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MAPT haplotype H1G is associated with increased risk of dementia with Lewy bodies

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Abstract

INTRODUCTION—The *MAPT* H1 haplotype has been associated with several neurodegenerative diseases. We were interested in exploring the role of *MAPT* haplotypic variation in risk of Dementia with Lewy bodies (DLB).

METHOD—We genotyped six *MAPT* haplotype tagging SNPs and screened 431 clinical DLB cases, 347 pathologically-confirmed high likelihood DLB cases, and 1049 controls.

RESULT—We performed haplotypic association tests and detected an association with the protective H2 haplotype in our combined series (Odds Ratio (OR)=0.75). We fine-mapped the

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locus and identified a relatively rare haplotype, H1G, that is associated with an increased risk of DLB (OR=3.30, P=0.0017). This association was replicated in our pathologically-confirmed series (OR=2.26, P=0.035).

DISCUSSION—These results support a role for H1 and specifically H1G in susceptibility to DLB. However, the exact functional variant at the locus is still unknown, and additional studies are warranted to fully explain genetic risk of DLB at the *MAPT* locus.

Keywords

Dementia with Lewy bodies; Lewy body disease; genetic association study; MAPT; tau protein

1. Background

Dementia with Lewy bodies (DLB) has been described as the second most common cause of dementia after Alzheimer's disease (AD) representing up to 25% of dementias worldwide.[1] A Mayo Clinic study reports an incidence rate of 3.5/100,000 persons per year overall and the rate is about four times higher in men after age 60 compared to women of the same age group (up to 44.5/100,000 persons per year in men).[2] Despite the common occurrence of the disease, the etiology remains obscure, and few studies have examined the underlying genetic causes. Variants in the *GBA* and *APOE* genes were identified as risk factors following candidate gene association studies.[3–9] The first large scale genetic study on DLB was published by Bras *et al.* and identified *APOE*, *SNCA* and *SCARB2* as risk factors through a screening of 54 AD and Parkinson's disease (PD) loci in 788 DLB patients and 2624 controls.[10] Although variants in the microtubule associated protein tau (*MAPT*) gene did not reach genomewide significance, the odds ratio of 0.78 is very similar to what has been observed previously for the protective *MAPT* H2 haplotype in other synucleinopathies.

The *MAPT* gene sits on chromosome 17 and is characterized by two main haplotypes, termed H1 and H2, with H2 resulting from a 900kb inversion of H1 that occurred about 3 million years ago.[11] H2 is rare or absent from African and Asian populations but represents 20% of alleles in populations of European descent.[11] Haplotype H1 subsequently diversified to give rise to additional *MAPT* subhaplotypes.[12] The H2 haplotype has been associated with a decreased risk of PD[13], Progressive supranuclear palsy (PSP)[14] and corticobasal degeneration[15] through genomewide association studies (GWAS). In AD, *APOE* seems to mask the *MAPT* signal: the association with the chromosome 17 locus is detected only among non- *APOE* ε4 carriers.[16] The H1 subhaplotypes also carry significance, H1 haplotype C (H1C) is highly associated with PSP[12] and some studies have shown association with AD[17, 18] and H1P has been associated to Parkinson's disease with dementia (PDD).[19]

Considering the clinical and pathological overlap of DLB with AD and PD, one would anticipate shared genetic risk underpinnings. Moreover, the Bras *et al.* study presented a nominally significant association between *MAPT* and DLB.[10] In this context, we were interested in investigating further the genetic diversity of the *MAPT* locus in DLB patients looking specifically at the *MAPT* haplotypes previously described.[12] Our series consists of 431 patients with clinical DLB and 1049 controls, and a series consists of 347 with

pathologically-confirmed Lewy body disease (LBD) and high likelihood of clinical DLB. We first genotyped a H1 tagging SNP, and found a suggestive association with DLB for the H1 haplotype. We then genotyped additional *MAPT* haplotype tagging SNPs that define most of the variability at the locus[12, 20] and observed a rare haplotype, H1G, significantly associated with an increased risk of DLB.

