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Genetic Influences on Cognition in Progressive Supranuclear Palsy

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Abstract

Background—Cognitive dysfunction is common in progressive supranuclear palsy but the influence of genetics on cognition not been well studied in this disorder.

Objective—To investigate genetic influences on cognition in progressive supranuclear palsy. Specifically, to investigate the effect of genes previously identified as risk alleles, including microtubule-associated protein tau, myelin-associated oligodendrocyte basic protein, eukaryotic

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Author Roles

1. Research project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

A.G.: 2A, 2B, 2C, 3A, 3B
E.D.R.: 2C, 3A, 3B
G.D.S.: 1A, 1B, 1C, 3B
D.G.S.: 1C, 3B
D.R.S.: 1C, 3B
B.K.: 1C, 3B
I.L.: 1A, 1B, 1C, 2C, 3A, 3B

translation initiation factor 2-alpha kinase 3, and syntaxin 6, as well as apolipoprotein E, on cognitive function in progressive supranuclear palsy.

Methods—The sample was composed of 305 participants who met criteria for possible or probable progressive supranuclear palsy. Genetic information was determined by TaqMan genotyping assays. A neuropsychological battery was administered to all study participants. Measures included in the battery evaluated for general cognition, executive function, memory, attention, language, and visuospatial ability.

Results—Cognition did not vary significantly between individuals homozygous or heterozygous for the microtubule-associated protein tau H1 haplotype. However, cognition varied significantly at the subhaplotype level, with carriers of the microtubule-associated protein tau rs242557/A allele, which marks the H1c subhaplotype, performing better than non-carriers on measures of general cognitive function, executive function, and attention. No associations were found for other genes.

Conclusions—The results of the current study indicate that variations in microtubule-associated protein tau influence cognition in progressive supranuclear palsy. Although the H1c-specific rs242557/A allele is a risk factor for progressive supranuclear palsy, it may function as a protective factor against cognitive decline for patients with this disorder. Further studies are needed.

Keywords

progressive supranuclear palsy; *MAPT*; cognition; GWAS

Introduction

Progressive supranuclear palsy (PSP) is a rare neurodegenerative disorder that primarily affects adults over the age of 60(1). Individuals with the PSP-Richardson phenotype (PSP-RS) present with postural instability and falls, parkinsonism not responding to dopaminergic therapy, and slowing of vertical saccades(2). PSP is considered a tauopathy due to the accumulation of tau protein within neurons and glia in certain brain regions (e.g., basal ganglia, brainstem)(3). PSP is a primary tauopathies with tau being the primary protein that aggregates in the brain. In contrast, secondary tauopathies are characterized by accumulation of tau in combination with other protein aggregates. For example, Alzheimer's disease is characterized by the accumulation in the brain of both tau and amyloid-beta (Aβ).

Although PSP is most often characterized as a movement disorder, cognitive dysfunction is common(1, 4–6). Consistent with prior studies, our group demonstrated that up to half of patients with PSP exhibit some level of general cognitive impairment at early stages(5). Executive dysfunction was particularly prominent, with milder difficulties noted in verbal memory, construction, and language. This previous study by our group supported an earlier large-scale study of cognition in PSP(6).

Results of a genome-wide association study (GWAS) of autopsy-proven cases of PSP identified several single nucleotide polymorphisms (SNPs) as risk alleles: microtubule-associated protein tau (*MAPT*) rs8070723 and rs242557, myelin-associated oligodendrocyte basic protein (*MOBP*) rs1768208, eukaryotic translation initiation factor 2-alpha kinase

3(*EIF2AK3*) rs7571971, and syntaxin 6 (*STX6*) rs1411478(3). In this same study, certain alleles of *APOE* were less frequently present in PSP than in the general population. *MAPT* encodes tau and the accumulation of tau in the brain has been linked to cognitive decline(7–10). The region of chromosome 17 encoding *MAPT* has two haplotypes, H1 and H2, which are in complete linkage disequilibrium due to an inversion variant. The H1 haplotype is strongly linked to PSP(11) and also affects risk of mild cognitive impairment (MCI)(12), progression from MCI to dementia(13) and, progression from Parkinson's disease to Parkinson's disease dementia(14). *APOE* is the strongest genetic risk factor for AD and affects the rate at which Aβ accumulates in the brain which is inversely related to cognitive abilities (15, 16). However, prior investigations into the associations of *MAPT* and *APOE* with cognition in PSP have been hindered by both sample size limitations and the evaluation of only general cognitive function(17, 18) Although *MOBP* rs1768208 is associated with brain atrophy in patients with frontotemporal lobar degeneration(19), its effect on cognition is not well understood and its association to the cognitive dysfunction often seen in PSP has not been investigated. Finally, to our knowledge, the association of *EIF2AK3* and *STX6* with cognition has not been previously investigated in any patient group.

