Role for the microtubule-associated protein tau variant p.A152T in risk of α -synucleinopathies

Catherine Labbé, PhD
Kotaro Ogaki, MD, PhD
Oswaldo Lorenzo-Betancor, MD, PhD
Alexandra I. Soto-Ortolaza, BSc
Ronald L. Walton, BSc
Sruti Rayaprolu, BSc
Shinsuke Fujioka, MD
Melissa E. Murray, PhD
Michael G. Heckman, MS
Andreas Puschmann, MD, PhD
Allan McCarthy, MD, MRCPI
Timothy Lynch, MD, FRCPI
Joanna Siuda, MD
Grzegorz Opala, MD, PhD
Monika Rudzinska, MD
Anna Krygowska-Wajs, MD, PhD
Maria Barcikowska, MD, PhD
Krzysztof Czyzewski, MD
Yanosh Sanotsky, MD, PhD
Irena Rektorová, MD, PhD
Pamela J. McLean, PhD
Rosa Rademakers, PhD
Nilüfer Ertekin-Taner, MD, PhD
Anhar Hassan, MD
J. Eric Ahlskog, MD, PhD
Bradley F. Boeve, MD
Ronald C. Petersen, MD, PhD
Demetrius M. Maraganore, MD
Charles H. Adler, MD, PhD
Tanis J. Ferman, PhD
Joseph E. Parisi, MD
Neill R. Graff-Radford, MD
Ryan J. Uitti, MD
Zbigniew K. Wszolek, MD
Dennis W. Dickson, MD
Owen A. Ross, PhD

Correspondence to
Dr. Ross:
ross.owen@mayo.edu

**Supplemental data
at Neurology.org**

ABSTRACT

Objective: To assess the importance of MAPT variant p.A152T in the risk of synucleinopathies.

Methods: In this case-control study, we screened a large global series of patients and controls, and assessed associations between p.A152T and disease risk. We included 3,229 patients with clinical Parkinson disease (PD), 442 with clinical dementia with Lewy bodies (DLB), 181 with multiple system atrophy (MSA), 832 with pathologically confirmed Lewy body disease (LBD), and 2,456 healthy controls.

Results: The minor allele frequencies (MAF) in clinical PD cases (0.28%) and in controls (0.2%) were not found to be significantly different (odds ratio [OR] 1.37, 95% confidence interval [CI] 0.63–2.98, $p = 0.42$). However, a significant association was observed with clinical DLB (MAF 0.68%, OR 5.76, 95% CI 1.62–20.51, $p = 0.007$) and LBD (MAF 0.42%, OR 3.55, 95% CI 1.04–12.17, $p = 0.04$). Additionally, p.A152T was more common in patients with MSA compared to controls (MAF 0.55%, OR 4.68, 95% CI 0.85–25.72, $p = 0.08$) but this was not statistically significant and therefore should be interpreted with caution.

Conclusions: Overall, our findings suggest that MAPT p.A152T is a rare low penetrance variant likely associated with DLB that may be influenced by coexisting LBD and AD pathology. Given the rare nature of the variant, further studies with greater sample size are warranted and will help to fully explain the role of p.A152T in the pathogenesis of the synucleinopathies. **Neurology®**

2015;85:1680–1686

GLOSSARY

AD = Alzheimer disease; **CDLB** = Consortium on Dementia with Lewy bodies; **DLB** = dementia with Lewy bodies; **FTD** = frontotemporal dementia; **LBD** = Lewy body disease; **MAF** = minor allele frequencies; **MSA** = multiple system atrophy; **OR** = odds ratio; **PD** = Parkinson disease.

