MAPT H1 Haplotype is Associated with Late-Onset Alzheimer’s Disease Risk in APOE ε4 Noncarriers: Results from the Dementia Genetics Spanish Consortium

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Abstract. The MAPT H1 haplotype has been linked to several disorders, but its relationship with Alzheimer’s disease (AD) remains controversial. A rare variant in MAPT (p.A152T) has been linked with frontotemporal dementia (FTD) and AD. We genotyped H1/H2 and p.A152T MAPT in 11,572 subjects from Spain (4,327 AD, 563 FTD, 648 Parkinson’s disease (PD), 84 progressive supranuclear palsy (PSP), and 5,950 healthy controls). Additionally, we included 101 individuals from 21 families with genetic FTD. MAPT p.A152T was borderline significantly associated with FTD [odds ratio (OR) = 2.03; \( p = 0.063 \)], but not with AD. MAPT H1 haplotype was associated with AD risk (OR = 1.12; \( p = 0.0005 \)). Stratification analysis showed that this association was mainly driven by APOE/\( \epsilon^4 \) noncarriers (OR = 1.14; \( p = 0.0025 \)). MAPT H1 was also associated with risk for PD (OR = 1.30; \( p = 0.0003 \)) and PSP (OR = 3.18; \( p = 8.59 \times 10^{-8} \)) but not FTD. Our results suggest that the MAPT H1 haplotype increases the risk of PD, PSP, and non-APOE/\( \epsilon^4 \) AD.

Keywords: A152T, Alzheimer’s disease, frontotemporal dementia, genetic association, H1H2, MAPT

INTRODUCTION

Tau protein plays an essential role in the central nervous system by promoting microtubule assembly and stability in neuronal cells. Neurofibrillary tangles composed of truncated and hyperphosphorylated tau proteins are one of the hallmarks of Alzheimer’s disease (AD) pathology [1]. Neurofibrillary tangles are also present in a substantial subgroup of frontotemporal dementia patients (FTD), and in other FTD-spectrum tauopathies, such as progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). Tau deposits also colocalize with alpha-synuclein in Lewy bodies of Parkinson’s disease (PD) patients [1–4].

Tau protein is encoded by the MAPT gene (MAPT: OMIM: *157140), located at chromosome 17q21-22. There are two common MAPT extended haplotypes in Caucasians resulting from an ancestral inversion: H1 and H2. The H1 haplotype has been linked with sporadic and familial neurodegenerative disorders like PSP [5–8], CBD [9], FTD [10], PD [11–13], and inconsistently with AD [14]. In fact, the last AlzGene meta-analysis including case-control data showed no significant association between MAPT H1 haplotype and AD [15] and, so far, available genome-wide association study found no MAPT risk variants in AD subjects [16], and only very recently the IGAP consortium has found a significant association with AD near MAPT in subjects not carrying APOE/\( \epsilon^4 \) [17].

Mutations in MAPT have been identified in familial FTD syndromes [18–24]; however, the role of rare genetic MAPT variants in sporadic neurodegenerative diseases is not well established. More recently, a rare variation in MAPT exon 7 (p.A152T) has been linked to both sporadic FTD and AD risk [25–27]; however, to date, p.A152T association has not been replicated in large independent populations.
In the present study, we assessed the risk effect of the rare variant MAPT p.A152T and the common extended MAPT H1/H2 haplotypes in a large series of participants with sporadic and genetic neurodegenerative disorders from Spain.

**MATERIALS AND METHODS**

**Ethics statement**

A signed informed consent to participate in genetic research was obtained from all participants or patients’ relatives. The study protocols were approved by local ethical committees.

**Study subjects**

A total of 4,327 AD patients (mean age at onset 76.5 ± 9.3 years, 69.0% women), 563 FTD patients (mean age at onset 64.2 ± 10.3 years, 45.3% women), and 5,950 healthy controls (mean age at clinical assessment 64.1 ± 14.8 years, 62.1% women) were included through a collaborative effort involving 11 specialized centers across Spain belonging to the Dementia Genetics Spanish Consortium (DEGESCO). Additionally, we studied 21 families (101 individuals) with different genetic FTD mutations belonging to the Biodonostia Center (San Sebastian; Basque Country, Spain).