To address these knowledge gaps, we examined the association between cognition and *MAPT*, *APOE*, *MOBP*, *EIF2AK3* and *STX6* in a large sample of PSP patients. Commonly used neuropsychological tests measuring a wide range of abilities (e.g., frontal/executive functioning, verbal memory, naming, general cognitive functioning) were utilized. Based on a review of the literature, we hypothesized that cognition would be poorer for those patients with *MAPT* H1/H1 and/or *APOE ε*4. Due to the lack of existing studies on the topic, analyses investigating the role of *MOBP*, *EIF2AK3* and *STX6* were considered exploratory.

Methods

Participants

Following approval of institutional review boards at each site, 350 adults with PSP were recruited at 15 sites (Baylor College of Medicine, University of Colorado, Cornell University, Case Western Reserve, Emory University, University of Kansas, University of Louisville, University of Maryland, Mayo Clinic Jacksonville, Rush University, Toronto Western Hospital, University of Alabama at Birmingham, University of California at Los Angeles, University of Utah, and University of Washington). All patients met the National Institute of Neurological Disorders and Stroke and Society for PSP, Inc. (NINDS-SPSP) criteria(20) for clinically possible or probable PSP, which correspond to the recently published probable Movement Disorder Society (MDS-PSP) criteria(21). A mini-mental state examination (MMSE(22)) score ≥ 24 was also required for inclusion. This MMSE cut-off score was intended to limit the number of PSP patients with dementia. Participants were also excluded if they had other central nervous system disorders or were unable to provide informed consent. Three hundred and five of the 350 PSP patients had genetic data collected and were included in this study. Autopsy has been conducted on 20 patients, with 18 showing PSP pathology. The other two patients showed corticobasal degeneration pathology (CBD), which is another 4R-tauopathy that can present clinically with a PSP-phenotype.

After informed consent, participants were evaluated by a clinical team consisting of a movement disorder specialist and trained research assistant who completed a detailed history and examination including the validated PSP Rating Scale (PSPRS) and Unified Parkinson Disease Rating Scale (UPDRS). Finally, a baseline neuropsychological evaluation was completed by medical personnel who had received training on the battery from a neuropsychologist. Accuracy of the evaluations was periodically checked at each site by a neuropsychologist.

Genotyping

Genotypes were determined by TaqMan genotyping assays (Life Technologies). Predesigned assays are: for rs242557 in MAPT, C__1016016_1; for rs8070723 in MAPT, C__29297996_10; for APOE rs7412, C__904973_10 and rs429358, C__3084793_20; for MOBP rs1768208, C___75367_10; and for EIF2AK3 rs7571971, C___20893_10. STX6 was genotyped by a custom assay design ID AHGJ5AO with the forward primer, GGTAGGCAAAAGGTGCTATGGA; reverse primer, GTCCCAGCACCCTGTCAA; reporter 1 sequence, CCCAGAGAAGAAGAC; and reporter 2 sequence, CCAGAGGAGAAGAC.

Measures

The PSPRS assesses level of impairment in PSP.(23) Impairment is assessed across six categories: health history, mentation, bulbar function, eye and lid movement, limb movement, and trunk movement, with most items being rated on a 0–4 Likert scale (0=no presence of symptom; 4=severe presence of symptom). The total score is the sum of all items and ranges from 0 to 100. Higher scores indicate greater impairment.

The UPDRS was originally developed for use in evaluating impairment in Parkinson’s disease,(24) but it has also been shown to be a valid and reliable measure when evaluating PSP patients. The UPDRS is comprised of 42 items, rated on a 0–4 Likert scale (0=no presence of symptom; 4=severe presence of symptom). Three categories are rated: mentation, behavior, and mood; activities of daily living; and motor functioning. A total score is the sum of all items and ranges from 0 to 124. Higher scores are indicative of greater impairment.

The Dementia Rating Scale – 2 (DRS-2(25)) is a measure of general cognitive functioning that yields a total score (ranges from 0 to 144) and scores on six subscales (i.e., Attention, Initiation/Perseveration, Construction, Conceptualization, and Memory). For total as well as subscale scores, higher values indicate better cognitive functioning.