2. Methods

2.1 Study subjects

For the first portion of this case-control study where the association between *MAPT* haplotypes and risk of DLB was assessed, a total of 431 patients with clinical DLB, 347 pathologically-confirmed Lewy body disease (LBD) cases with a high likelihood of clinical DLB (i.e. the "pathological high DLB likelihood" series), and 1049 controls were included. These subjects represent all individuals of the given disease groups with available genetic information. Forty-seven subjects are common to both the clinical DLB series and the pathological high DLB likelihood series, and therefore the combined series consisted of 731 different clinical DLB or pathological high DLB likelihood cases. All subjects are unrelated non-Hispanic Caucasians of European descent. Patients with known pathogenic mutations in PD or AD genes were excluded. Clinical DLB patients and controls are from a US series collected at Mayo Clinic Jacksonville (158 cases and 881 controls) and Rochester (273 cases and 168 controls). Clinical DLB samples were part of the NIH-funded studies on aging and dementia [Alzheimer's Disease Research Center (ADRC) or Mayo Clinic Study of Aging (MCSA)]. Diagnosis of clinical DLB was made according to published criteria.[21–23]

Our pathological high DLB likelihood replication series is a pathologically-defined series collected and examined at Mayo Clinic Jacksonville by our neuropathologist (DWD) between April, 1990 and July, 2013 that satisfied the following criteria: (1) had Lewy body pathology, (2) did not have amygdala predominant or incidental Lewy body disease, (3) did not have coexisting pathology (i.e. progressive supranuclear palsy, corticobasal degeneration, Pick's disease, or multiple system atrophy), and (4) were assessed as high DLB likelihood by CDLB criteria.[21] Our controls were individuals free of dementia or movement disorder at the time of examination. Characteristics of patients with clinical DLB, pathological high likelihood DLB, and controls are summarized in Table 1 for each series.

For the second portion of the study examining the association of *MAPT* haplotypes with Lewy body count and neurofibrillary tangle (NFT) count in LBD patients, we included all 667 cases received at the Mayo Clinic Jacksonville brain bank for neurodegenerative disorders between April 1990 and July 2013 that had Lewy body pathology, did not have amygdala predominant or incidental Lewy body disease, did not have coexisting pathology, and had Lewy body counts measured in at least one of five brain regions (cingulate gyrus, interior parietal, mid frontal, parahippocampal, superior temporal, Appendix table A1) or NFT counts measured in at least one of 14 brain regions (Cortex entorhinal layer II, Cortex entorhinal deep, CA1, Subiculum, CA2/3, Endplate, Nucleus basalis of Meynert, Lateral amygdala, Medial amygdala, Superior temporal, Inferior parietal, Mid frontal, Visual cortex, Motor cortex, Appendix table A2). These 667 Lewy body disease patients were all unrelated and were included irrespective of DLB likelihood (i.e. Lewy body disease patients with low,

moderate, and high DLB likelihood were all included in the second portion of the study). The number of cases with available data varies by brain region from 497 cases to 666 cases (Appendix tables A1 and A2). Neuropathological methods have been described in detail previously.[24] The Mayo Clinic Institutional Review Board approved the study and all subjects or legal next of kin provided written informed consent.

2.2 Genetic analysis

Genomic DNA was extracted from peripheral blood monocytes or brain tissue using the standard protocols.[25] Six tagging SNPs were chosen to assess the most common *MAPT* subhaplotypes as described previously.[12, 20] The genotyping of *MAPT* haplotype tagging variants rs1467967, rs242557, rs3785883, rs2471738, rs8070723 (the H2-tagging variant), and rs7521 was performed using TaqMan SNP genotyping assays on an ABI 7900HT Fast Real-Time PCR system (Applied Bio- systems, Foster City, CA, USA) according to the manufacturer's instructions (primer sequences are available upon request). Genotype calls were made using Taqman Genotyper Software v1.3 (Applied Bio- systems, Foster City, CA, USA). The genotype call-rate was 100%. There was no evidence of a departure from Hardy-Weinberg equilibrium in study controls for any of the 6 *MAPT* variants (all $P \geq 0.05$ after Bonferroni correction).

