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Association of *MAPT* H1 Subhaplotypes With Neuropathology of Lewy Body Disease

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Abstract

Background: Genetic variation at the microtubule-associated protein tau locus is associated with clinical parkinsonism. However, it is unclear as to whether microtubule-associated protein tau H1 subhaplotypes are associated with the burden of neuropathological features of Lewy body disease.

Objectives: To evaluate associations of microtubule-associated protein tau haplotypes with severity of Lewy body pathology and markers of SN neuronal loss in Lewy body disease cases.

Methods: Five hundred eighty-five autopsy-confirmed Lewy body disease cases were included. Six microtubule-associated protein tau variants (rs1467967, rs242557, rs3785883, rs2471738, rs8070723, and rs7521) were genotyped to define common microtubule-associated protein tau haplotypes. Lewy body counts were measured in five cortical regions. Ventrolateral and medial SN neuronal loss were assessed semiquantitatively. Nigrostriatal dopaminergic degeneration was quantified by image analysis of tyrosine hydroxylase immunoreactivity in the dorsolateral and ventromedial putamen.

Results: The common microtubule-associated protein tau H2 haplotype did not show a strong effect on pathological burden in Lewy body disease. The rare H1j haplotype (1.3%) was significantly associated with a lower dorsolateral putaminal tyrosine hydroxylase immunoreactivity (and therefore greater dopaminergic degeneration) compared to other microtubule-associated protein tau haplotypes ($P = 0.0016$). Microtubule-associated protein tau H1j was also nominally ($P \leq 0.05$) associated with a lower ventromedial putaminal tyrosine hydroxylase immunoreactivity ($P = 0.010$), but this did not survive multiple testing correction. Other nominally significant associations between microtubule-associated protein tau H1 subhaplotypes and neuropathological outcomes were observed.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Conclusions: A rare microtubule-associated protein tau H1 subhaplotype (H1j) may be associated with more severe putaminal dopaminergic degeneration in Lewy body disease cases. Microtubule-associated protein tau H1j has been associated previously with an increased risk of PD, and therefore our exploratory findings provide insight into the mechanism by which H1j modulates PD risk.

Keywords

genetics; haplotype; Lewy body disease; *MAPT*; neuropathology

Parkinson's disease (PD), PD with dementia (PDD), and dementia with Lewy bodies (DLB) are neurodegenerative disorders in which Lewy bodies (LBs) and Lewy neurites are considered to play an important role in pathogenesis and clinical phenotype. They are therefore grouped under the pathological classification of Lewy body disease (LBD).[1] In PD, LB pathology is often concentrated in vulnerable brainstem nuclei and the basal forebrain, with less frequent involvement of limbic and neocortical regions.[2] In contrast, LB pathology is more diffuse in PDD and DLB.[3] SN neuronal loss (particularly in the ventrolateral area) and striatal dopamine depletion are other key neuropathological characteristics of LB disorders; these features occur most notably in PD and PDD and to a lesser degree in DLB.[2,4]

Both PD (with or without dementia) and DLB have a well-recognized genetic component.[5-8] The microtubule-associated protein tau (*MAPT*) H1 haplotype is one of the strongest genetic risk factors for PD,[6] and it has also been associated with PDD[9] and DLB.[8,10] The *MAPT* gene contains two major haplotypes; the H1 haplotype is common, occurring in approximately 80% of neurologically normal subjects, whereas H2 is the rarer and generally only occurs in individuals of European ancestry.[11,12] Previous studies have investigated whether in addition to altering risk of PD and DLB, *MAPT* H1 may also modify neuropathological features of LBD in general; findings have pointed toward a lack of association.[13,14]

However, the *MAPT* H1 haplotype can be further classified into approximately 20 different common subhaplotypes,[15] and therefore an examination of *MAPT* H1 without consideration of H1 subhaplotypes has potential to overlook important associations. A number of studies have identified associations between specific H1 subhaplotypes and risk of various neurodegenerative diseases.[15-21] Therefore, the aim of this study was to evaluate the associations of *MAPT* haplotypes (i.e., the H2 haplotype and H1 subhaplotypes) with neuropathological features of LBD, including severity of LB pathology, SN neuronal loss, and striatal dopamine depletion.

