Background: Dementia in Parkinson disease (PD) causes nursing home placement, caregiver distress, higher health care burden, and increased mortality.

Objective: To determine whether the microtubule-associated protein tau (MAPT) H1 haplotype and MAPT subhaplotypes play a role in the risk of PD and Parkinson disease–dementia (PDD) complex.

Design: Case-control genetic analysis.

Setting: Movement Disorders and Memory Units, Hospital de Sant Pau, Barcelona, Spain.

Participants: Two hundred two patients with PD (48 of whom developed dementia >2 years after disease onset), 41 patients with Lewy body dementia (LBD, pathologically confirmed in 17), 164 patients with Alzheimer disease (AD), and 374 controls.

Methods: The MAPT haplotype was determined by testing for a 238-base pair deletion between exons 9 and 10, which is characteristic of the H2 haplotype. Haploview was used to visualize linkage disequilibrium relationships between all genetic variants (5 single-nucleotide polymorphisms and the del-In9 variant) within and surrounding the MAPT region.

Results: The H1 haplotype was significantly overrepresented in PD patients compared with controls (P = .001). Stratifying the PD sample by the presence of dementia revealed a stronger association in PDD patients (sex- and age-adjusted odds ratio, 3.73; P = .002) than in PD patients without dementia (sex- and age-adjusted odds ratio, 1.89; P = .04). Examination of specific subhaplotypes showed that a rare version of the H1 haplotype (named H1p) was overrepresented in PDD patients compared with controls (2.3% vs 0.1%; P = .003). No positive signals for any of the MAPT variants or H1 subhaplotypes were found in AD or LBD.

Conclusions: Our data confirm that MAPT H1 is associated with PD and has a strong influence on the risk of dementia in PD patients. Our results also suggest that none of the MAPT subhaplotypes play a significant role in other neurodegenerative diseases, such as LBD or AD.

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One of the most common nonmotor symptoms in Parkinson disease (PD) is the co-occurrence of dementia, with a mean prevalence of 30%. Dementia in PD is an important cause for nursing home placement, caregiver distress, higher health care burden, and increased mortality. The combination of dementia and parkinsonism is also a key feature that characterizes dementia with Lewy bodies (LBD), the second most common cause of neurodegenerative dementia in the elderly after Alzheimer disease (AD). A recent genome-wide association study has provided unequivocal evidence for a genetic association of the microtubule-associated protein tau (MAPT) (GenBank NG_007398.1 and OMIM 157140) locus with PD in the population with European origin. However, these results were not replicated in an independent genome-wide association study performed in an Asian population. With up to 21 studies performed to date, MAPT seems to be undoubtedly associated with PD risk (http://www.pdgene.org). In particular, the MAPT H1 variant, an extended haplotype that results from a common genomic inversion of approximately 800 kb in chromosome 17q21 containing the MAPT gene, has been found to be related to PD risk. Interestingly, the H1 variant has also been associated with cognitive decline in a longitudinal study of PD with a 3½-year follow-up. In a subsequent study by some of the same authors, the MAPT H1 allele was the strongest independent predictor of dementia among PD patients, with an
odds ratio (OR) of 12.1 during 5 years of follow-up.\textsuperscript{15} Research addressing the effect of MAPT in other neurodegenerative disorders, such as AD, has yielded inconclusive results.\textsuperscript{16-19} A fine-mapping study of the MAPT H1/H2 clades described the H1c subhaplotype, a version of the H1 haplotype, to be the specific variant associated with AD risk.\textsuperscript{18} However, this association has been inconsistently found in subsequent studies.\textsuperscript{20,21} The specific MAPT subhaplotype linked to PD, Parkinson disease–dementia (PDD) complex, or LBD remains unknown.

Therefore, in this study, we sought to determine whether MAPT H1/H2 is associated with PD and whether it influences the occurrence of dementia during the PD clinical course. We also checked whether variability in the H1 background, ie, specific variants of the H1 clade, could lead to PD and PDD. To assess the role of the MAPT gene in other neurodegenerative diseases, we explored MAPT genetic variability in LBD and AD patients from a well-defined clinical and pathologic series from the north of Spain.