Synucleinopathies are a diverse group of pathologically defined neurodegenerative diseases that present with abnormal accumulation of the protein α -synuclein in glial cells and neurons.¹ Synucleinopathies occur in 3 main types: Parkinson disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA).² PD and DLB cases that present with Lewy body inclusions at pathology can be further categorized as Lewy body disease (LBD).²

PD is the most common synucleinopathy and more than 25 independent risk loci have been associated with disease through large genome-wide association approaches.³ The microtubule-associated protein tau gene (*MAPT*) is one of the most replicable associations with susceptibility to PD.^{3–5} Mutations in *MAPT* were first discovered as causing frontotemporal dementia (FTD) with parkinsonism linked to chromosome 17.⁶ *MAPT* causal mutations were shown to disrupt

From the Departments of Neuroscience (C.L., K.O., O.L.-B., A.I.S.-O., R.L.W., S.R., M.E.M., P.J.M., R.R., N.E.-T., D.W.D., O.A.R.), Neurology (S.F., N.E.-T., N.R.G.-R., R.J.U., Z.K.W.), and Psychiatry and Psychology (T.J.F.), Division of Biomedical Statistics and Informatics (M.G.H.), and Mayo Graduate School (P.J.M., O.A.R.), Mayo Clinic, Jacksonville, FL; Dublin Neurological Institute at the Mater Misericordiae University Hospital (A.M., T.L.), Conway; Institute of Biomolecular & Biomedical Research (A.M., T.L.), University College Dublin, Ireland; Department of Clinical Sciences (A.P.), Lund University, and Department of Neurology, Skåne University Hospital, Sweden; Department of Neurology (J.S., G.O.), Medical University of Silesia, Katowice; Department of Neurology (M.R., A.K.-W.), Jagiellonian University, Krakow; Department of Neurodegenerative Disorders (M.B.), Medical Research Centre, Polish Academy of Sciences, Warsaw; Department of Neurology (K.C.), Central Hospital of the Ministry of Interior and Administration, Warsaw, Poland; Lviv Regional Clinical Hospital (Y.S.), Ukraine; Department of Neurology and School of Medicine (I.R.), Central European Institute of Technology, Masaryk University, Brno, Czech Republic; Departments of Neurology (A.H., J.E.A., B.F.B., R.C.P.) and Pathology and Laboratory Medicine (J.E.P.), Mayo Clinic, Rochester, MN; Department of Neurology (D.M.M.), NorthShore University Health System, Evanston, IL; and Department of Neurology (C.H.A.), Mayo Clinic, Scottsdale, AZ.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

the protein resulting in abnormal tau accumulation.⁷ They have been implicated in several tauopathies, including Alzheimer disease (AD) and FTD spectrum disorders.

A rare MAPT variant p.A152T was first identified in a patient with an unusual tauopathy phenotype at autopsy.⁸ Subsequently, it was demonstrated through a case-control study of over 15,000 subjects that p.A152T substitution conferred an increased risk to tauopathies.⁹ A small series of patients with PD were included in this previous study (662 patients with PD, 176 patients with LBD) and although not statistically significant the results showed a trend toward increased risk. Given these findings, we set out to assess the importance of the MAPT p.A152T variant in susceptibility to clinical PD, DLB, MSA, and pathologically defined LBD.

METHODS Study subjects. A total of 3,229 patients with clinical PD, 442 with clinical DLB, 181 with MSA, 832 with LBD, and 2,456 controls were included in this case-control study. These were all subjects in the aforementioned disease groups with available genetic DNA. The clinical diagnoses were established according to the consensus criteria for PD,¹⁰ DLB,¹¹ and MSA.¹² All subjects were unrelated non-Hispanic Caucasians of European descent. Patients with clinical PD and controls are from a US series collected at Mayo Clinic's 3 campuses (Jacksonville, 893 cases and 1,370 controls; Rochester, 854 cases and 176 controls; and Scottsdale, 126 cases and 50 controls; and 83 patients from the Mayo Clinic Florida Brain Bank: total 1,873 patients, 1,679 controls), a Polish series (825 patients, 362 controls), an Irish series (366 patients, 371 controls), a Swedish series (122 patients, 44 controls), a Czech series (33 patients), and a Ukrainian series (10 patients). In the US series, 656 cases and 1,325 controls are part of the previous study that associated MAPT p.A152T with tauopathies.⁹ Our DLB series (442 samples) and MSA series (181 samples; 94 are pathologically confirmed) also consist of samples collected at Mayo Clinic. Our LBD cases series (832 non-Hispanic Caucasian patients) is a pathologically defined series collected and examined at Mayo Clinic Jacksonville and categorized according to the Consortium on Dementia with Lewy bodies (CDLB) pathologic criteria of low, intermediate, or high likelihood of having clinical DLB based on the severity of coexisting AD pathology (measured by Braak tangle stage).^{13,14} A total of 115 patients with LBD were part of the aforementioned study involving p.A152T and tauopathies.⁹ Characteristics of patients with PD, DLB, MSA, LBD, and controls are summarized in table 1 for each series. Controls were individuals free of PD or a related movement disorder at the time of examination.