Patients and Methods

Study Patients

This study included 585 neuropathologically diagnosed LBD cases from the brain bank for neurodegenerative disorders that were evaluated by a single neuropathologist (D.W.D.) at the Mayo Clinic in Jacksonville, Florida. LBD cases with significant coexisting non-

Alzheimer's disease (AD) pathology (e.g., PSP, corticobasal degeneration, Pick disease, or MSA) were excluded, as were cases of amygdala-predominant LBs in the setting of advanced AD and also cases without information available for any of the neuropathological outcome measures examined in this study. Also excluded were cases with a pathogenic mutation in the α-synuclein (*SNCA*) gene or the leucinerich repeat kinase 2 (*LRRK2*) gene. Cases with infarcts or hemorrhages in the putamen or midbrain were not assessed for SN neuronal loss or putaminal dopaminergic degeneration.

All LBD cases were unrelated non-Hispanic whites. Autopsies were performed after obtaining informed consent of the legal next of kin or someone with legal power of attorney. The Mayo Clinic Institutional Review Board has determined that research on autopsy tissue is exempt from human subjects regulations. Summary characteristics of LBD cases are shown in Table 1.

Assessment of Neurofibrillary Tangles, Senile Plaques, and LBs

A detailed description of the neuropathological methodology that was used to assess neurofibrillary tangles (NFTs), senile plaques (SPs), and LBs has been reported previously.[22] Briefly, neuroanatomical sampling and thioflavin-S fluorescence microscopy was performed using procedures of Terry and colleagues,[23] where counts of NFTs and SPs were measured manually in six cortical regions, four sectors of the hippocampus, and two regions of the amygdala. Formalin-fixed, paraffin-embedded tissue samples from limbic and cortical regions were cut at a 5-μm thickness, mounted on glass slides, and processed for immunohistochemistry with an α-synuclein antibody (NACP, 1:3,000 rabbit polyclonal, Mayo Clinic antibody). Pretreatment with 95% formic acid abolished physiological α-synuclein. Immunostaining was standardized by processing under identical conditions with an autostainer (DAKO Auto Machine Corporation, Carpinteria, CA) with the DAKO Envision+ HRP System. LB counts were measured in five cortical regions: middle frontal, superior temporal, inferior parietal, cingulate, and parahippocampal. The staging scheme of Kosaka and colleagues was used to categorize the distribution of LB pathology as either brainstem, transitional, or diffuse.[24] Braak NFT stage[25] and Thal amyloid phase[26] were assigned according to the distributions of NFTs and SPs, respectively. These neuropathological measures are summarized in Table 1.

Quantification of Striatal Dopaminergic Degeneration

Quantitative assessment of striatal dopaminergic degeneration by measurement of tyrosine hydroxylase (TH) immunoreactivity (TH-ir) has been described in detail previously.[14] To summarize, assessment of the putamen was made at the level of the anterior commissure from a section made from the hemibrain in a standardized dissection plane defined by three points in the fundibulum, uncus, and posterior margin of the anterior commissure in the third ventricle. Digital images of the putamen were parcellated into ventromedial and dorsolateral areas,[27] and TH immunoreactivity was assessed with a commercially available antibody to TH (rabbit polyclonal, 1:600; Affinity Bioreagants, Golden, CO) with Proteinase K pretreatment for 5 minutes. The immunostained sections were captured by ScanScope XT (Aperio Technologies, Vista, CA), and images were annotated with ImageScope (version 12.1). Regions of interest were manually edited to exclude artifacts, large blood vessels and

their perivascular spaces, and large fiber bundles. The putamen was divided into ventromedial and dorsolateral regions. Quantification of TH-ir used an algorithm that detected positive pixels based on optical density. TH-ir was expressed as a percentage, calculated as the positive pixels divided by the sum of inverse pixels and background pixels. A lower TH-ir value represents a greater degree of putaminal dopaminergic degeneration. Summaries of dorsolateral and ventromedial putaminal TH-ir in the 585 LBD cases are detailed in Table 1.

Assessment of SN Pigmented Neuronal Loss

A transverse section of midbrain at the level of the third nerve, similar to what has been recommended for diagnostic evaluation of PD,[28] was used to assess SN cell loss at 100× magnification. We restricted our assessment to pigmented neurons of SNpc and divided it into medial and ventrolateral sections, similar to previous studies.[29,30] We used a human atlas of SN cell groups to identify medial and ventrolateral regions of the SN.[31] The density of non-pigmented neurons was not taken into consideration for assessment of the semiquantitative scores, which were based on a 4-point scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe; Table 1).