All individuals were Spanish and of European origin. Patients were diagnosed using established clinical research criteria for AD [28], FTD [29], PSP [30], or PD [31]. The familial FTD sample included 15 families (n=90 individuals) with a progranulin mutation (GRN IVS6-1G>A) that has only been reported in the Basque Country. The phenotypic profile associated with this mutation has been described elsewhere [32]. Additionally, we included six families with other FTD gene mutations: three families with the C9orf72 repeat expansion and three families with GRN mutations in Cys139Arg, Arg177His, and Pro357fs.

**Genotyping**

Genotyping of MAPT p.A152T (rs143624519) and H1/H2 (rs1800547) variants was performed in four centers using TaqMan SNP Genotyping Assays (Applied Biosystems, Foster City, CA). To minimize genotyping errors, a human DNA sample validated by Sanger sequencing, carrying the rare A-allele (rs143624519-A) or H1/H2 in a heterozygous state was distributed to all genotyping centers to be included as a positive control in all genotyping plates.

**Statistical analysis**

Allelic and genotypic frequencies were compared using χ² statistics. Adjusted analyses were performed using multiple logistic regression. Age, gender, and APOE e4 status were included in the model as covariates. Allelic frequencies, HWE analysis, and pair-wise LD D’ and r² measurements were calculated using Haploview software [34]. Univariate and multivariate genotype assessments were performed using SPSS software version 19 (SPSS Inc., Chicago, IL). The student’s T test was performed to analyze the effect of MAPT p.A152T on age of disease onset. Power calculations were performed with PS software (version 2.1.30).

**RESULTS**

No deviation from Hardy Weinberg equilibrium (Pearson’s Chi-Square) was found in controls for both studied variants (p=0.78 for MAPT p.A152T and p=0.86 for MAPT H1/H2).

**Role of p.A152T in sporadic neurodegenerative diseases**

We found that 0.97% of AD, 1.42% of FTD, and 0.77% of patients with PD carried the MAPT p.A152T variant compared to 0.71% of controls. None of the PSP patients carried MAPT p.A152T. Comparing AD versus controls and PD versus controls for the variant showed no statistical difference between groups (Table 1). MAPT p.A152T frequency among FTD was double compared to controls showing a trend toward significance (OR = 2.03; 95% CI = 0.95–4.34; p = 0.06). Differences remained non-significant when

<table>
<thead>
<tr>
<th>Group</th>
<th>MAPT p.A152T carriers (%)</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD (n=4,327)</td>
<td>42 (0.97)</td>
<td>1.38 (0.90–2.20)</td>
<td>0.20</td>
</tr>
<tr>
<td>FTD (n=567)</td>
<td>8 (1.42)</td>
<td>3.03 (0.95–4.34)</td>
<td>0.05</td>
</tr>
<tr>
<td>PSP (n=648)</td>
<td>0 (0.01)</td>
<td>0.99 (0.43–2.17)</td>
<td>ref</td>
</tr>
<tr>
<td>PD (n=648)</td>
<td>0 (0.01)</td>
<td>0.98 (0.43–2.17)</td>
<td>ref</td>
</tr>
<tr>
<td>Controls (n=5,950)</td>
<td>42 (0.71)</td>
<td>1.09 (0.43–2.77)</td>
<td>ref</td>
</tr>
</tbody>
</table>

Table 1 MAPT p.A152T frequencies across groups
we adjusted these tests by age and gender in the entire sample, and for APOE e4 status in the AD group. Age of symptom onset was not modified by MAPT p.A152T for AD or FTD.