The Frontal Assessment Battery (FAB(26)) assesses frontal lobe/executive function across six items (i.e., similarities, lexical fluency, motor series, conflicting instructions, Go-No-Go, and prehension behavior). Each item is scored on a 3-point scale with 18 possible points comprising the FAB Total score. Higher scores indicate better cognition.

The California Verbal Learning Test – Second Edition, Short Form (CVLT-II SF) is a measure of verbal learning and memory, in which subjects learn 9 words over four learning trials. (27) After a 10-minute delay, free recall of the list is queried. Higher scores indicate

better memory. Although the CVLT-II SF yields many scores, the variables used in this analysis include Total recall (i.e., number of words correctly recalled across four learning trials) and Long Delay Free Recall (i.e., number of words correctly recalled after a 10-minute delay).

The Boston Naming Test (BNT(28)) is a 60-item measure of confrontational naming. Higher scores indicate better naming abilities.

Data Analyses

In total, four sets of analyses were conducted. First, a series of chi-square tests was conducted to determine if distributions of gender and race differed by genotype (i.e., racial status by genotype). Another series of chi-square tests was conducted to determine if differences in *MAPT*, *APOE*, *MOBP*, *EIF2AK3* and *STX6* were associated with differences in gender or racial distribution (i.e., genotype by racial status). Second, a series of independent *t*-tests was conducted to investigate the relationship between *MAPT*, *APOE*, *MOBP*, *EIF2AK3* and *STX6* with age, education, and parkinsonian severity (i.e., UPDRS and PSPRS Total scores). A second series of independent t-tests were conducted to determine if differences in *MAPT*, *APOE*, *MOBP*, *EIF2AK3* and *STX6* were associated with varying levels of cognitive performance. A series of independent *t*-tests were also conducted to determine if the combined effect of the H1c-specific rs242557/A allele and *APOE e*4/4 was significantly greater than the effect of rs242557/A alone. Third, to characterize the neurocognitive profiles of the total sample and of the different genetic phenotypes, descriptive statistics including means and standard deviation were calculated for neuropsychological measures. Finally, a series of binary logistic regression analyses were conducted to examine the association between *MAPT* rs242557 and cognition. For these regression analyses, race was entered into block 1 for the purpose of statistical control.

Of note, only two participants were *MAPT* H1 non-carriers (i.e., were H2/H2), consistent with the dramatically reduced risk of PSP in H1 non-carriers. Thus, these two participants were not included in analyses conducted to examine *MAPT* H1 subhaplotype.

An *a priori* Bonferroni adjustment was not employed for a number of reasons. Bonferroni assumes that each hypothesis test is independent(29) and this assumption is virtually never met when conducting cognitive research. Bonferroni also applies only to the general null hypothesis, implies that a given comparison will be interpreted differently according to how many other tests were performed, and—most importantly—oftentimes unnecessarily inflates type II error rates(30–32) (Rothman, 1990; Savitz and Olshan, 1995; Perneger, 1998). Perneger(32) notes that “simply describing what tests of significance have been performed, and why, is generally the best way of dealing with multiple comparisons.” Thus, due to the number of comparisons, an *a priori*.01 level of significance was applied to strike a balance between type I and type II error rates.

Results

Cohort Characteristics

None of the genotypes that we studied varied by sex or race (Table 1), although *MAPT* rs242557, which tags the H1c subhaplotype, approached significance by race with a larger percentage of Caucasians being rs242557/A allele carriers than non-whites. Mean disease duration and age at onset were 4.4 (2.4) and 64.5 (7.2), respectively.

Neither demographic variables (i.e., age, education, sex, race) nor disease severity (i.e., UPDRS and PSPRS total scores) differed according to *MAPT* (Table 2) or *APOE*, *MOBP*, *EIF2AK3* or *STX6* genotype (Table 3). Neither disease duration or age at onset differed according to genetic information.