Genetic Analysis

Using standard protocols, genomic DNA was extracted from brain tissue.[32] A total of six *MAPT* variants (rs1467967, rs242557, rs3785883, rs2471738, rs8070723 [which tags the H2 haplotype], and rs7521) were genotyped to assess the most common *MAPT* haplotypes as described previously.[15] Genotyping was performed using TaqMan single-nucleotide polymorphism genotyping assays on a QuantStudio 7 Flex Real-Time PCR system (Applied Biosystems, Foster City, CA), according to manufacturer instructions (primer sequences available upon request). Genotype calls were made using TaqMan Genotyper Software (v1.3; Applied Biosystems), and call rates were 100% for each variant. There were no departures from Hardy-Weinberg equilibrium in controls (all $P > 0.01$ after Bonferroni correction). Allele and genotype frequencies for each variant are provided for LBD cases in Supporting Information Table S1. The 22 different *MAPT* haplotypes that were observed in ≥1% of individuals in any of the analyses that were performed are shown in Supporting Information Table S2.

Statistical Analysis

The Spearman test of correlation was used to examine pair-wise correlations between the different neuropathological outcomes that were assessed. Associations between six-variant *MAPT* haplotypes and each different neuropathological outcome measure were examined using score tests of association[33] with adjustment for age at death and sex, where haplotypes that occurred in <1% of LBD cases in the given association analysis were excluded. Specifically, score tests of association were performed under a proportional odds logistic regression framework for ordered categorical outcomes (LBD subtype, ventrolateral and medial SN neuronal loss scores); odds ratios (ORs) and 95% confidence intervals (CIs) were estimated and are interpreted as the multiplicative increase on the odds of a more severe LBD subtype or neuronal loss score for each additional copy of the given haplotype. For continuous outcomes (cortical LB counts, dorsolateral and ventromedial putaminal TH-ir),

score tests of association were performed under a linear regression framework; regression coefficients (referred to as β) and 95% CIs were estimated and correspond to the change in the mean outcome measure for each additional copy of the given haplotype. Because of their skewed distributions, LB counts and ventromedial putaminal TH-ir were examined on the square root scale in association analysis, whereas dorsolateral putaminal TH-ir was considered on the natural logarithm scale.

In additional analysis, we examined the association between the specific H1j haplotype and age at death using a score test of association (under a linear regression framework) that was adjusted for sex. A regression coefficient and 95% CI was estimated and is interpreted as the change in the mean age at death for each additional copy of the H1j haplotype.

We applied a Bonferroni correction for multiple testing separately for each neuropathological outcome measure. Specifically, tests of association were performed for between 20 and 21 haplotypes depending on the outcome measure, and as such *P* values of either ≤0.0025 (0.05/20) or ≤0.0024 (0.05/21) were considered to be statistically significant. All statistical tests were two-sided. Statistical analyses were performed using R Statistical Software (version 3.2.3; R Foundation for Statistical Computing, Vienna, Austria).

Results

Correlations between all of the neuropathological outcome measures that were assessed are shown in Supporting Information Table S3. All neuropathological measures were significantly correlated with one another (all $P \leq 0.002$). The magnitude of correlation was strongest for LBD subtype and cortical LB counts (Spearman's *r*: ranging from 0.74 to 0.89), dorsolateral and ventromedial putaminal TH-ir (Spearman's *r*: 0.71), and ventrolateral and medial SN neuronal loss scores (Spearman's *r*: 0.51).

When examining associations of *MAPT* subhaplotypes with neuropathological outcome measures, we identified one association that was statistically significant after correcting for multiple testing, and this involved the rare H1j haplotype (1.3%), which was associated with a lower dorsolateral putaminal TH-ir (and therefore greater dopaminergic degeneration) when compared with other *MAPT* haplotypes (β, −1.24; $P = 0.0016$; Table 2). *MAPT* H1j was also nominally ($P \leq 0.05$) associated with a lower ventromedial putaminal TH-ir (β, −1.15; $P = 0.010$), but was not significantly associated with neuronal loss scores in either the ventrolateral (OR, 3.18; $P = 0.20$) or medial (OR, 1.43; $P = 0.48$) SN (Table 2).

Other nominally significant associations of *MAPT* haplotypes with putaminal TH-ir outcomes were noted regarding associations between H1h and a higher ventromedial putaminal TH-ir (β, 0.38; $P = 0.043$), and also between H1z and a lower ventromedial putaminal TH-ir (β, −0.74; $P = 0.038$; Table 2). Additionally, for SN neuronal loss outcomes, H1i was nominally associated with a lower ventrolateral neuronal loss score (OR, 0.33; $P = 0.008$), H1o was associated with a higher ventrolateral neuronal loss score (OR, 3.74; $P = 0.015$), and H1p was associated with a lower medial neuronal loss score (OR, 0.30; $P = 0.047$; Table 2).