Role of p.A152T in genetic FTD

We found that MAPT p.A152T co-segregated, completely or partially, with GRN IVS6-1G>A, an intronic mutation carried by 15 FTD families from the Basque Country. MAPT p.A152T was also present in eight families, co-segregating in 70.5% of GRN IVS6-1G>A mutation carriers (Table 2). Linkage disequilibrium (LD) analysis in the families disclosed that p.A152T and GRN, both located in chromosome 17, were in partial LD (D' = 0.78; r2 = 0.46). At the time of this study, none of the four MAPT p.A152T carriers negative for GRN IVS6-1G>A harbored a history of neurodegenerative or psychiatric disease: one individual passed away at 86 years of age, two other individuals remain healthy at 80 and 86 years of age, and the fourth individual is 52 years old who remains asymptomatic. Age of symptom onset was not associated with the MAPT p.A152T genetic variant in GRN IVS6-1G>A mutation carriers; mean age at onset was 60.9 ± 7.5 years in p.A152T-carriers and 61.4 ± 9.2 years in noncarriers (p = 0.87). We found no MAPT p.A152T carriers in three families with other GRN mutations (Cys139Arg, Arg177His, and Pro357Ile), nor families with the CHRNA7 expansion. Sanger sequencing of GRN in 97 MAPT p.A152T carriers from all participant centers did not reveal GRN mutations.

Role of APOE e4 status and MAPT H1/H2 haplotype in neurodegenerative diseases

APOE e4 status did not change the effect of MAPT p.A152T on AD risk. Table 3 shows the allelic and genotypic frequency distribution of the SNP rs1800547 tagging the MAPT H1/H2 haplotype. We found a statistically significant overrepresentation of MAPT H1 haplotype, present in 72.1% of AD compared to 69.8% of controls (p = 0.0085). When we stratified the sample by APOE e4 status, the association of H1 haplotype was driven by noncarriers of APOE e4 (p = 0.0025) (Table 3) and older subjects (genotype trend p = 0.005) (Fig. 1). As described for other European series, we also found a highly significant association between MAPT H1 and PD (OR = 1.30, 95% CI = 1.13–1.50; p = 0.0003) and PSP (OR = 3.18, 95% CI = 2.03–4.97; p = 8.59 × 10−5). FTD risk was not associated with the MAPT haplotype (p = 0.40).

DISCUSSION

In our first analysis, we tested whether the MAPT p.A152T rare genetic variant was associated with risk for various neurodegenerative diseases (AD, FTD, PSP, and PD). We found that MAPT p.A152T occurs more frequently in Spanish patients with neurodegenerative disease compared with the study by Coppola et al. [25], whose cohort was primarily comprised of the US population (AD:0.97% versus 0.69%; FTD: 1.42% versus 0.89% and PD: 0.77% versus 0.48% respectively). Because the frequency of MAPT p.A152T was also significantly higher in our healthy controls than the healthy control cohort of Coppola et al. (0.71% versus 0.30%, respectively) [25], the association between AD risk and MAPT p.A152T was not significant in our population. Although our OR for AD risk associating with p.A152T occurred in same direction as in the previous study [25], our OR was considerably lower and thus did not reach statistical significance (OR =1.4; 95% CI = 0.9–2.1 versus OR = 2.3; 95% CI = 1.3–4.2, respectively). Similarly, the OR we obtained for p.A152T in FTD risk trended toward significance, but was also lower than the OR for FTD risk in the previous study (OR = 2.0; 95% CI = 0.9–4.3 versus OR = 3.0; 95% CI = 1.6–5.6, respectively) [25].

Several factors may explain the lack of replication of previous results. Rare genetic variant frequencies can differ across populations, and MAPT p.A152T appears to occur more frequently in the general Spanish population than in the US. Another consideration is that the real ORs for diseases associated with the variant may be lower than the ORs in the discovery cohort due to the “winner’s curse” effect, a common phenomenon observed in pioneer genetic epidemiological studies [35]. Another potential influence on the difference

<table>
<thead>
<tr>
<th>Table 2</th>
<th>MAPT p.A152T in individuals belonging to 15 families with PGR IVS6-1G mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic (n)</td>
<td>Asymptomatic (n)</td>
</tr>
<tr>
<td>PGR+/A152T+</td>
<td>22</td>
</tr>
<tr>
<td>PGR+/A152T−</td>
<td>10</td>
</tr>
<tr>
<td>PGR−/A152T+</td>
<td>0</td>
</tr>
<tr>
<td>PGR−/A152T−</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
</tr>
</tbody>
</table>