2.3 Statistical analysis

All statistical analysis was performed using R Statistical Software (version 3.0.2; R Foundation for Statistical Computing, Vienna, Austria). For the first portion of the study, all analysis was performed separately for the clinical DLB series, the pathological high DLB likelihood series, and the combined series. For the 47 patients in the combined series who were in both the clinical DLB and pathological high DLB likelihood series, these were only included once in analyses involving the combined series. For the single variant analyses, associations between each of the 6 individual *MAPT* variants and risk of disease were evaluated using logistic regression models adjusted for age (age at onset in clinical DLB patients, age at death in pathological high DLB likelihood patients, age at blood collection in controls) and gender, where each variant was examined under an additive model (i.e. effect of each additional minor allele). Models comparing the clinical DLB patients to controls were additionally adjusted for Mayo Clinic site (Jacksonville or Rochester). OR and 95% confidence intervals (CIs) were estimated, and p-values ≤ 0.05 were considered as statistically significant in this initial analysis.

In our primary analysis, associations between *MAPT* haplotypes and risk of disease were examined using the R haplo.score[26] and haplo.glm[27] functions, where haplotypes occurring in less than 1% of subjects were excluded and adjustments were made for age, gender, and Mayo Clinic site as previously described. Specifically, using haplo.score, we performed score tests of association comparing the frequency of each different haplotype between cases and controls, while we obtained ORs and 95% CIs in comparison to a common reference haplotype (H1C) from logistic regression models using haplo.glm. The common H1C haplotype was chosen as the reference haplotype as it was the haplotype that occurred at a frequency >10% that showed the least degree of evidence of an association with risk of disease in the individual series. In order to correct for multiple testing in our

primary haplotype analyses, we utilized a Bonferroni adjustment. Specifically, when comparing clinical DLB patients to controls in our initial screening sample, p-values ≤ 0.0028 (18 tests) were considered as statistically significant. Power to detect associations between haplotypes and clinical DLB is displayed in Appendix Table A3. For pathological high DLB likelihood vs. control haplotype analysis, we were primarily interested in replicating significant associations that were observed in the screening sample. Given that only one haplotype (H1G) was significantly associated with risk of DLB in the screening sample, no adjustment for multiple testing was made, and a p-value ≤ 0.05 is considered as statistically significant for replication of this result. Although not of primary interest, for completeness, associations of remaining haplotypes with risk of disease were also evaluated in the replication series.

For the second portion of the study involving the entire series of 667 Lewy body disease patients, we employed score tests for association using the R haplo.score function to assess the associations of *MAPT* haplotypes with Lewy body count and NFT count in each brain region. Haplotypes that occurred in less than 1% of subjects were not considered, and adjustments were made for age at death and gender. In order to correct for the multiple statistical tests that were performed in these analyses, we again utilized a Bonferroni adjustment. There were a total of 20 haplotypes that occurred with a frequency of 1% or greater in the overall Lewy body disease series, and therefore p-values ≤ 0.0025 were considered as statistically significant for this part of the analysis. Additionally, although not directly related to the primary aim of the study, we assessed associations between Lewy body count and NFT count in a given brain region using Spearman's test of correlation, where p-values ≤ 0.0167 were considered as significant after Bonferroni correction for the three associations that were examined.

3. Results

In order to initially assess the importance of the *MAPT* H1/H2 haplotypes in DLB, we genotyped the H2-tagging rs8070723 variant in our clinical DLB and pathological high DLB likelihood series and detected a suggestive association in the combined series (OR: 0.83, P=0.051) (Table 2). To further define the variability at the locus, we genotyped additional *MAPT* sub-haplotype tagging SNPs. Single-variant associations with risk of clinical DLB and pathological high DLB likelihood are presented in Table 2. None of the individual *MAPT* variants displayed a significant association with risk of disease (in comparison to controls), though an additional suggestive trend was observed for rs242557 in the combined series (OR: 1.17, P=0.051).