As shown in Table 3 (analysis of cortical LB counts) and Supporting Information Table S4 (analysis of LBD subtype), there were no associations between *MAPT* haplotypes and outcomes related to severity of LB pathology that survived correction for multiple testing. Nominally significant associations were observed between H1q and a higher superior temporal LB count (β, 0.69; $P = 0.041$; Table 3), between H1i and a higher parahippocampal LB count (β, 0.74; $P = 0.016$; Table 3), and between H1o and a less widespread distribution of LB pathology (OR, 0.45; $P = 0.043$; Supporting Table S4).

The common H2 haplotype was not associated with any neuropathological outcome measures (all $P \geq 0.14$; Tables 2 and 3 and Supporting Information Table S4). Given the aforementioned significant association of the *MAPT* H1j haplotype with dorsolateral and ventromedial putaminal TH-ir, we subsequently examined whether H1j was associated with age at death, and did not observe evidence of an association (β = 2.20; 95% CI: −3.63 to 8.04; $P = 0.48$).

Discussion

Although the *MAPT* H1 haplotype is a well-known genetic risk factor for LBD (PD in particular), studies to date have not indicated that the common *MAPT* H1 haplotype modifies neuropathological features in individuals with LBD.[13,14] However, these previous investigations have not taken into account *MAPT* haplotype diversity, and it is this gap in knowledge that we set out to address in the current study. Interestingly, although the H2 haplotype was not notably associated with any of the LBD neuropathological outcomes that were assessed as has been previously shown,[13,14] we observed a significant association between the rare H1j subhaplotype and a greater degree of dorsolateral putaminal dopaminergic degeneration, with a similar (but only nominally significant) association with increased dopaminergic depletion in the ventromedial region. Additionally, although not significant after multiple testing correction, we observed nominally significant associations between several other H1 subhaplotypes and neuropathological outcomes, where some subhaplotypes had toxic effects on neuropathology and others had protective effects; it will be important to validate these weaker nominally significant associations.

As previously mentioned, the strongest association between *MAPT* haplotypes and LBD neuropathological outcomes that we observed involved an association between the rare *MAPT* H1j subhaplotype and increased putaminal dopaminergic depletion. Ventrolateral SN neuronal loss was also notably greater for H1j carriers (OR = 3.18 for more severe neuronal loss), though this did not approach statistical significance ($P = 0.20$), possibly because of the low power to detect associations with outcomes for this rare H1 subhaplotype. The observed association between *MAPT* H1j and increased dopaminergic depletion in the putamen in LBD cases is in line with previous findings, where H1j has been associated with an increased risk of PD by several groups. Specifically, *MAPT* H1j was significantly associated with PD risk in a study by Vandrocova and colleagues that included 572 PD patients and 660 controls (OR, 3.04; $P = 0.012$)[19] and, although not quite statistically significant, was also observed in a higher frequency in PD by Li and colleagues in an investigation of 600 PD patients and 981 controls (OR, 2.27; $P = 0.093$).[34] Conversely, in an examination of 731 DLB patients and 1,049 controls, Labbé and colleagues did not observe an association

between the H1j subhaplotype and risk of DLB (OR, 1.17; $P = 0.68$).[10] The findings of our study indicate that the aforementioned associations between H1j and PD may be attributed to a direct association between this haplotype and greater putaminal dopaminergic degeneration specifically, given that H1j was not associated with severity of LB pathology.

It is worth noting that in addition to PD, the *MAPT* H1j subhaplotype has been associated with risk of several other neurodegenerative diseases with widely varying clinical and neuropathological features. Specifically, H1j has been linked with an increased risk of pathologically confirmed MSA (OR, 3.88; $P = 0.021$)[16] and AD (OR, 1.32; $P = 0.049$),[20] but was observed at a lower frequency in PSP patients in case-control series from the United Kingdom (0.0% vs. 2.4%; $P = 0.033$) and the United States (0.0% vs. 3.0%; $P = 0.055$).[15] Although the *MAPT* H1 haplotype has been very well studied in neurodegeneration, these previous findings taken together with those of our study suggest that further examination of the role that the specific H1j subhaplotype plays in susceptibility to neurodegenerative disorders may be useful.

We did not observe any dramatic associations between *MAPT* haplotypes and severity of LB pathology. In a previous study, PD genetic risk variants that were identified in a meta-analysis of genome-wide association studies were assessed for association with severity of LB pathology, and though several nominally significant correlations were noted (as was also the case in our study), no major associations were identified.[13] The findings of our current study provide further support for the hypothesis that factors other than PD susceptibility loci are responsible for the variation in severity of LB pathology in LBD patients.