Standard protocol approvals, registrations, and patient consents. The Mayo Clinic institutional review board approved the study, each individual site received local institutional review board approval, and all subjects provided written informed consent.

Genetic analysis. Genomic DNA was extracted from peripheral blood monocytes or brain tissue using standard protocols.¹⁵

Genotyping of *MAPT* exon 7 variant rs143624519 (NM_005910.5; c.454G>A, p.A152T) was performed using a custom TaqMan Allelic Discrimination Assay on an ABI 7900HT Fast Real-Time PCR system (Applied Biosystems, Foster City, CA) according to the manufacturer's instructions (primer sequences are available upon request). Genotype calls were made using SDS 2.2.2 software. Carrier status was confirmed using standard Sanger sequencing methods. The genotype call rate was $\geq 99\%$ in each population. For quality control purposes, minor allele frequencies (MAF) were compared to the European Exome Variant Server MAF (Exome Variant Server, NHLBI GO Exome Sequencing Project, Seattle, WA [http://evs.gs.washington.edu/EVS/] [accessed August 2014]) and the Exome Aggregation Consortium (Cambridge, MA [http://exac.broadinstitute.org] [accessed October 2014]).

Statistical analysis. Frequencies of MAPT p.A152T were compared between controls and the different disease groups using univariate logistic regression models. For the DLB, LBD, and MSA patient groups, comparisons with controls involved only controls from the US series given that these disease groups were also exclusively from the United States. Odds ratios (ORs) and 95% confidence intervals were estimated. There was no evidence of a departure from Hardy-Weinberg equilibrium in controls for any of the series (all $\chi^2 p > 0.05$). We did not adjust these models for age or sex as this additional model complexity would not be appropriate for this rare variant. *p* Values of 0.05 or lower were considered statistically significant. All statistical analyses were performed using PLINK (version 1.07) (http://pngu.mgh.harvard.edu/purcell/plink/).¹⁶

RESULTS Our previous genetic study on the role of MAPT p.A152T in different neurodegenerative diseases included 15,369 subjects, including 656 patients with PD and 1,325 healthy controls in our current series.⁹ These data suggested a tendency toward increased risk conferred by the MAPT p.152T allele in patients with clinical PD, but this finding was not statistically significant (OR 2.03, *p* = 0.32, table 2, old series). In order to assess the importance of this allele as a risk factor for PD, we genotyped the variant in a larger series of US and European subjects (total combined series 3,229 patients with PD, 2,456 controls). We detected 18 PD and 10 control heterozygotes for variant p.A152T; no homozygous carriers were detected. The MAF was 0.28% in patients with PD and 0.20% in controls, which is similar to the European Exome Variant Server MAF (0.27%) and the Exome Aggregation Consortium (0.17%).

Table 2 displays a comparison of the frequency of variant p.A152T between patients with PD and controls. Although not statistically significant, risk of PD was higher for the p.152T allele carriers in the US series (OR 1.80, *p* = 0.34) and the Irish series (OR 1.79, *p* = 0.36). However, a nonsignificant protective association was observed in the Polish series (OR 0.66, *p* = 0.65), and when combining the series there was no notable association between allele p.152T and PD risk (OR 1.37, *p* = 0.42).