In order to study the haplotype diversity at the *MAPT* locus, we next evaluated the association of *MAPT* haplotypes with risk of clinical DLB. A total of 18 different haplotypes consisting of the 6 genotyped variants (rs1467967, rs242557, rs3785883, rs2471738, rs8070723, and rs7521) were identified (Table 3). Of those, H2 (defined here by the 6 *MAPT*-tagging SNPs) was the most frequent (23.6% in controls, 19.2% in DLB, P=0.075) while 4 additional haplotypes had frequencies above 5% (H1B, H1C, H1E and H1D), the remaining 13 haplotypes had frequencies below 5% in cases and controls. We identified a significant association between the H1G haplotype and increased risk of clinical

DLB in comparison to controls (3.3% vs. 1.0%, OR=3.30, P=0.0017). This association between H1G and disease risk was also observed in our pathological high DLB likelihood replication series (2.6% vs. 1.0%, OR=2.26, P=0.035) and in the combined group of clinical DLB patients and pathological high DLB likelihood patients (2.8% vs. 1.0%, OR=2.17, P=0.005); note that the lower OR in the combined group compared to both of the individual disease groups is caused by the aforementioned overlap of 47 patients in these groups. Additionally, the H2 haplotype was observed at a lower frequency in the combined disease group in comparison to controls, though this was only nominally significant (20.9% vs. 23.6%, OR=0.75, P=0.047). No other notable associations between haplotypes and disease risk were observed (Table 3).

We were additionally interested in studying whether the association between the H1G haplotype and risk of DLB is independent of the rare MAPT exon 7 variant p.A152T (rs143624519) that we recently found to be associated to DLB.[28] Therefore, we additionally adjusted our haplotypic association tests for this variant and observed similar results for both the clinical DLB series (OR: 3.23, P=0.0021) and the pathological high DLB likelihood series (OR: 2.26, P=0.039), which supports the independence of these two signals.

We next hypothesized that H1G and potentially H2 could be related to severity of pathology; hence we subsequently used our pathologically confirmed series of 667 LBD cases to explore the relationship between *MAPT* haplotypes and Lewy body counts. We did not observe any significant associations with Lewy body counts in any of the 5 brain regions examined for the H1G (all P≥0.14) or H2 (all P≥0.11) haplotypes. Similarly, we hypothesized that an associated *MAPT* haplotype would influence the number of NFTs, which consists of aggregates of hyperphosphorylated tau protein. However we did not detect an association between NFT counts in any of the 14 brain regions that were evaluated and either the H1G haplotype (all P≥0.080) or the H2 haplotype (all P≥0.015) that withstood adjustment for multiple testing (P≤0.0025 considered significant). The one nominally significant association that we did observe for H2 occurred in the CA 2/3 region (P=0.015), where mean NFT count for H2 carriers was 0.89 times that of patients with the common H1C haplotype.

Of note, when assessing associations between Lewy body count and NFT count within a given brain region, we observed a significant positive correlation in the superior temporal region (Spearman's *r*: 0.24, P<0.0001), but no notable correlation in the inferior parietal (Spearman's *r*: 0.05, P=0.27) or mid frontal (Spearman's *r*: −0.03, P=0.51) regions.

4. Discussion

Most of the genetics underlying the pathogenesis of DLB is unknown. The study of Bras *et al.* has nominated three susceptibility loci (*APOE*, *SNCA* and *SCARB2*)[10], however the likelihood of obtaining false-negative findings is very high given their sample size and significance threshold after multiple testing correction, and therefore many more loci may be involved in determining disease risk. As previously mentioned, in the Bras *et al* study, the *MAPT* gene does not reach significance following conservative thresholds but the results

show a trend towards association (OR 0.78, P=0.001).[10] In addition, the *MAPT* H1 haplotype has been linked to increase α-synuclein deposition in brain tissue of DLB patients.[29]