Several limitations of our study are important to note. Although the pathological measures were assessed by a single neuropathologist and the sample size is relatively large for a series of neuropathologically diagnosed LBD cases, the sample size is nonetheless somewhat limited for a genetic association study, and thus we may be underpowered to detect associations with specific subhaplotypes. Although this limitation is tempered to a degree by the fact that all of the neuropathological outcomes that were assessed were either continuous or ordinal (where power to detect associations is much higher in comparison to evaluation of a binary outcome such as case/control status), the possibility of a type II error (i.e., a false-negative finding) is important to bear in mind, especially after adjustment for multiple testing. Additionally, many of the H1 subhaplotypes are rare, including the aforementioned H1j haplotype that showed the strongest evidence of association with outcomes. Therefore, validation of findings involving rare *MAPT* H1 subhaplotypes in larger series of LBD cases will be important; collaborative approaches may be required to achieve sufficient sample sizes, and this may now be possible because of advances in digital imaging and automated quantitative measures of pathology. Sample sizes required to have 80% power to detect a significant association with a continuous outcome measure after adjustment for multiple testing are shown for rarer H1 subhaplotypes (1–5%) in Supporting Information Table S5.

In conclusion, the findings of our study provide evidence that although the *MAPT* H2 haplotype does not appear to influence neuropathological severity of LBD, the specific H1j subhaplotype may be associated with a greater degree of putaminal dopaminergic degeneration in LBD cases. It should be highlighted that this finding would not have

remained statistically significant if we had corrected for all tests performed in our study (rather than correcting separately for each outcome measure as we did), and as a result it is more exploratory in nature. Nonetheless, these results provide insight into how H1j may modulate risk of PD and additionally indicate that the *MAPT* H1j subhaplotype may be responsible for a small degree of the neuropathological heterogeneity observed in LBD patients. Further study of this rare haplotype in larger series of LBD patients is warranted, and studies of clinical PD and DLB cohorts will be important to evaluate whether the H1j haplotype (and H1 subhaplotypes in general) is associated with any specific clinical features of these two LB disorders. Additionally, given the role of the *MAPT* H1 haplotype in susceptibility to PD (with a weaker and less replicated association seen in DLB), it will be of interest to examine the role of specific *MAPT* H1 subhaplotypes in determining risk of PD and DLB in large case-control or meta-analytic studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1.

Characteristics of LBD cases

Variable	Summary (N = 585)
Age at death (years)	79 (50, 99)
Sex (men)	345 (59.0%)
Braak NFT stage	
0	13 (2.2%)
I	20 (3.4%)
II	99 (16.9%)
III	148 (25.3%)
IV	92 (15.7%)
V	94 (16.1%)
VI	119 (20.3%)
Thal amyloid phase	
0	61 (11.2%)
1	51 (9.4%)
2	27 (5.0%)
3	112 (20.6%)
4	46 (8.4%)
5	248 (45.5%)
LBD subtype	
Brainstem	72 (12.3%)
Transitional	208 (35.6%)
Diffuse	305 (52.1%)
Lewy body counts	
Middle frontal gyrus	3 (0, 35)
Superior temporal gyrus	7 (0, 50)
Inferior parietal gyrus	2 (0, 30)
Cingulate gyrus	8 (0, 35)
Parahippocampal gyrus	14 (0, 45)
Putaminal TH-ir	
Dorsolateral	4.26 (0.26, 42.18)
Ventromedial	9.99 (0.26, 39.18)
Substantia nigra neuronal loss score	
Ventrolateral	
0 = none	3 (0.6%)
0.5 = none/mild	10 (2.1%)
1 = mild	56 (11.8%)
1.5 = mild/moderate	55 (11.6%)
2 = moderate	61 (12.9%)
2.5 = moderate/severe	55 (11.6%)
3 = severe	233 (49.3%)

Variable	Summary (N = 585)
Medial	
0 = none	24 (5.4%)
0.5 = none/mild	26 (5.8%)
1 = mild	83 (18.6%)
1.5 = mild/moderate	53 (11.9%)
2 = moderate	56 (12.6%)
2.5 = moderate/severe	54 (12.1%)
3 = severe	150 (33.6%)

The sample median (minimum, maximum) is given for continuous variables. Information was unavailable for Thal amyloid phase (N = 40), Lewy body counts in the middle frontal (N = 20), superior temporal (N = 21), inferior parietal (N = 21), cingulate (N = 27), and parahippocampal (N = 88) gyri, dorsolateral putaminal TH-ir (N = 107), ventromedial putaminal TH-ir (N = 107), ventrolateral SN neuronal loss score (N = 112), and medial SN neuronal loss score (N = 139).