**METHODS**

**SUBJECTS**

A total of 390 unrelated patients were prospectively recruited from the outpatient Movement Disorders and Memory Units at the Hospital de Sant Pau, Barcelona. All patients were examined by neurologists with expertise in neurodegenerative diseases. A total of 202 patients fulfilled the diagnostic criteria described by Hughes et al\textsuperscript{22} for idiopathic PD and were prospectively recruited from among outpatients regularly attending the Movement Disorders Unit. Motor symptoms and disease severity were assessed in accordance with the Unified Parkinson's Disease Rating Scale (UPDRS)\textsuperscript{23} and the Hoehn and Yahr scale.\textsuperscript{24} Of the total group of PD patients, 48 fulfilled current diagnostic criteria for probable PDD.\textsuperscript{25} Diagnosis of dementia was based on a score of 1 or more on the Clinical Dementia Rating scale and fulfillment of the 294.1 criteria for PDD in the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision). Patients with PD without any cognitive decline were classified as the PDD group (n = 154).

Twenty-four patients with current consensus diagnostic criteria for LBD were included.\textsuperscript{26} In accordance with published research criteria, we used the 1-year rule to distinguish between PDD and LBD.\textsuperscript{27} We also included 17 patients with neuropathologically confirmed LBD. Brain tissue was provided by the Neurological Tissue Bank, Hospital Clinic de Barcelona at the University of Barcelona. Neuropathologic staging of Lewy body–related pathology was performed in accordance with proposed diagnostic criteria for LBD\textsuperscript{28} and PD-related pathology.\textsuperscript{29} We assessed AD–related pathology according to Alafuzoff et al\textsuperscript{30} and Braak et al\textsuperscript{31} for neurofibrillary pathology, according to the Consortium to Establish a Registry for Alzheimer's Disease criteria for neuritic plaque density,\textsuperscript{32} and according to the National Institute of Aging/Reagan Institute Consensus recommendations for the postmortem diagnosis of AD. We used consensus recommendations to estimate the likelihood that AD lesions underlie dementia.\textsuperscript{33} In order to include only those patients whose death was most likely due to LBD, we assessed Lewy bodies and AD pathology in accordance with McKeith et al's recommendations.\textsuperscript{32}

A total of 164 patients fulfilled clinical diagnostic criteria for possible or probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association criteria for AD.\textsuperscript{33}

We recruited 374 unrelated controls from the Department of Neurology at Hospital Universitario Marqués de Valdecilla (Santander, Spain). All had complete neurologic and medical examination findings that showed they were free of significant illness. They also had Mini-Mental State Examination scores of 28 or higher (corrected for age), verified by at least 1 annual follow-up assessment. Although we did not perform a formal screening process regarding patients' descent from the data available concerning their origin (name and place of birth), it was deduced that all were of European ancestry.

All participants or their families provided written informed consent, and the study was approved by the respective ethics committees.

**GENOTYPING**

The MAPT haplotype was determined by testing for the presence of a 238–base pair deletion between exons 9 and 10, which is characteristic of the H2 haplotype.\textsuperscript{34} Genotyping of the surrounding tagging single-nucleotide polymorphisms (SNPs) rs1467967, rs242557, rs3785883, rs2471738, and rs7521, within the 17q21 region, was conducted by Taqman Assays-on-Demand on the ABI PRISM 7900HT Sequence Detection System (Applied Biosystems, Foster City, California), followed by analysis with SDS 7500 software, version 2.0.1 (Applied Biosystems, Carlsbad, California).

**STATISTICAL ANALYSIS**

Hardy-Weinberg equilibrium was assessed by the \(\chi^2\) test. Haplowiev was used to visualize linkage disequilibrium relationships between all genetic variants (3 SNPs and the del-In9 variant) within and surrounding the MAPT region.\textsuperscript{35} Linkage disequilibrium blocks were constructed following the D' method by Gabriel et al,\textsuperscript{36} also implemented in Haploviev. Genotype and allele frequencies were estimated by direct counting and were compared between patients and controls by means of \(\chi^2\) analysis with 1 degree of freedom. Multiple logistic regression models were used to adjust for covariants, such as age and sex. Data were analyzed using the Statistical Package for the Social Sciences, version 17.0.0 (SPSS Inc, Chicago, Illinois). Haplotypes were reconstructed and population frequencies were estimated using the program PHASE, version 2.1 (Matthew Stephens Lab, Chicago, Illinois).\textsuperscript{37} Global differences in haplotype frequencies between controls and cases were assessed using 1000 permutations for each comparison. Individual haplotype frequency differences were assessed by haplotype trend regression analysis,\textsuperscript{38} with 10 000 permutations. Haplotype-specific score statistics adjusted for age and sex were assessed with the \(R\) package Haplo.score,\textsuperscript{39} with 10 000 simulations for each empirical \(P\) value. The \(t\) test was performed to compare means between groups.