Neurocognitive Performance

We focused first on the effects of MAPT genotype on neurocognitive performance (Table 4). No differences were found between PSP patients at the haplotype level. However, aspects of cognition varied significantly according to *MAPT* subhaplotype. Participants who were *MAPT* rs242557/A allele carriers exhibited significantly better general cognitive functioning (i.e., DRS-2 Total score), attention (i.e., DRS-2 Attention), and general/basic executive function (i.e., DRS-2 Initiation/Perseveration) than did non-carriers (. Differences in visuospatial/constructional ability (i.e., DRS-2 Construction), abstraction/judgment (i.e., DRS-2 Conceptualization), and immediate recall for verbal list learning (i.e., CVLT-2 SF Immediate Recall) approached significance, with carriers again performing better than non-carriers. Effects of the *MAPT* H1c-specific rs242557/A allele on DRS-2 Total (p=0.005) and DRS-2 Attention (p=0.009) remained significant in follow-up logistic regression analyses with race being entered into block 1 for the purpose of statistical control. DRS-2 Initiation/Perseveration was no longer significant at the 0.01 level in logistic regression analysis but approached significance (p=0.028). No significant differences were found on any cognitive variables between rs242557/A homozygotes and rs242557/A heterozygotes.

We next examined the effects of *APOE*, *MOBP*, *EIF2AK3* and *STX6* on cognition (Table 5). Delayed recall for verbal list learning (i.e., CVLT-2 Long Delay Free Recall) approached significance for *EIF2AK3* rs7571971, with participants with T/T performing poorer than participants with either T/C or C/C. No other significant effects of genotype on cognitive performance were observed in this sample of patients with PSP.

The combined cognitive effect of the H1c-specific rs242557/A allele and APOE ε4 carrier (n=177) was not significantly greater than the cognitive effect of the H1c-specific rs242557/A allele alone (n=233): DRS-2 Total (t[231]=0.1, p=0.908), DRS-2 Attention (t[231]=0.6, p=0.522), DRS-2 Initiation/Perseveration (t[231]=0.8, p=0.438), DRS-2 Construction (t[231]=0.8, p=0.438), DRS-2 Conceptualization (t[231]=0.4, p=0.670), DRS-2 Memory (t[231]=0.7, p=0.467), FAB (t[231]=0.9, p=0.356), CVLT-II SF Immediate Recall (t[231]=0.8, p=0.414), CVLT-II SF Long Delay Free Recall (t[231]=0.3, p=0.730), and BNT (t[231]=0.8, p=0.422).

Discussion

In the current study, we investigated the relationship between *MAPT*, *APOE*, *MOBP*, *EIF2AK3* and *STX6* and cognition in a large sample of patients with PSP. In a previous GWAS of autopsy-proven cases of PSP, risk alleles on *MAPT*, *MOBP*, *EIF2AK3* and *STX6* were identified, with *APOE*-ε4 being noted as less prevalent(3). Despite cognitive dysfunction being a common feature of PSP(1, 5, 6), the genetic influences on cognition in PSP are not well understood. Moreover, although cognition in general has been shown to be affected by *MAPT* status(12, 13) and *APOE* genotype(33), and *APOE ε*4 has been noted as a risk factor for Alzheimer's disease pathology in PSP(34), the impact of these genes on cognition in PSP has not been investigated using either large samples or comprehensive neuropsychological batteries. In the current sample, cognition varied significantly according to *MAPT* status, with H1c-specific rs242557/A allele carriers exhibiting better cognitive ability in a number of areas than non-carriers. No other significant genotype effects emerged in this sample of PSP patients and, in contrast to AD, cognition did not vary according to *APOE* genotype. These results are the first to demonstrate a connection between genotype and cognition in PSP.

Consistent with a priori expectations, cognition varied according to *MAPT* in this sample of patients with PSP. Given that the H1 haplotype has been shown to be associated with mild cognitive impairment (MCI)(12) and progression from MCI to dementia(13), we expected H1/H1 PSP patients to perform more poorly on our cognitive battery. However, significant differences in cognitive performance were not observed between PSP patients with H1/H1 and with H1/H2. Because all but two study participants were H1 carriers at *MAPT* rs8070723, we were not able to investigate cognitive differences in PSP patients with H2/H2. However, we detected differences at the *MAPT* subhaplotype level, with participants with the H1c-specific rs242557/A allele performing better on our neuropsychological test battery. Specifically, cognitive performance on measures of general cognitive function, attention, and executive function were significantly better for *MAPT* H1c-specific rs242557/A allele carriers than for non-carriers, with performance in a number of other cognitive areas approaching significance.

