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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 ε4 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; $p = 8.59 \times 10\text{-}8$) but not FTD. Our results suggest that the *MAPT* H1 haplotype increases the risk of PD, PSP, and non-APOE ε4 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* ε4 [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 χ^2 statistics. Adjusted analyses were performed using multiple logistic regression. Age, gender, and *APOE* ε4 status were included in the model as covariates. Allelic frequencies, HWE analysis, and pair-wise LD D' and r^2 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 1
MAPT p.A152T frequencies across groups

	AD ($n = 4,327$)	FTD ($n = 563$)	PSP ($n = 84$)	PD ($n = 648$)	Controls ($n = 5,950$)
p.A152T carriers (%)	42 (0.97)	8 (1.42)	0 (0.0)	5 (0.77)	42 (0.71)
OR (95%CI)	1.38 (0.90–2.12)	2.03 (0.95–4.34)	–	1.09 (0.43–2.77)	ref
P-value	0.14	0.06	–	0.85	ref

we adjusted these tests by age and gender in the entire sample, and for *APOE* ε4 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; $r^2 = 0.46$). 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 Pro357fs), nor families with the *C9orf72* expansion. Sanger sequencing of *GRN* in 97 *MAPT* p.A152T carriers from all participant centers did not reveal *GRN* mutations.

Role of APOE ε4 status and MAPT H1/H2 haplotype in neurodegenerative diseases

APOE ε4 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 ($p = 0.0005$). When we stratified the sample by *APOE* ε4 status, the association of H1 haplotype was driven by noncarriers of *APOE ε4* ($p = 0.0025$) (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 = 2.034–4.974 $p = 8.59 \times 10^{-8}$). FTD risk was not associated with the *MAPT* haplotype ($p = 0.40$).

Table 2
MAPT p.A152T in individuals belonging to 15 families with *PGR* VS6-1G mutation

	Symptomatic (*n*)	Asymptomatic (*n*)	Total (*n*)
PGR+/A152T+	22	9	31
PGR+/A152T–	10	3	13
PGR–/A152T+	0	4	4
PGR–/A152T–	0	42	42
Total	32	58	90

PGR+, carrier individual of PGR VS6-1G mutation; PGR-, noncarrier individual of PGR VS6-1G mutation; A152T+, carrier individual of MAPT p.A152T variant; A152T-, noncarrier individual of MAPT p.A152T variant.

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: 077% 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 course" effect, a common phenomenon observed in pioneer genetic epidemiological studies [35]. Another potential influence on the difference