In the present study, we replicate the association with H2 (as defined by the 6 *MAPT* haplotype tagging SNPs). The signal reaches nominal significance in our combined analyses (OR=0.75, p=0.047) and the OR is similar to what is observed elsewhere in large genetics studies of PD (OR=0.77 in Nalls *et al.*)[30]. An association between *MAPT* and DLB is not surprising given that multiple previous studies have shown that the *MAPT* H1 haplotype increases the risk of developing several different neurodegenerative diseases including tauopathies and synucleinopathies.[13–15]

We further defined the association at the *MAPT* locus by studying the H1 subhaplotypes. Interestingly, we found a significant H1 subhaplotype, H1G, associated with clinical DLB (OR=3.30, P=0.0017) and this association is also seen in pathological high DLB likelihood (OR=2.26, P=0.035) and the combined series (OR=2.16, P=0.005).

The exact functional variant on the H1G haplotype is unknown, but it is possible that a rare coding variant would carry the risk. We recently identified a significant association between rare MAPT exon 7 variant p.A152T and increased risk of developing DLB (OR=5.76, P=0.007).[31] We tested the interdependence of H1G and p.A152T but found no correlation. It is therefore likely that another variant in MAPT, or in another of the ~10 genes at the locus, is responsible for the association to H1G.

Given the lack of coding variant, an intergenic variant located in a regulatory element that influences gene expression could explain the risk. The H1 haplotype has been shown to be correlated to differential expression of the *MAPT* gene with H1 generally associated with increased *MAPT* expression in the brain.[20, 32, 33] H1 subhaplotypes have also been suggested to influence expression; among the suggestive associations to differential expression of *MAPT* are the H1B, H1I and H1L subhaplotypes in AD[20] and the H1C subhaplotype in PSP.[33] Interestingly, the H1 haplotype has been associated with differential expression, in addition to *MAPT*, of five other genes located at the *MAPT* locus: increased expression of *MAPT*, *LRRC37A4*, and *PLEKH1M* and decreased expression of *MGC57346*, *LRRC37A* and *CRHR1*.[32] In PSP cases, H1 and H1C increased expression of *MAPT* appears to be correlated to increased levels of the 4R-tau isoforms which could be the basis for the imbalance in the 3R/4R tau ratio leading to the disease.[33] Increased levels of 4R-tau in H1C carriers have also been reported in AD.[18]

The pathological consequences of carrying haplotype H1G are still unclear. We hypothesized that H1G could be related to severity of disease so we looked at Lewy body and NFT burden in our LBD series but find no significant correlation. Considering the relatively low frequency of H1G (~3% in cases) and our small sample size, it is possible that these associations exist in truth but our study is underpowered to detect them, or that the pathological changes associated to H1G are not detectable using regular immunostaining techniques. We detected one nominally significant association (P=0.015) in one region of the brain, CA 2/3, where carriers of the H2 haplotype have lower NFT counts.

Further fine-mapping and functional studies will be essential to identify the causal variant on *MAPT* H1G and assess its effect on the pathology. Specifically, deep re-sequencing of the locus, including intronic and intergenic regions, in a sufficient number of well-phenotyped samples, homozygote carriers of the rare H1G haplotype will allow for the identification of candidate variants. Variants on H1G could be intronic and influence the splicing of *MAPT* exon 10 which, when present, gives rise to 4R-tau isoforms and when absent, to 3R-tau isoforms. As mentioned earlier, H1G variant could also be located in regulatory regions and modulate expression levels. If a candidate variant happens to be coding, there would be a great opportunity for multi-modal protein modeling and simulations to study the predicted effects of the variant (for example on folding, binding to microtubules, oligomerization, protein-protein interactions,) and direct future work. Subsequently, using genome-editing techniques, we will be able to create cell models with identical genetic background, and from there the possibilities of different functional assays to study the specific effects of the variants will be almost limitless. Ultimately the question of why variants at the *MAPT* locus influence disease risk in synucleinopathies remains to be answered. Functional studies assessing the effects of specific tau isoform expression on α-synuclein oligomerization and spreading may prove crucial.[34]