MAPT rs242557 partially tags H1c, with the A allele being H1c specific and the G allele being H1c nonspecific(35). The *MAPT* H1c-specific rs242557/A allele is associated with increased brain *MAPT* levels(36) and also increased overall risk of PSP(3). Thus, the observation that rs242557/A allele seems to have protective effects on cognition in PSP is surprising. One possibility is that the observed protection could be an artifact of "survivorship bias," if the *MAPT* H1c-specific rs242557/A allele in fact worsened cognition, causing many of these participants to be excluded from the sample due to the requirement for MMSE ≥ 24. However, this seems somewhat unlikely since the sample is still heavily weighted toward H1c-specific rs242557/A allele participants (233/303). Alternatively, the H1c-specific rs242557/A allele may drive increased overall risk of PSP, but shape the PSP subtype toward a disease phenotype with relatively less cognitive impairment. Another possibility is that persons without the allele may be more likely to have mixed underlying pathologies (e.g., vascular, Alzheimer's disease), which could worsen cognition. Finally, other nearby genes, not investigated in this study, could be acting as confounding variables.

Cognition was not significantly affected by *APOE* genotype. However, this finding was not unexpected given recent hypotheses regarding the manner in which amyloid beta influences cognition. The amount of Aβ in the brain has been shown to affect cognition(33), and a connection between *APOE* status and Aβ brain accumulation has been empirically established(37–41). Although a direct association between *APOE* ε4 and cognition has been shown in previous studies(42–44), recent evidence suggests that tau may act as a mediator between Aβ brain accumulation and cognitive impairment in AD(45). Thus, we conducted follow-up analyses to determine if the combined effect of *APOE* and *MAPT* rs242557 was greater on cognition than was *MAPT* rs242557 alone. Results showed that a combined effect of rs242557/A and *APOE* ε4/4 was not present in our sample. However, it should be noted that the exclusion of PSP patients with MMSE scores <24 may have excluded subjects with both PSP and Alzheimer's disease pathology(34). Regardless, this finding may indicate that variations associated with the gene responsible for encoding tau has a primary rather than a mediatory effect on cognition in the primary tauopathy of PSP.

The neurocognitive performance of the sample utilized in the current study was very similar to a smaller, albeit related, sample of patients with PSP(5). In regards to general cognitive function, the overall DRS-2 averages between our current study and the previous study were within two points (i.e., approximate one percentile difference). Performances between the two samples on tests of executive function, language, and attention/concentration showed a similar pattern. For memory tests, performances between the two samples were the most similar and virtually identical. Moreover, the concordance between the pattern of test results highlighted in the current study and our previous study lends further support the notion that executive dysfunction is the cardinal feature of cognitive impairment in PSP(5). Thus, the findings of the current study confirm our earlier results and further indicate that cognitive dysfunction is more prevalent in PSP than commonly thought, even in a sample selected for relatively preserved cognition by excluding those with MMSE < 24.

While the current study provides insights into the genetic effects on cognition in PSP, some limitations should be noted. First, similar to other multisite studies of rare disorders, the current sample may not fully correspond to the general PSP population. For example, current participants agreed to several hours of testing, exhibited a MMSE score ≥24 (to exclude frank dementia), and were able to provide informed consent. Thus, the participants composing the current sample may represent a select inclusion group of patients with PSP, and these results might not generalize to all patients with PSP. Second, all patients composing the current sample met NINDS-PSP criteria for probable or possible PSP. These criteria identify well PSP-RS but are limited in the identification of other PSP phenotypes. Thus, to provide a more complete description of behavioral abnormalities in PSP, future studies should classify patients according to their subtype as the methodology for distinguishing between subtypes improve. Regardless, the current study is the first to empirically establish a relationship between *MAPT* subhaplotype and cognition in PSP. Further studies are needed to further understand our findings.

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Table 1

Gender and Race by Genotype.