A total of 390 patients (comprising PD, AD, and LBD patients) and 374 controls were recruited (Table 1 for sample details). Of the 202 PD patients, 48 developed dementia (PDD subgroup) and 154 remained free of dementia (PDnD subgroup). The mean (SD) interval from PD onset to dementia was 11.3 (7.1) years, ranging from 2 to 30 years. Therefore, none of the PDD patients included in our series developed dementia within 2 years of PD onset. The mean (SD) age of dementia onset was 74.3 (7.0) years. Comparison of clinical characteristics
Table 1. Demographic and Clinical Characteristics of Patients and Controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controls (n=374)</th>
<th>PD (n=202)</th>
<th>PDnD (n=154)</th>
<th>PDD (n=48)</th>
<th>LBD (n=24)</th>
<th>AD (n=164)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, No. (%)</td>
<td>119 (31.8)</td>
<td>109 (53.9)</td>
<td>79 (51.3)</td>
<td>30 (62.5)</td>
<td>15 (62.5)</td>
<td>50 (30.5)</td>
</tr>
<tr>
<td>Age, mean (SD) [range], y</td>
<td>81.3 (6.9) [65-99]</td>
<td>58.1 (10.8) [40-84]</td>
<td>56.6 (10.3) [40-84]</td>
<td>63.0 (11.2) [40-84]</td>
<td>74.5 (7.2) [61-89]</td>
<td>77.0 (5.5) [65-89]</td>
</tr>
<tr>
<td>Disease duration, mean (SD) [range], y</td>
<td>NA</td>
<td>11.8 (6.4) [1-31]</td>
<td>11.2 (5.9) [1-27]</td>
<td>13.5 (7.4) [3-31]</td>
<td>5.0 (1.7) [3-10]</td>
<td>3.1 (2.4) [1-18]</td>
</tr>
<tr>
<td>UPDRS-III score, mean (SD)</td>
<td>NA</td>
<td>29.5 (13.1)</td>
<td>27.1 (12.7)</td>
<td>37.2 (11.3)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hoenh and Yahr scale score, mean (SD)</td>
<td>NA</td>
<td>2.66 (0.94)</td>
<td>2.4 (0.86)</td>
<td>3.4 (0.85)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; LBD, Lewy body dementia; NA, not applicable; PD, Parkinson disease; PDD, Parkinson disease–dementia; PDnD, Parkinson disease without any cognitive decline. Patients with neuropsychologically confirmed diagnosis were not included.

Table 2. Single-Locus Association

<table>
<thead>
<tr>
<th>Variant</th>
<th>Location in MAPT</th>
<th>Major Allele</th>
<th>PD (P Value) OR (95% CI)</th>
<th>PDnD (P Value) OR (95% CI)</th>
<th>PDD (P Value) OR (95% CI)</th>
<th>Controls (n=374)</th>
<th>PD (n=202)</th>
<th>PDnD (n=154)</th>
<th>PDD (n=48)</th>
<th>LBD (n=24)</th>
<th>AD (n=164)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs1467967</td>
<td>5’ Exon1</td>
<td>A</td>
<td>0.71 (0.54-0.92)</td>
<td>0.77 (0.57-1.03)</td>
<td>0.54 (0.34-0.85)</td>
<td>1.13 (0.69-2.11)</td>
<td>0.89 (0.66-1.19)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>rs242557</td>
<td>5’ Exon1</td>
<td>G</td>
<td>63.8 (0.17)</td>
<td>71.2 (0.50)</td>
<td>63.0 (0.44)</td>
<td>66.0 (0.53)</td>
<td>66.0 (0.53)</td>
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</tr>
<tr>
<td>rs3785883</td>
<td>Intron 3</td>
<td>G</td>
<td>78.9</td>
<td>52.9 (0.15)</td>
<td>78.4 (0.91)</td>
<td>80.8 (0.49)</td>
<td>80.8 (0.49)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>rs2471738</td>
<td>Intron 9</td>
<td>C</td>
<td>1.21 (0.89-1.66)</td>
<td>1.48 (1.04-2.12)</td>
<td>0.69 (0.42-1.14)</td>
<td>1.01 (0.95-1.06)</td>
<td>1.12 (0.81-1.56)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>del-In9</td>
<td>Intron 9</td>
<td>H1</td>
<td>1.57 (1.21-3.00)</td>
<td>1.38 (1.02-1.86)</td>
<td>2.69 (1.47-4.95)</td>
<td>1.07 (0.64-1.81)</td>
<td>1.10 (0.83-1.47)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs7521</td>
<td>3’ Exon 14</td>
<td>G</td>
<td>56.9</td>
<td>54.6 (0.46)</td>
<td>57.2 (0.93)</td>
<td>45.3 (0.34)</td>
<td>61.8 (0.41)</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; CI, confidence interval; CO, controls; LBD, Lewy body dementia; MAPT, microtubule-associated protein tau; OR, odds ratio; PD, Parkinson disease; PDD, Parkinson disease–dementia; PDnD, Parkinson disease without any cognitive decline.

