [CI]: 1.02-1.52; $P = 0.035$; Supplementary Table 3); however, it was not associated with RBD in cohort A. Burden analysis did not identify association between rare MAPT variants and PD or RBD (see Supplementary file).

Analysis of *MAPT* Haplotypes and Association With Risk for PD and RBD

The H1 haplotype was associated with an increased risk for PD (OR, 1.60; 95% CI: 1.12-2.28; $P = 0.009$), and the H2 haplotype was associated with a reduced risk for PD (OR, 0.68; 95% CI: 0.48-0.96; $P = 0.03$). However, the H1 and H2 haplotype were not associated with RBD both in cohort A of idiopathic RBD patients and in cohort B with DLB-RBD. With the data from the targeted NGS, we demonstrate that the H2 haplotype includes eight coding variants (Supplementary Fig. 2), which are all in full or almost full LD: p.P202L (rs63750417); p.D285N (rs62063786); p.R370W (rs17651549); p.S447P (rs10445337); p.P493P (rs1052551); p.T540T (rs62063845); p.A562A (rs1052553); and p.N590N (rs17652121).

Subsequently, we analyzed the H1 subhaplotypes to determine whether any of them is associated with PD or RBD (Table 2). A total of 20 H1 subhaplotypes with frequency > 0.01 were identified in cohort A, and 16 H1 subhaplotype with frequency > 0.01 were identified in cohort B. Two subhaplotypes, H1J and H1Z, were nominally associated with PD in the unadjusted analysis, but lost significance when adjusted for age, sex, and principal components. Similarly, the H1H and H1O were nominally associated with RBD in cohort A in the unadjusted model (data not shown), but lost significance after the adjustment for age, sex, and principal components. In cohort B, the previously reported DLB-associated haplotype H1G was associated with DLB-RBD (OR, 2.85; 95% CI: 1.30-6.27; $P = 0.009$; Supplementary Table 4). However, it was also associated with DLB without RBD (from cohort B, data not shown), and in cohort A, this haplotype had identical frequencies of 0.011 in RBD patients and controls ($P = 0.78$; Table 2), suggesting that the association is driven by DLB and not by RBD.

Discussion

The current study increases our understanding of the role of *MAPT* haplotypes in PD and RBD by: (1)

TABLE 2. Haplotype analysis of *MAPT* H1 subhaplotypes in PD and RBD patients

		Allele Frequency			PD vs. Control		RBD vs. Control	
Haplotype	Haplotype Structure[a]	PD	RBD	Controls	OR (95% CI)[b]	*P* Value[b]	OR (95% CI)[b]	*P* Value[b]
H2	GAGGGCGG	0.221	0.246	0.259	0.68 (0.47-0.96)	0.030	0.94 (0.63-1.41)	0.768
H1B	AGGAGCAA	0.157	0.133	0.140	1.29 (0.93-1.78)	0.123	1.06 (0.73-1.55)	0.763
H1C	AAAAGTAG	0.084	0.082	0.084	1.31 (0.88-1.95)	0.184	1.23 (0.76-1.99)	0.401
H1D	AAAAGCAA	0.056	0.067	0.065	0.85 (0.50-1.45)	0.553	0.98 (0.55-1.73)	0.931
H1E	AAGAGCAA	0.123	0.110	0.111	0.89 (0.60-1.33)	0.566	0.91 (0.56-1.49)	0.713
H1F	AGGAACAA	0.016	0.014	0.019	0.50 (0.17-1.49)	0.213	0.56 (0.16-1.89)	0.347
H1G	AGAAACAA	0.013	0.011	0.011	2.85 (0.84-9.72)	0.094	0.76 (0.11-5.12)	0.779
H1H	AAGAACAA	0.055	0.066	0.048	0.88 (0.52-1.50)	0.649	0.96 (0.52-1.79)	0.905
H1I	AGAAGCAA	0.030	0.036	0.039	0.66 (0.33-1.32)	0.238	0.65 (0.28-1.49)	0.309
H1J	AAGAGCAG	0.027	0.026	0.017	2.27 (0.87-5.91)	0.093	2.16 (0.65-7.20)	0.210
H1L	AAGAACAG	0.011	0.014	0.013	0.59 (0.21-1.68)	0.321	0.43 (0.11-1.68)	0.223
H1M	AGAAGCAG	0.021	0.023	0.028	0.48 (0.19-1.23)	0.125	0.35 (0.11-1.12)	0.077
H1O	AAAAACAA	0.010	0.021	0.013	0.71 (0.13-3.81)	0.685	1.56 (0.38-6.36)	0.535
H1P	AGGAGTAG	0.018	0.015	0.015	2.10 (0.69-6.39)	0.191	2.54 (0.71-9.04)	0.150
H1Q	AAAAGTAA	0.015	0.017	0.016	0.63 (0.21-1.87)	0.401	0.82 (0.29-2.28)	0.699
H1U	AAAAGCAG	0.040	0.040	0.035	1.70 (0.89-3.26)	0.111	1.48 (0.66-3.31)	0.341
H1V	AGGAATAG	0.014	0.011	0.016	1.38 (0.50-3.78)	0.531	0.88 (0.22-3.57)	0.857
H1W	AGGAGCAG	0.018	0.017	0.019	0.80 (0.27-2.37)	0.688	1.11 (0.32-3.83)	0.869
H1X	AGAAATAG	0.017	0.010	0.014	0.74 (0.23-2.34)	0.602	0.78 (0.20-3.12)	0.730
H1y	AAAAATAG	0.011	0.015	0.011	1.45 (0.40-5.23)	0.570	1.15 (0.28-4.71)	0.846
H1Z	AGAAGTAG	0.045	0.028	0.030	1.72 (0.85-3.48)	0.132	0.94 (0.39-2.31)	0.899