	Gender			Race		
Genotype	**Male**	**Female**	χ^2, *p*	**Caucasian**	**Other**	χ^2, *p*
***MAPT* rs8070723**			0.6, 0.456			0.6, 0.716
H1/H1	139 (88.5)	135 (91.2)		254 (90.1)	20 (87.0)	
Not H1/H1	18 (11.5)	13 (8.8)		28 (9.9)	3 (13.0)	
***MAPT* rs242557/A**			1.1, 0.345			5.4, 0.037[†]
carrier	116 (73.9)	117 (79.1)		220 (78.0)	13 (56.5)	
non-carrier	41 (26.1)	31 (20.9)		62 (22.0)	10 (43.5)	
***APOE* ε4**			2.1, 0.179			0.1, 0.999
carrier	43 (27.4)	30 (20.3)		68 (24.1)	5 (21.7)	
non-carrier	114 (72.6)	118 (79.7)		214 (75.9)	18 (78.3)	
***MOBP* rs1768208**			0.2, 0.730			2.2, 0.191
C/C	69 (43.9)	68 (45.9)		130 (46.1)	7 (30.4)	
C/T or T/T	88 (56.1)	79 (53.4)		151 (53.5)	16 (69.6)	
***EIF2AK3* rs7571971**			0.9, 0.442			1.6, 0.262
T/T	13 (8.3)	17 (11.5)		26 (9.2)	4 (17.4)	
T/C or C/C	144 (91.7)	131 (88.5)		256 (90.8)	19 (82.6)	
***STX6* rs1411478**			0.5, 0.557			0.2, 0.780
A/A	27 (17.2)	30 (20.3)		52 (18.4)	5 (21.7)	
A/G or G/G	130 (82.7)	118 (79.7)		230 (81.6)	18 (78.3)	

Note. Frequency and percent (%). χ^2, *p* = chi-square statistic and *p* value.

[†]indicates $p < 0.05$, which approached but did not reach the predetermined alpha of 0.01.

Table 2

Demographics and Disease Severity for Entire Cohort and for MAPT.

		MAPT rs8070723			*MAPT* rs242557/A		
Demographic	**Entire Cohort (n=305)**	**H1/H1 (n=274)**	**Not H1/H1 (n=31)**	**t/χ^2, p**	**carrier (n=233)**	**non-carrier (n=70)**	**t/χ^2, p**
Age	69.0 (6.9)	68.9 (6.9)	70.5 (7.0)	1.3, 0.196	69.0 (7.2)	68.9 (6.0)	0.1, 0.904
Gender	184 M, 166 F	139 M, 135 F	18 M, 13 F	0.6, 0.439	116 M, 117 F	40 M, 30 F	1.2, 0.280
Education	15.1 (3.4)	15.1 (3.5)	15.3 (3.4)	0.3, 0.795	15.1 (3.5)	15.1 (3.4)	0.1, 0.911
Race				0.2, 0.635			5.8, 0.016†
Caucasian	282 (92.5%)	254 (92.7%)	28 (90.3%)		220 (79%)	60 (21%)	
Other	23 (7.5%)	20 (7.3%)	3 (9.7%)		13 (57%)	10 (43%)	
Disease Severity							
UPDRS Total	52.7 (18.0)	52.5 (17.7)	54.7 (20.7)	0.7, 0.516	52.9 (17.9)	52.2 (18.3)	0.3, 0.773
PSPRS Total	37.0 (11.4)	37.0 (11.1)	36.4 (13.6)	0.3, 0.779	37.1 (11.2)	37.0 (11.8)	0.1, 0.971

Note. Mean and (standard deviation) are listed for age, education, UPDRS, and PSPRS. Frequency is listed for gender. Frequency and percent (%) are listed for race.

t/χ^2, p = t or chi-square statistic and p value.

† indicates $p < 0.05$, which approached but did not reach the predetermined alpha of 0.01. UPDRS = Unified Parkinson Disease Rating Scale and PSPRS = Progressive Supranuclear Palsy Rating Scale.

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Table 3

Demographics and Disease Severity for APOE, MOBP, EIF2AK2, and STX6.