Several limitations of this study should be noted. Although the sample size is relatively large for a genetic study of DLB, it is relatively small for a genetic association study in general; this results in limited power to detect associations, particularly for rare haplotypes. Therefore, the possibility of obtaining false-negative findings is important to consider, and emphasis is best placed on 95% confidence limits for odds ratio estimates when interpreting results. Along these lines, the H1G haplotype that we have nominated as a risk factor for DLB is rare, and therefore it will be important to validate the association between this haplotype and risk of DLB in larger studies. Additionally, the relatively small sample sizes in the individual clinical DLB and pathological high DLB likelihood series likely contributed to between-series heterogeneity in association estimates due to the aforementioned imprecision in the magnitude of associations with disease risk. Given that large sample sizes involving patients with this relatively rare disease can be difficult for any one group to achieve, meta-analytic approaches will likely be needed in order to understand the role of *MAPT* and other genes in DLB with a high level of precision.

The *MAPT* locus influences risk to a number of neurodegenerative diseases but it is becoming clear that the risk is carried by different haplotypes/variants. For example, H1C is associated with PSP, but not seen in PD where studies support association to the main H1 haplotype only.[35] Furthermore, the association of PD with *MAPT* H1 seemed to be of greater effect size in PDD compared to PD. [19] The overlap in the clinical manifestation and pathological presentation between DLB and PD or PDD strongly support shared genetic risk. [36] It is intriguing that a single locus carries risk for several different diseases and it suggests a common underlying biological pathway, a common origin, possibly based on tau expression, leading to neurodegeneration. Perhaps, an individual's set of *MAPT* variants influences the clinical course and long term outcome of the disease via differential levels of MAPT isoforms.

Although we show that *MAPT* haplotype H1G increases risk of DLB, many questions remain. However, identification of the related genetic variation will provide functional insight into the underlying pathomechanism and thus provide rationale therapeutic intervention strategies for dementia with Lewy bodies, as well as other synucleinopathies. Indeed, multimodal modeling and simulation may well provide enhanced filters for candidate selection and development in this area may be critical for rare variants whereby genetic evidence alone will not be adequate to confirm an effect and robust functional studies are not currently available.

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Abbreviations

DLB	Dementia with Lewy bodies
PSP	Progressive supranuclear palsy
PD	Parkinson's disease
PDD	Parkinson's disease dementia
SNP	single nucleotide polymorphism
OR	Odds ratio
GWAS	genome-wide association studies
NFT	neurofibrillary tangle

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RESEARCH IN CONTEXT

1. Systematic review: Pubmed was used to review the literature related to genetics of dementia with Lewy body (DLB). We also searched for our locus of interest *MAPT*. Specifically, the search terms used in Pubmed were: “dementia with Lewy bodies”, “Lewy body disease”, “*MAPT*”, “*MAPT* haplotypes”. Relevant literature has been cited appropriately.
2. Interpretation: Our findings confirm a role for the *MAPT* gene in the risk of DLB. We replicate the association with the *MAPT* H1 haplotype. Furthermore, we present a novel *MAPT* subhaplotype, H1G associated with increased risk of DLB in carriers.
3. Future directions: Identification of the causal variant(s) on the *MAPT* H1G subhaplotype is the next challenge. Additionally, a look into the precise biological effects of H1G and other *MAPT* causal variants at the locus is essential to better understand the pathogenesis of DLB.

Table 1

Subjects characteristics

Group	N	Median (range) age*	No. (%) male
Controls	1049	66 (45, 92)	488 (46.5%)
Mayo Clinic Jacksonville	881	68 (45, 92)	380 (43.1%)
Mayo Clinic Rochester	168	61 (45, 76)	108 (64.3%)
Clinical DLB patients	431	73 (49, 100)	321 (74.5%)
Mayo Clinic Jacksonville	158	73 (49, 92)	119 (75.3%)
Mayo Clinic Rochester	273	74 (51, 100)	202 (74.0%)
Pathological high DLB likelihood patients	347	78 (50, 103)	220 (63.4%)
Lewy body disease patients	667	79 (50, 99)	388 (58.2%)

* Age at collection is given for controls, age at DLB onset is given for clinical DLB patients, and age at death is given for pathological high DLB likelihood and Lewy body disease patients. DLB=dementia with Lewy bodies. Pathological high DLB likelihood=high DLB likelihood Lewy body disease.