PGR+, carrier individual of PGR IVS6-1G+ mutation; PGR−, noncarrier individual of PGR IVS6-1G mutation; A152T+, carrier individual of MAPT p.A152T variant; A152T−, noncarrier individual of MAPT p.A152T variant.
A surprising finding of the present study was the co-segregation of MAPT p.A152T in 70% of carriers of the GRN mutation IVS6-1G>A (g.1872G>A) unique to the Basque Country [32]. This is a splicing mutation located at chromosome 17 (base pair position 139486) that causes truncated GRN protein due to mRNA degradation [33]. The fact that the MAPT p.A152T variant co-occurred with the GRN mutation only in families in a limited geographical region suggests that these individuals share the same haplotype, most likely from a common ancestor. However, MAPT

between our results and those of Coppola et al. [25] is the mean age at which controls were deemed healthy; for example, p.A152T carriers in one cohort may have been classified as controls at a younger age, prior to disease onset. Since the controls of Coppola et al. [25] were significantly younger (50 ± 16 years) than those analyzed in our study (64.1 ± 14.8 years), it is less likely that misclassification of our p.A152T carriers as controls who might manifest future degenerative disease could explain the higher p.A152T allelic frequency observed in our cohort.
p.A152T variant in patients carrying the GRN IVS6-1G>A mutation did not influence age at onset. Future studies are necessary to probe the influence of the co-

The number and magnitude of etiological factors that

Our last finding was that MAPT H1 haplotype is

In our study, we found a very significant overrepresen-
tation of the MAPT H1 haplotype in patients with AD [15] despite numerous experimental evidence of the involvement of tau protein in AD pathogenesis [36]. In our study, we found a very significant overrepresentation of the MAPT H1 haplotype in patients with AD [15] despite numerous experimental evidence of the involvement of tau protein in AD pathogenesis [36].

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In summary, we did not find a significant association between the rare variant MAPT p.A152T and AD risk, although our findings trended toward significance for p.A152T being associated with FTD risk. Despite our large sample size, our results should be interpreted with

<table>
<thead>
<tr>
<th>Genotype</th>
<th>OR (95%CI)</th>
<th>Allelic P-value</th>
<th>Allelic OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H2H2</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H1H2</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H1H1</td>
<td>1.00</td>
<td></td>
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</tr>
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p.A152T and AD risk, would be necessary to start the disease’s pathological mechanisms. However, in the absence of APOE e4, the participation of an ensemble of alternative etiological factors, and for longer periods of time, might be necessary to elicit the disease. For instance, if MAPT H1 haplotype confers a modest risk for AD independent of APOE e4, we may be able to detect this association only in elderly individuals not carrying APOE e4; otherwise, APOE e4’s effect on AD risk might mask the ability to detect the effect of MAPT H1 on AD risk. The association between the MAPT haplotype and AD is consistent with studies suggesting that H1/H1 status is associated with an increased rate of conversion from mild cognitive impairment to AD [37].

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In summary, we did not find a significant association between the rare variant MAPT p.A152T and AD risk, although our findings trended toward significance for p.A152T being associated with FTD risk. Despite our large sample size, our results should be interpreted with
caution, as our study may be underpowered to detect the
effect of such an infrequent genetic variant if the real OR
is lower in our population than found in previous stud-
ies. Our finding that MAPT p.A152T and the progranulin
IVS6-1G>A mutation cosegregate in families from
the Basque region raises interesting questions about
the influence of multiple risk genetic variants coincid-
ing in neurodegenerative diseases; future studies will
address these questions [39]. Finally, we found a robust
statistical association between MAPTH1 extended hap-
лотypes and risk of late-onset AD in APOE ε4 noncarriers.
Our results, in a large sample of Spanish population,
represent strong evidence supporting a link between
common MAPT genetic variants and AD. The mod-
est risk effect conferred by MAPTH1 haplotype and
the fact that it is restricted to APOE ε4 negative sub-
jects might contribute to clarify controversial results in
previous studies.

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