TABLE 2.

Association of *MAPT* haplotypes with putaminal TH-ir (dorsolateral and ventromedial) and SN neuronal loss (ventrolateral and medial)

		Association With Dorsolateral Putaminal TH-ir		Association With Ventromedial Putaminal TH-ir		Association With Ventrolateral SN Neuronal Loss Score		Association With Medial SN Neuronal Loss Score	
Haplotype	**Haplotype Frequency (%)**	**Regression Coefficient (95% CI)**	***P* Value**	**Regression Coefficient (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**
H1b	16.5	−0.06 (−0.22, 0.11)	0.48	−0.01 (−0.19, 0.18)	0.93	1.08 (0.77, 1.53)	0.65	1.05 (0.75, 1.47)	0.78
H1c	11.9	−0.03 (−0.20, 0.15)	0.76	−0.15 (−0.35, 0.05)	0.14	0.92 (0.64, 1.31)	0.63	1.01 (0.71, 1.44)	1.00
H1d	7.3	0.08 (−0.17, 0.33)	0.52	0.09 (−0.19, 0.38)	0.54	1.15 (0.68, 1.96)	0.57	1.27 (0.75, 2.14)	0.31
H1e	8.5	−0.07 (−0.29, 0.16)	0.59	−0.09 (−0.35, 0.17)	0.51	0.77 (0.49, 1.22)	0.24	1.05 (0.67, 1.65)	0.89
H1f	1.1	0.18 (−0.55, 0.91)	0.57	−0.10 (−0.94, 0.74)	0.82	1.12 (0.24, 5.36)	0.86	2.23 (0.48, 10.28)	0.32
H1g	1.8	−0.13 (−0.61, 0.36)	0.55	−0.34 (−0.90, 0.21)	0.22	1.40 (0.47, 4.11)	0.52	1.66 (0.60, 4.58)	0.32
H1h	3.9	0.16 (−0.17, 0.49)	0.36	**0.38 (0.00, 0.76)**	**0.043**	1.20 (0.60, 2.42)	0.59	0.93 (0.47, 1.80)	0.85
H1i	2.9	0.16 (−0.24, 0.56)	0.40	−0.11 (−0.57, 0.35)	0.64	**0.33 (0.15, 0.77)**	**0.008**	0.87 (0.38, 1.95)	0.67
H1j	1.3	**−1.24 (−1.95, −0.53)**	**0.0016**	**−1.15 (−1.97, −0.35)**	**0.010**	3.18 (0.59, 17.12)	0.20	1.43 (0.34, 5.97)	0.48
H1I	2.5	0.06 (−0.37, 0.49)	0.73	0.06 (−0.43, 0.55)	0.81	1.19 (0.48, 2.96)	0.74	1.11 (0.48, 2.61)	0.80
H1m	1.9	−0.40 (−0.91 0.12)	0.11	−0.43 (−1.03, 0.16)	0.14	0.67 (0.24, 1.90)	0.51	1.56 (0.51 4.78)	0.37
H1o	2.9	0.08 (−0.35, 0.52)	0.61	0.28 (−0.22, 0.77)	0.25	**3.74 (1.31, 10.67)**	**0.015**	0.93 (0.37, 2.35)	0.79
H1p	1.2	0.12 (−0.53, 0.78)	0.70	0.50 (−0.24, 1.25)	0.20	1.06 (0.27, 4.14)	0.90	**0.30 (0.11, 1.00)**	**0.047**
H1q	1.2	−0.22 (−0.84, 0.39)	0.51	0.08 (−0.62, 0.79)	0.83	2.31 (0.52, 10.23)	0.25	0.59 (0.17, 2.08)	0.43
H1r	1.7	−0.15 (−0.75, 0.44)	0.52	−0.23 (−0.91, 0.45)	0.45	1.31 (0.38, 4.56)	0.74	2.33 (0.68, 8.02)	0.13
H1s	1.5	−0.40 (−0.91, 0.12)	0.68	−0.43 (−1.03, 0.16)	0.36	0.67 (0.24, 1.90)	0.55	1.56 (0.51, 4.78)	0.93
H1u	3.0	−0.01 (−0.42, 0.39)	0.96	0.00 (−0.47, 0.46)	>0.99	1.18 (0.49, 2.81)	0.75	1.13 (0.50, 2.57)	0.78
H1x[a]	1.2	—	—	—	—	2.32 (0.55, 9.77)	0.32	1.43 (0.38, 5.44)	0.62
H1y	1.5	0.35 (−0.24, 0.94)	0.28	0.29 (−0.38, 0.97)	0.30	0.78 (0.23, 2.57)	0.86	0.39 (0.11, 1.35)	0.16
H1z	1.1	−0.39 (−1.06, 0.27)	0.21	**−0.74 (−1.47, −0.01)**	**0.038**	0.83 (0.22, 3.20)	0.80	1.54 (0.38, 6.26)	0.55
H2	22.5	0.09 (−0.04, 0.23)	0.18	0.10 (−0.05, 0.25)	0.20	0.90 (0.68, 1.19)	0.46	0.88 (0.67, 1.15)	0.35