Table 2

Single variant associations with DLB

		Clinical DLB vs. controls				Pathological high DLB likelihood vs. controls			Combined series vs. controls		
Variant	**MA**	**MAF in controls (%) (N=1049)**	**MAF in patients (%) (N=431)**	**OR (95% CI)**	**P**	**MAF in patients (%) (N=347)**	**OR (95% CI)**	**P**	**MAF in patients (%) (N=731)**	**OR (95% CI)**	**P**
rs1467967	G	32.1	33.3	1.05 (0.85, 1.30)	0.64	31.7	1.03 (0.83, 1.29)	0.76	32.4	1.03 (0.87, 1.21)	0.77
rs242557	A	36.4	41.2	1.14 (0.94, 1.39)	0.19	37.0	1.05 (0.85, 1.29)	0.67	39.4	1.17 (1.00, 1.36)	0.051
rs3785883	A	16.6	17.2	0.94 (0.72, 1.24)	0.67	18.0	1.08 (0.83, 1.41)	0.57	17.6	1.01 (0.83, 1.24)	0.91
rs2471738	T	20.4	21.2	1.01 (0.80, 1.29)	0.91	19.0	0.92 (0.71, 1.19)	0.52	20.5	1.01 (0.84, 1.22)	0.91
rs8070723	G	23.8	19.5	0.80 (0.62, 1.02)	0.075	22.8	0.92 (0.72, 1.17)	0.48	21.1	0.83 (0.69, 1.00)	0.051
rs7521	A	46.2	49.7	1.14 (0.94, 1.39)	0.19	49.6	1.14 (0.94, 1.40)	0.19	49.4	1.13 (0.97, 1.31)	0.12

ORs, 95% CIs, and p-values (P) result from logistic regression models adjusted for age (age at DLB onset in DLB patients, age at death in high DLB likelihood Lewy body disease, age at blood collection in controls) and gender, with additional adjustment for Mayo Clinic site (Jacksonville or Rochester) when comparing clinical DLB patients vs. controls. ORs correspond to each additional minor allele.
DLB=dementia with Lewy bodies; Pathological high DLB likelihood=high DLB likelihood Lewy body disease; MA= minor allele; MAF= minor allele frequency OR=odds ratio; CI=confidence interval