between PDnD and PDD patients revealed that disease duration was longer in PDD patients (13.5 years in PD patients vs 11.2 years in PDnD patients; P = .03). Also, age of onset was lower in PD patients compared with PDnD patients (63.0 vs 56.6 years; P < .001). Finally, total UPDRS motor score and Hoehn and Yahr scale scores were higher in PD patients compared with scores in PDnD patients (37.2 vs 27.1 for the UPDRS; P < .001; and 3.4 vs 2.4 for the Hoehn and Yahr scale; P < .001). No differences in sex were found between PD patients with and without dementia.

Genotype frequencies did not differ significantly from the predictions of the Hardy-Weinberg equilibrium in controls. Single-locus analysis of the genetic variants analyzed within the MAPT region disclosed a highly significant overrepresentation of the H1 allele in the entire PD group (comprising both PDD and PDnD) compared with controls (P = .002) (Table 2). Interestingly, although this association remained significant in both subgroups of PD patients, the effect was greater in PDD patients than in PDnD patients (OR, 2.69, 95% confidence interval [CI], 1.47-4.95; P = .001 in the PDD subgroup; and OR, 1.38; 95% CI, 1.02-1.86; P = .04 in the PDnD subgroup). Because PDD patients were not age- and sex-matched with controls, we performed a logistic regression analysis adjusting the H1 risk for these 2 variables. Again, although the H1-adjusted effect persisted in the overall PD group (OR, 2.47; 95% CI, 1.44-4.22; P = .001), the risk-adjusted H1 for the PD subgroup was twice that for the PDnD subgroup (OR, 3.73; 95% CI, 1.64-8.46; P = .002 in the PDnD subgroup; and OR, 1.89; 95% CI, 1.03-3.47; P = .04 in the PDnD subgroup).

When we focused on other SNPs surrounding the H1/H2 allele, a protective effect was detected for the H1 allele on both the PD risk (P = .01) and the PDD risk (P = .007) (Table 2). This polymorphism did not have any effect on the PDnD group. Only 1 SNP (rs3785883) was marginally significant in the PDnD group compared with controls (P = .04). None of the 6 variants analyzed within the MAPT region had any role in either LBD or AD risk.

To refine the association found between PD and the MAPT del-In9 variation and to assess whether any of the H1 subclades could be influencing LBD or AD risk, we performed a haplotype association study comparing the predictions of the Hardy-Weinberg equilibrium in controls.
of patients and controls (Table 3). Linkage disequilibrium analysis between the aforementioned polymorphisms produced a D’ plot that was very similar to the pattern already described for other populations with European origin (Figure). Significant overall differences were found in haplotype frequencies between the 2 subgroups of PD patients and controls (overall PD, \(P = .01\); PDnD, \(P = .002\); and PDD, \(P = .01\)) (Table 3). Haplotype H2a, which derives from the del-In9 variant and defines the H2 haplotype, was significantly underrepresented in both PD and PDD groups compared with the controls. However, the most striking difference was found within the PDD group (27.2% in controls vs 20.5% in overall PD and 12.5% in PDD). These data suggest that MAPT haplotype differences between the total PD group and the controls were due mainly to the lower H2a frequency in the PDD subgroup. The haplotype-specific score adjusted for age and sex related to H2a for the PDD group was −2.86 (simulated \(P = .004\); data not shown). This negative score strongly indicates a protective effect of the H2a haplotype on PDD. None of the other common subhaplotypes (haplotypes H1b to H1e, with frequencies >5%) differed between PD patients and controls. Surprisingly, detailed analyses of uncommon haplotypes (haplotypes H1f to H1w) showed an overrepresentation of the H1p haplotype in the PDD group compared with its representation in controls (2.3% vs 0.1%; \(P = .003\)).