P values result from score tests of association that were adjusted for age and sex, where haplotypes that occurred in <1% of LBD cases in a given association analysis were excluded from that analysis. Regression coefficients correspond to the change in the mean outcome measure (on the natural logarithm scale for dorsolateral putaminal TH-ir; on the square root scale for ventromedial putaminal TH-ir) for each additional copy of the given haplotype. ORs are interpreted as the multiplicative increase on the odds of a higher neuronal loss score for each additional copy of the given haplotype. *P* values ≤0.0025 (associations with dorsolateral and ventromedial putaminal TH-ir; 20 tests each) and ≤0.0024 (associations with ventrolateral and medial neuronal loss score; 21 tests each) were considered to be statistically significant after applying a Bonferroni correction for the number of tests of association that were performed for each outcome.

[a] Indicates a haplotype that was observed at an overall frequency of <1% in a particular analysis and was therefore excluded from that analysis; sample sizes utilized in different analyses varied because of the varying degree of missing information for each outcome measure. Associations between haplotypes and outcomes that had a *P* values ≤0.05 are shown in bold.

TABLE 3.

Association between *MAPT* haplotypes and cortical LB counts

		Association With Middle Frontal LB Count		Association With Superior Temporal LB Count		Association With Inferior Parietal LB Count		Association With Cingulate LB Count		Association With Parahippocampal LB Count	
Haplotype	**Frequency (%)**	**Regression Coefficient (95% CI)**	***P* Value**	**Regression Coefficient (95% CI)**	***P* Value**	**Regression Coefficient (95% CI)**	***P* Value**	**Regression Coefficient (95% CI)**	***P* Value**	**Regression Coefficient (95% CI)**	***P* Value**
H1b	16.5	−0.08 (−0.28, 0.11)	0.40	0.00 (−0.23, 0.22)	0.97	−0.05 (−0.24, 0.13)	0.58	−0.07 (−0.27, 0.13)	0.52	−0.10 (−0.34, 0.14)	0.42
H1c	11.9	−0.03 (−0.24, 0.17)	0.72	−0.15 (−0.38, 0.09)	0.20	−0.12 (−0.31, 0.07)	0.21	−0.05 (−0.26, 0.16)	0.62	−0.10 (−0.36, 0.15)	0.38
H1d	7.3	0.07 (−0.21, 0.36)	0.63	0.12 (−0.21, 0.45)	0.50	0.13 (−0.14, 0.39)	0.37	0.11 (−0.18, 0.41)	0.47	0.09 (−0.27, 0.46)	0.65
H1e	8.5	−0.07 (−0.33, 0.18)	0.58	−0.13 (−0.43, 0.16)	0.38	−0.13 (−0.37, 0.11)	0.31	−0.12 (−0.39, 0.14)	0.37	−0.17 (−0.49, 0.14)	0.27
H1f[a]	1.1	−0.78 (−1.62, 0.07)	0.078	−0.40 (−1.38, 0.58)	0.45	−0.53 (−1.33, 0.26)	0.21	−0.47 (−1.35, 0.41)	0.28	—	—
H1g	1.8	0.27 (−0.25, 0.78)	0.33	0.01 (−0.59, 0.60)	0.98	0.37 (−0.12, 0.85)	0.16	0.21 (−0.33, 0.74)	0.45	0.25 (−0.39, 0.90)	0.46
H1h	3.9	0.05 (−0.34, 0.44)	0.81	0.20 (−0.26, 0.65)	0.40	0.21 (−0.15, 0.58)	0.27	0.10 (−0.31, 0.51)	0.63	0.06 (−0.42, 0.55)	0.79