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Table 3

Association of *MAPT* haplotype with risk of DLB

		Clinical DLB vs. controls				Pathological high DLB likelihood vs. controls			Combined series vs. controls		
Haplotype	**Sequence**	**Freq. controls (%) (N=1049)**	**Freq. patients (%) (N=431)**	**P**	**OR (95% CI) vs. common H1C haplotype**	**Freq. patients (%) (N=347)**	**P**	**OR (95% CI) vs. common H1C haplotype**	**Freq. patients (%) (N=731)**	**P**	**OR (95% CI) vs. common H1C haplotype**
H1C	AAGTAG	11.5	12.7	0.53	1.00 (reference)	10.3	0.86	1.00 (reference)	11.9	0.25	1.00 (reference)
H1G	GAACAA	1.0	3.3	0.0017	3.30 (1.34, 8.12)	2.6	0.035	2.26 (0.88, 5.81)	2.8	0.005	2.16 (1.03, 4.49)
H1L	AGACAG	2.7	1.5	0.041	0.37 (0.15, 0.92)	2.5	0.70	1.20 (0.56, 2.58)	2.0	0.31	0.66 (0.35, 1.24)
H2	AGGCGG	23.6	19.2	0.075	0.74 (0.51, 1.09)	22.6	0.45	0.93 (0.63, 1.39)	20.9	0.047	0.75 (0.56, 1.00)
H1J	AGGCAG	1.0	1.4	0.18	1.93 (0.67, 5.52)	N/A *	N/A	N/A	1.1	0.68	1.17 (0.46, 2.96)
H1I	GAGCAA	4.2	3.2	0.26	0.51 (0.24, 1.06)	2.2	0.49	0.66 (0.29, 1.50)	2.8	0.62	0.68 (0.39, 1.19)
H1B	GGGCAA	16.4	17.9	0.33	1.08 (0.72, 1.61)	17.5	0.55	1.14 (0.74, 1.75)	17.8	0.32	1.00 (0.73, 1.36)
H1R	AGGTAG	1.0	1.7	0.41	1.35 (0.45, 4.03)	N/A *	N/A	N/A	1.4	0.43	1.23 (0.51, 2.94)
H1D	AAGCAA	7.0	9.7	0.53	1.02 (0.60, 1.71)	8.8	0.45	1.16 (0.68, 1.99)	9.4	0.13	1.07 (0.72, 1.60)
H1U	AAGCAG	2.5	3.0	0.54	1.10 (0.52, 2.35)	2.6	0.54	0.90 (0.40, 2.02)	2.9	0.61	1.01 (0.55, 1.87)
H1O	AAACAA	2.0	1.5	0.56	1.01 (0.37, 2.72)	2.1	0.11	1.82 (0.73, 4.56)	1.9	0.29	1.06 (0.51, 2.21)
H1E	AGGCAA	9.0	8.1	0.56	0.97 (0.59, 1.58)	9.2	0.99	0.98 (0.60, 1.62)	8.1	0.62	0.75 (0.51, 1.09)
H1P	GGGTAG	1.5	0.9	0.65	0.60 (0.18, 2.01)	1.7	0.59	1.32 (0.47, 3.69)	1.3	0.68	0.72 (0.31, 1.68)
H1x	GAATAG	1.3	1.4	0.72	0.66 (0.23, 1.89)	1.7	0.86	1.01 (0.37, 2.77)	1.6	0.81	0.76 (0.35, 1.66)
H1H	AGACAA	4.0	4.5	0.73	0.81 (0.42, 1.55)	5.1	0.54	1.14 (0.60, 2.16)	4.8	0.80	0.94 (0.58, 1.51)
H1z	GAGTAG	0.9	1.1	0.82	1.23 (0.31, 4.85)	1.3	0.20	2.26 (0.67, 7.71)	N/A *	N/A	N/A
H1M	GAGCAG	2.8	1.9	0.96	0.92 (0.42, 2.04)	1.7	0.25	0.67 (0.28, 1.59)	1.7	0.19	0.60 (0.31, 1.14)
H1y	AAATAG	1.4	1.4	>0.99	0.93 (0.28, 3.07)	0.8	0.25	0.38 (0.07, 2.08)	1.1	0.72	0.69 (0.25, 1.86)

P-values (P) result from score tests of association that were adjusted for age (age at DLB onset in DLB patients, age at death in high DLB likelihood Lewy body disease patients, age at blood collection in controls) gender, and Mayo Clinic site (Jacksonville vs. Rochester; clinical DLB vs. control comparison only), and where the association between the given haplotype and disease is being tested. ORs and 95% CIs given in comparison to the reference category of the common H1C haplotype result from logistic regression models with the previously described adjustments for age, gender, and Mayo Clinic site. ORs and 95% CIs given in comparison to the reference category of the common H1C haplotype result from logistic regression models. Note that the p-value (which results from a test of association between the given haplotype and risk of disease in comparison to all other haplotypes) and the OR and 95% CI (which result from a test of association between the given haplotype and risk of disease in comparison to the common H1C haplotype) do not directly correspond to one another. The common H1C haplotype was chosen as the reference category as it was the haplotype that occurred at a frequency of greater than 10% that showed the least degree of evidence of an association with risk of disease in the individual series.

*Denotes a haplotype that occurred in less than 1% of subjects for the given disease group vs. control comparison and that was therefore excluded from that specific haplotype analysis.

DLB=dementia with Lewy bodies; Pathological high DLB likelihood=high DLB likelihood Lewy body disease; Freq = frequency; OR=odds ratio; CI=confidence interval.