We did not find any association between MAPT subhaplotypes in either AD or LBD. The MAPT association remained negative when the LBD sample was stratified into pathologic and clinical diagnoses (data not shown).

This study supports previous evidence that the MAPT H1 haplotype is associated with PD and furthers our understanding of its role in PDD. Our data augment the findings of recent studies indicating that the MAPT genotype has a clear effect on the development of dementia among PD patients. The mechanism linking MAPT variants and dementia in PD remains unknown. However, several lines of evidence support the biologic basis of this association. First, mutations in MAPT lead to frontotemporal dementia with parkinsonism linked to chromosome 17q21; second, atypical parkinsonian syndromes, such as progressive supranuclear palsy and corticobasal degeneration, both accompanied with a progressive cognitive decline leading to dementia, have been consistently associated with the MAPT H1 haplotype; third, tau and α-synuclein, the pathologic hallmark of PD, can interact and fibrillize synergistically in vitro; and fourth, tau and α-synuclein are known to colocalize in brains with Lewy body pathology.
To our knowledge, our study represents the first comprehensive analysis of MAPT subhaplotypes and their role in PD, PDD, and LBD. We found a striking protective effect between the H2a subhaplotype and the risk of PDD. Interestingly, when we investigated uncommon subhaplotypes, we found that up to 2% of PDD chromosomes had the H1p haplotype, whereas only 0.1% of control chromosomes carried this variant. This is pivotal because it refines the MAPT association and delineates the specific variant that could be related to the disease. There is a clinical and pathologic overlap between PDD and LBD, and current criteria use the timing of the onset of cognitive symptoms in relation to motor symptoms to differentiate the 2 entities: 1 year or less defines LBD and more than 1 year defines PDD.25,46 Therefore, the question arises as to whether PD, LBD, and PDD are different stages along the continuum of a single disorder with a common biologic substrate or whether they represent separate clinical entities with different genetic backgrounds. Our data suggest that LBD and PDD could be related to distinct genetic factors because we found no hints of association between MAPT and LBD. Although to our knowledge this is the first study to assess the role of MAPT in LBD risk, our negative results should be interpreted with caution in view of the low sample size.

We were unable to replicate previous associations between the H1c subhaplotype and the risk of AD.18 One explanation for these conflicting data may be related to differences in participants’ origin (the cohort in the study by Myers et al18 were from the United Kingdom and the United States). However, samples in both studies share European ancestry and haplotype frequencies (9% for the H1c haplotype in the Myers et al cohort and 7.4% in our cohort). It is therefore unlikely that the discrepancies between the 2 studies can be attributed to geographic factors.

One limitation of our study is that controls were not age- and sex-matched with our PD and LBD cohorts. However, in view of their age and good cognitive status, we presume our control cohort has genetic protective factors that prevented the development of neurodegenerative disorders. Another limitation is lack of definite neuropathologic diagnoses in most of our samples. However, because all patients were evaluated by neurologists highly specialized in movement disorders or dementia, a low rate of misdiagnosis could be expected.

Of the 6 variants analyzed in the present study, rs1467967 was the second most important genetic variant associated with PDD after the H1 polymorphism. Interestingly, it is located at the most 5’ region of the gene, relatively close to the transcription regulation region. Although it is unlikely that this association is due to a direct functional consequence of this SNP, the most plausible explanation would be that this polymorphism may be in linkage disequilibrium with another functional variant within the 5’ genomic region of the MAPT gene. Therefore, regardless of the exact mechanism underlying the association between this variant and PDD, genetic variability in the expression of tau protein likely increases the risk of developing dementia in PD. Determining precisely which element of the MAPT locus is responsible for the association will be difficult because of the strong and extensive linkage disequilibrium across this genomic region.

The present analyses also replicate previous clinical data that reported higher age and more severe symptoms to be major risk factors for the development of dementia related to PD.47 In summary, our data confirm that the MAPT H1 haplotype plays a significant role in PD patients’ predisposition to developing dementia and strongly suggest that the rs1467967 variant and the H1p subhaplotype could contribute to PDD. This genetic finding, combined with appropriate clinical assessments such as specific neuropsychologic tests,48 may have implications in the early identification of subgroups of PD patients with a high risk of dementia. This knowledge would therefore be an invaluable help in the selection of patients who could benefit from future therapeutic trials aimed at improving or slowing the progression of cognitive impairment in PD.

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