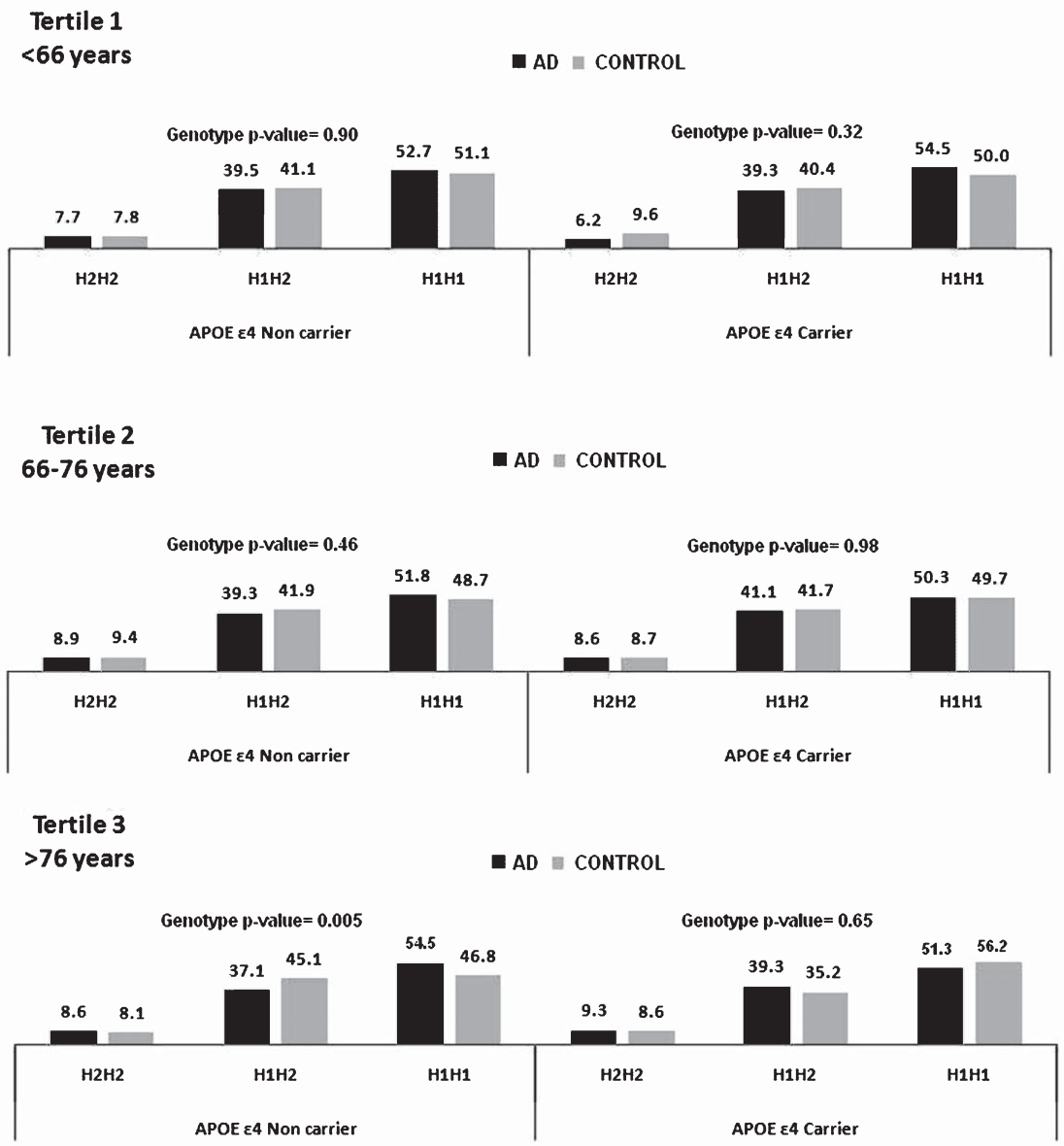

Fig. 1. Genotype frequency distribution of the rs1800547 SNP tagging *MAPT* H1/H2 haplotype stratified by APOE ε4 status and Age tertile.

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.

A surprising finding of the present study was the co-segregation of *MAPT* p.A152T in 70% of carriers of the *GRN* mutation *I*VS6-1G>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*

Table 3
MAPT H1/H2 haplotype frequencies and AD risk

	Control (%)	AD (%)	Genotype *P*-value	Allelic -value	Allelic OR (95%CI)
ALL					
H2H2	532 (9.15)	344 (8.34)			
H1H2	2444 (42.03)	1614 (39.11)	$p = 0.001$ [$p = 0.016$]*	$p = 0.00051$	1.12 (1.05–1.19)
H1H1	2839 (48.82)	2169 (52.56)			
H1 frequency	0.698	0.721			
APOE4+					
H2H2	78 (9.07)	139 (8.50)			
H1H2	345 (40.12)	655 (40.04)	$p = 0.88$ [$p = 0.86$]	$p = 0.65$	1.03 (0.91–1.18)
H1H1	437 (50.81)	842 (51.47)			
H1 frequency	0.709	0.715			
APOE4-					
H2H2	343 (8.46)	160 (8.16)			
H1H2	1701 (41.97)	730 (37.24)	$p = 0.001$ [$p = 0.005$]	$p = 0.0025$	1.14 (1.05–1.24)
H1H1	2009 (49.57)	1070 (54.59)			
H1 frequency	0.706	0.732			

In brackets *p*-values adjusted by age and gender . *p-values adjusted by age, gender, and APOE status.

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-ocurrence of *MAPT* p.A152T and *GRN* IVS6-1G>A on the FTD clinical or neuropathological phenotype.

Our last finding was that *MAPT* H1 haplotype is overrepresented in patients with AD, PD, and PSP compared to controls. Although the association of *MAPT* with PD and PSP risk is well documented [5–8, 11–13], its association with AD is much more controversial. To date, genome-wide association studies and case-control data meta-analyses such as *AlzGene* have not been able to link *MAPT* genetic variants to 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 compared to controls. The mildly increased risk for AD conferred by the H1 haplotype emerged only in our subgroup of noncarriers for *APOE* ε4, especially in the oldest subjects. This is in line with a recent publication re-analyzing the IGAP consortium data in APOE ε4 carriers and non-carriers. That study reported genome-wide significant association with many SNPs across a region on chromosome 17 including MAPT and with the H1 haplotype, however, the association was accounted for by SNPs located between two genes (KANSL1 and LRRC37A) adjacent to MAPT [17].

Our results are consistent with the hypothesis that AD pathology could develop through different causal pathways with several genetic factors likely to be involved, *APOE* ε4 being the strongest one. *APOE* ε4 lowers the threshold for AD susceptibility, which 1) associates with an earlier age of disease onset, and 2) may decrease the number and magnitude of etiological factors that would be necessary to start the disease's pathological mechanisms. However, in the absence of *APOE* ε4, 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* ε4, we may be able to detect this association only in elderly individuals not carrying *APOE* ε4; otherwise, *APOE* ε4'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]. Our results are also in line with a recent publication studying *MAPT* haplotypes in a large sample of late onset AD from the US that found that H2 haplotype carriers were protected from AD and had lower MAPT levels in brain [38]. An alternative explanation to our results could be that within the APOE ε4 non-carriers group the number of subjects with dementia due to pure tauopathies (PSP, CBD, or FTD-tau) misdiagnosed as AD might be higher than those among the APOE ε4 carriers group. We suggest that in large population samples this phenomena is likely to occur to a certain degree, but we consider unlikely that these disorders with a low prevalence are contributing significantly to our results. Additionally, the fact by which most patients included in our study come from specialized memory units from academic hospitals increases the likelihood of a correct AD diagnosis.

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 studies. Our finding that *MAPT* p.A152T and the progranulin IVS6-1G>A mutation cosegregates in families from the Basque region raises interesting questions about the influence of multiple risk genetic variants coinciding in neurodegenerative diseases; future studies will address these questions [39]. Finally, we found a robust statistical association between *MAPT* H1 extended haplotype 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 modest risk effect conferred by *MAPT* H1 haplotype and the fact that it is restricted to *APOE* ε4 negative subjects might contribute to clarify controversial results in previous studies.

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