[a]Eight SNPs defining the haplotypes are given in the 5' to 3' order as follows: rs12185628, rs1467967, rs242557, rs1800547, rs3785883, rs2471738, rs8070723, and rs7521.
[b]Adjusted for age, sex, and the two major components in the population stratification PCA.

We confirm the association between *MAPT* H1/H2 haplotypes in PD, with an increased risk for H1 and decreased risk for H2. (2) *MAPT* is not associated with RBD, which provides further evidence for RBD having a different genetic background than PD, at least partially. (c) Our targeted NGS analysis defines the H2 haplotype, including several coding *MAPT* variants (nonsynonymous and synonymous, Supplementary Figure 2), although probably not expressed in the central nervous system (CNS).[16]

The lack of association of *MAPT* with RBD suggests that RBD has a genetic background that does not fully overlap with that of PD. Whereas *GBA* mutations are associated with both PD and RBD,[17-19] previous studies had demonstrated that *LRRK2* pathogenic mutations that may cause PD are not associated with RBD,[20,21] and that PD patients with *LRRK2* mutations had little or no RBD.[22,23] In addition, the *APOE* ε4 haplotype, which is strongly associated with Alzheimer's disease and DLB, was also not associated with RBD.[24] Therefore, RBD may represent a subtype of synucleinopathy with its own genetic background, but this hypothesis should be tested in larger cohorts by using whole-genome methods. Whether these genetic associations and lack thereof suggest lack of role for tauopathy in RBD should be examined by pathological studies of PD and DLB patients with and without RBD, as well as in idiopathic RBD.

The association of the H1/H2 haplotypes with PD is well defined across various populations.[2,10,11] Because this haplotype includes multiple, potentially regulatory noncoding variants, as well as coding synonymous and nonsynonymous variants, these data alone do not allow us to identify the specific variant that affects the risk within this haplotype. Exons 4a and 6, in which the nonsynonymous variants are found, are thought to not be expressed in the CNS.[16] However, because the peripheral nervous system is involved early at the course of PD, and may even be where PD begins, we cannot rule out a role for these variants in PD.[25]

The current study has several limitations. The differences in age and sex of patients and controls can potentially bias results of age-related effects of genetic factors. However, we accounted for this potential bias by adjusting for both in the regression models. Similarly, there could be an effect of the different European populations; therefore, we further adjusted for the two top principal components of ethnicity as detected by PCA. Another potential limitation is the study size, despite being the largest genetic study on RBD, to the best of our knowledge. It is still possible that an association could only be observed in a larger cohort of patients and controls. Therefore, subsequent, larger studies are needed to further examine this association.

Overall, our data confirm the association of *MAPT* with PD, and suggest that *MAPT* genetic variants have

minor or no role in RBD. Further studies are needed to replicate these results, and to examine the specific effects of variants within the H2 haplotype, but also other haplotypes, on PD risk and mechanism. ■

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