				***MOBP* rs1768208**			***EIF2AK3* rs7571971**			***STX6* rs1411478**		
Demographic	**APOE ε4 carrier (n=73)**	***APOE* ε4 non-carrier (n=232)**	**t/χ^2, p**	**C/C (n=137)**	**C/T or T/T (n=167)**	**t/χ^2, p**	**T/T (n=30)**	**T/C or C/C (n=275)**	**t/χ^2, p**	**A/A (n=57)**	**A/G or G/G (n=248)**	**t/χ^2, p**
Age	68.4 (6.7)	69.2 (7.0)	0.9, 0.377	68.9 (7.1)	69.0 (6.8)	0.2, 0.880	69.2 (5.9)	69.0 (7.0)	0.1, 0.905	68.8 (7.0)	69.1 (7.1)	0.2, 0.821
Sex	43 M, 30 F	114 M, 118, F	2.2, 0.145	69 M, 68 F	88 M, 79 F	0.2, 0.686	13 M, 17 F	144 M, 131 F	1.1, 0.573	27 M, 30 F	130 M, 118 F	0.9, 0.319
Education	15.2 (3.6)	15.1 (3.4)	0.3, 0.746	15.0 (3.5)	15.2 (3.4)	0.5, 0.589	15.8 (3.4)	15.0 (3.5)	1.1, 0.269	14.7 (3.2)	15.1 (3.5)	0.7, 0.485
Race			0.8, 0.514			2.2, 0.142			2.2, 0.331			0.1, 0.719
Caucasian	68 (93.2%)	214 (92.2%)		130 (94.9%)	151 (90.4%)	2.2, 0.191	26 (86.7%)	256 (93.1%)		52 (91.2%)	230 (92.7%)	
Other	5 (6.8%)	18 (7.8%)		7 (5.1%)	16 (9.6%)		4 (13.3%)	19 (6.9%)		5 (8.8%)	18 (7.3%)	
Disease Severity												
UPDRS Total	38.5 (12.3)	36.5 (11.0)	1.4, 0.177	52.4 (18.6)	53.0 (17.6)	0.3, 0.768	56.2 (19.6)	52.3 (17.8)	1.1, 0.265	52.3 (20.9)	52.3 (17.1)	0.1, 0.999
PSPRS Total	53.7 (19.3)	52.4 (17.6)	0.6, 0.577	36.7 (11.9)	37.3 (10.9)	0.4, 0.675	36.0 (11.4)	37.1 (11.4)	0.5, 0.683	37.4 (13.3)	37.0 (10.9)	0.3, 0.802

Note. Mean and (standard deviation) are listed for age, education, UPDRS, and PSP-RS. Frequency is listed for sex. Frequency and percent (%) are listed for race. t/χ^2, $p = t$ or chi-square statistic and p value. UPDRS = Unified Parkinson Disease Rating Scale and PSPRS = Progressive Supranuclear Palsy Rating Scale.

Table 4

Neurocognitive Performance of Cohort and Effect of MAPT Haplotype.

	Entire Cohort (n=305)	***MAPT* rs8070723**			***MAPT* rs242557/A**		
Measure		**H1/H1 (n=274)**	**Not H1/H1 (n=31)**	***t, p***	**carrier (n=233)**	**non-carrier (n=70)**	***t, p***
DRS-2 Test/Subtest							
Total Score	125.8 (11.8)	125.9 (11.5)	124.2 (14.6)	0.8, 0.447	126.8 (10.7)	121.8 (14.3)	3.2, 0.002 **
Attention	34.9 (2.2)	34.9 (2.2)	35.0 (2.2)	0.3, 0.764	35.1 (2.0)	34.3 (2.6)	2.7, 0.007 **
I/P	28.8 (6.1)	28.9 (5.9)	27.6 (7.3)	1.1, 0.255	29.2 (5.8)	27.1 (6.5)	2.6, 0.010 **
Construction	5.0 (1.5)	5.0 (1.4)	4.7 (1.7)	1.1, 0.271	5.1 (1.4)	4.7 (1.6)	2.0, 0.043 †
Conceptualization	34.6 (3.7)	34.7 (3.6)	34.4 (4.4)	0.3, 0.741	34.8 (3.4)	33.8 (4.7)	2.1, 0.036 †
Memory	22.4 (2.6)	22.4 (2.7)	22.4 (2.1)	0.1, 0.988	22.6 (2.3)	21.9 (3.6)	1.8, 0.065
FAB	13.0 (3.1)	13.0 (3.1)	13.1 (3.5)	0.1, 0.977	13.2 (2.9)	12.4 (3.7)	1.8, 0.073
CVLT-II SF							
Immediate Recall	22.5 (5.3)	22.5 (5.3)	22.1 (5.5)	0.4, 0.658	22.8 (5.2)	21.3 (5.6)	2.0, 0.042 †
LDFR	5.1 (2.3)	5.2 (2.3)	4.5 (2.2)	1.5, 0.146	5.2 (2.3)	4.6 (2.3)	1.9, 0.054
BNT	51.9 (8.6)	51.8 (8.6)	52.1 (8.7)	0.1, 0.891	52.3 (8.1)	50.2 (10.0)	1.8, 0.081

Note. Means and (standard deviations) are listed for cells pertaining to genes. *t, p* = *t* statistic and *p* value.