H1i	2.9	0.07 (−0.43, 0.57)	0.73	0.11 (−0.47, 0.69)	0.68	0.03 (−0.44, 0.50)	0.84	0.07 (−0.46, 0.60)	0.75	**0.74 (0.13, 1.36)**	**0.016**
H1j	1.3	−0.49 (1.32, 0.34)	0.29	−0.24 (−1.21, 0.72)	0.62	−0.23 (−1.91, 0.55)	0.59	−0.29 (−1.15, 0.58)	0.55	0.13 (−0.86, 1.13)	0.75
H1k[a]	1.2	—	—	—	—	—	—	—	—	−0.26 (−1.27, 0.75)	0.59
H1l	2.5	−0.06 (−0.53, 0.40)	0.80	0.21 (−0.33, 0.75)	0.44	0.08 (−0.36, 0.51)	0.73	−0.12 (−0.61, 0.37)	0.54	0.21 (−0.47, 0.88)	0.55
H1m	1.9	−0.27 (−0.79, 0.25)	0.32	−0.31 (−0.92, 0.29)	0.32	−0.20 (−0.69, 0.29)	0.41	−0.17 (−0.71, 0.37)	0.54	−0.15 (−0.82, 0.53)	0.67
H1o	2.9	−0.09 (−0.57, 0.39)	0.72	−0.29 (−0.85, 0.27)	0.34	−0.08 (−0.54, 0.37)	0.73	0.00 (−0.50, 0.50)	0.99	−0.51 (−1.11, 0.09)	0.11
H1p	1.2	−0.15 (−0.89, 0.58)	0.69	−0.58 (−1.42, 0.27)	0.19	−0.51 (−1.20, 0.18)	0.13	−0.35 (−1.11, 0.41)	0.37	−0.41 (−1.33, 0.51)	0.43
H1q	1.2	0.48 (−0.13, 1.08)	0.11	**0.69 (0.01, 1.38)**	**0.041**	0.42 (−0.15, 0.99)	0.14	0.48 (−0.15, 1.11)	0.12	0.46 (−0.30, 1.21)	0.20
H1r	1.7	0.42 (−0.19, 1.03)	0.14	0.10 (−0.61, 0.81)	0.77	0.49 (−0.08, 1.07)	0.068	0.23 (−0.41, 0.87)	0.47	0.45 (−0.38, 1.29)	0.24
H1s	1.5	−0.27 (−0.79, 0.25)	0.95	−0.31 (−0.92, 0.29)	0.74	−0.20 (−0.69, 0.29)	0.63	−0.17 (−0.71, 0.37)	0.58	−0.15 (−0.82, 0.53)	0.84
H1u	3.0	−0.21 (−0.65, 0.23)	0.38	−0.30 (−0.82, 0.21)	0.27	−0.20 (−0.61, 0.22)	0.37	−0.01 (−0.47, 0.45)	0.99	−0.05 (−0.67, 0.57)	0.94
H1x	1.2	−0.10 (−0.81, 0.60)	0.79	0.07 (−0.75, 0.89)	0.83	−0.22 (−0.88, 0.44)	0.52	−0.23 (−0.99, 0.53)	0.54	−0.31 (−1.22, 0.60)	0.55
H1y	1.5	−0.22 (−0.92, 0.47)	0.42	0.18 (−0.63, 0.99)	0.67	−0.26 (−0.91, 0.40)	0.30	−0.39 (−1.11, 0.34)	0.18	0.14 (−0.72, 0.99)	0.66
H1z	1.1	0.63 (−0.14, 1.41)	0.12	0.57 (−0.33, 1.47)	0.21	0.35 (−0.38, 1.08)	0.33	0.51 (−0.29, 1.32)	0.23	0.50 (−0.49, 1.49)	0.34
H2	22.5	0.10 (−0.05, 0.26)	0.19	0.12 (−0.06, 0.30)	0.18	0.11 (−0.04, 0.25)	0.15	0.12 (−0.04, 0.28)	0.14	0.10 (−0.10, 0.29)	0.33

P values result from score tests of association that were adjusted for age and sex, where haplotypes that occurred in <1% of LBD cases in a given association analysis were excluded from that analysis. Regression coefficients correspond to the change in the mean outcome measure (on the square root scale) for each additional copy of the given haplotype. *P* values ≤0.0024 were considered to be statistically significant after applying a Bonferroni correction for the 21 tests of association that were performed for each outcome.

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[a] Indicates a haplotype that was observed at an overall frequency of <1% in a particular analysis and was therefore excluded from that analysis; sample sizes utilized in different analyses varied because of varying missing LB count information in the different cortical regions. Associations between haplotypes and outcomes that had *P* values ≤0.05 are shown in bold.