** indicates a significant *p* value at the.01 level, which was the predetermined alpha for this study;

† indicates a *p* value below the.05 level. DRS-2=Dementia Rating Scale – Second Edition; I/P=Initiation/Perseveration; FAB=Frontal Assessment Battery; CVLT-II SF=California Verbal Learning Test – Second Edition, Short Form; LDFR=long delay free recall; BNT=Boston Naming Test.

Table 5

Neurocognitive Performance for APOE, MOBP, EIF2AK2, and STX6.

Measure	*APOE e4* carrier (n=73)	*APOE e4* non-carriers (n=232)	*t, p*	*MOBP* rs1768208 C/C (n=137)	*MOBP* rs1768208 C/T or T/T (n-167)	*t, p*	*EIF2AK3* rs7571971 T/T (n=30)	*EIF2AK3* rs7571971 T/C or C/C (n=275)	*t, p*	*STX6* rs1411478 A/A (n=57)	*STX6* rs1411478 A/G or G/G (n=248)	*t, p*
DRS-2 Test/Subtest												
Total Score	126.0 (14.0)	125.2 (11.1)	0.5, 0.613	125.7 (11.4)	125.8 (12.5)	0.1, 0.906	125.8 (11.4)	125.2 (15.3)	0.3, 0.784	125.9 (12.0)	125.0 (11.4)	0.6, 0.573
Attention	35.0 (2.0)	34.6 (2.5)	1.5, 0.133	34.8 (2.2)	35.1 (2.1)	1.0, 0.320	34.9 (2.1)	34.8 (3.0)	0.2, 0.815	35.0 (2.2)	34.7 (2.1)	0.8, 0.436
I/P	28.7 (5.9)	29.1 (6.4)	0.5, 0.602	28.9 (6.0)	28.7 (6.2)	0.3, 0.729	28.8 (6.0)	28.9 (6.6)	0.1, 0.914	28.9 (6.0)	28.4 (6.1)	0.6, 0.580
Construction	5.0 (1.5)	5.1 (1.4)	0.6, 0.534	5.1 (1.4)	5.0 (1.5)	0.6, 0.540	5.0 (1.4)	4.9 (1.8)	0.6, 0.551	5.0 (1.4)	5.0 (1.6)	0.2, 0.846
Conceptualization	34.8 (3.6)	34.0 (4.1)	1.6, 0.122	34.3 (3.7)	35.0 (3.7)	1.6, 0.122	34.7 (3.7)	34.2 (4.1)	0.7, 0.507	34.7 (3.8)	34.3 (3.5)	0.8, 0.434
Memory	22.5 (2.4)	22.3 (3.3)	0.5, 0.642	22.6 (2.5)	22.2 (2.8)	1.2, 0.225	22.4 (2.6)	22.6 (2.8)	0.3, 0.758	22.4 (2.6)	22.6 (2.7)	0.5, 0.588
FAB	13.1 (3.0)	12.9 (3.5)	0.4, 0.682	12.9 (3.0)	13.1 (3.3)	0.5, 0.594	13.0 (3.1)	13.5 (3.0)	0.9,0.374	13.1 (3.1)	12.6 (3.2)	1.1, 0.265
CVLT-II SF												
Immediate Recall	22.6 (5.1)	22.0 (6.1)	0.9, 0.385	22.5 (5.2)	22.4 (5.5)	0.1, 0.887	22.3 (5.3)	23.8 (5.7)	1.5, 0.142	22.5 (5.4)	22.4 (5.2)	0.1, 0.962
LDFR	5.1 (2.3)	5.1 (2.4)	0.1, 0.964	5.1 (2.2)	5.0 (2.5)	0.3, 0.738	5.0 (2.3)	6.1 (2.4)	2.5, 0.012†	5.1 (2.3)	5.2 (2.4)	0.3, 0.743
BNT	51.8 (8.7)	51.9 (8.4)	0.1, 0.941	51.4 (9.4)	52.4 (7.5)	1.1, 0.293	52.1 (8.4)	49.4 (10.1)	1.6, 0.111	52.0 (8.3)	51.1 (9.7)	0.7, 0.495

Note. Means and (standard deviations) are listed for cells pertaining to genes. *t, p* = *t* statistic and *p* value.

† indicates a *p* value at the.05 level, which approached but did not reach the predetermined alpha 0.01. DRS-2=Dementia Rating Scale – Second Edition; I/P=Initiation/Perseveration; FAB=Frontal Assessment Battery; CVLT-II SF=California Verbal Learning Test – Second Edition, Short Form; LDFR=long delay free recall; BNT=Boston Naming Test.