Table 1 Patient series characteristics

Parkinson disease series	Age at study, y, mean ± SD (min-max)	Age at onset, y, mean ± SD (min-max)	Male, n (%)	Total
US series				
Cases	68.01 ± 11.19 (28-97)	61.84 ± 11.67 (16-94)	1,165 (62.2)	1,873
Controls	68.46 ± 13.09 (18-95)		766 (45.6)	1,679
Polish series				
Cases	67.90 ± 11.60 (32-101)	57.46 ± 11.54 (23-88)	505 (61.2)	825
Controls	59.25 ± 15.16 (19-96)		190 (52.3)	362
Irish series				
Cases	62.85 ± 10.40 (32-87)	51.62 ± 10.67 (18-77)	205 (56.0)	366
Controls	66.06 ± 22.18 (17-97)		135 (36.4)	371
Swedish series				
Cases	69.22 ± 10.33 (39-88)	61.73 ± 10.00 (37-84)	76 (62.3)	122
Controls	68.35 ± 9.29 (46-86)		15 (34.1)	44
Czech series				
Cases	67.64 ± 11.22 (42-85)	58.85 ± 11.65 (32-80)	16 (48.5)	33
Ukrainian series				
Cases	59.70 ± 14.64 (37-76)	54.20 ± 15.05 (29-74)	6 (60)	10
Other series			Mean ± SD (range) or n (%)	
Dementia with Lewy bodies series				
Age at study, y			79.15 ± 9.02 (55-102)	
Age at onset, y			73.39 ± 8.28 (49-100)	
Male			329 (74.4)	
Pathologically confirmed and included in LBD series			72 (16.2)	
Total			442	
Multiple system atrophy series				
Age at death (pathologic samples), y			67.38 ± 8.92 (47-86)	
Age at study (clinical samples), y			66.51 ± 10.22 (45-90)	
Age at onset, y			65.35 ± 9.43 (44-83)	
Male			106 (58.6)	
Pathologically confirmed			94 (51.9)	
Total			181	
Lewy body disease series				
Age at death, y			79.69 ± 8.74 (48-103)	
Male			471 (56.6)	
CDLB: High			351	
CDLB: Intermediate			255	
CDLB: Low			226	
Total			832	

Abbreviations: CDLB = Consortium on Dementia with Lewy Bodies pathologic criteria¹⁴; LBD = Lewy body disease. The sample mean $\pm$ SD (minimum-maximum) is given for age-related variables. Missing data were as follows. In the Parkinson disease series, information was unavailable regarding age at study (985 US cases, 32 Polish cases, 99 Irish cases, 34 Swedish cases) and age at onset (44 US cases, 10 Polish cases, 113 Irish cases, 12 Swedish cases). In controls, information was unavailable regarding age at study (264 US controls, 3 Polish controls, 18 Swedish controls). In the multiple system atrophy series, information was unavailable regarding age at onset (n = 124). In the dementia with Lewy bodies series, information was unavailable regarding age at study (n = 198) and age at dementia with Lewy bodies onset (n = 4). In the LBD series, information was unavailable regarding age at death (n = 1 low CDLB likelihood patient).

Table 2 Frequency of MAPT p.A152T variant in clinical series

	Cases	Controls	Minor alleles, MAF cases, n (%)	Minor alleles, MAF controls, n (%)	OR (95% CI)	p Value
PD						
Old US series	656	1,325	4 (0.30)	4 (0.15)	2.03 (0.5-8.13)	0.32
New US series	1,217	354	4 (0.16)	0	NA	0.58 ^b
Total US series	1,873	1,679	8 (0.21)	4 (0.12)	1.80 (0.54-5.98)	0.34
Polish series	825	362	3 (0.18)	2 (0.28)	0.66 (0.11-3.95)	0.65
Irish series	366	371	7 (0.96)	4 (0.54)	1.79 (0.52-6.16)	0.36
Clinical PD overall	3,229	2,456	18 (0.28)	10 (0.20)	1.37 (0.63-2.98)	0.42
DLB						
Total DLB	442 ^a	1,679	6 (0.68)	4 (0.12)	5.76 (1.62-20.51)	0.007
MSA (52% of samples in this series are pathologically confirmed)						
Total MSA	181	1,679	2 (0.55)	4 (0.12)	4.68 (0.85-25.72)	0.08

Abbreviations: CI = confidence interval; DLB = dementia with Lewy bodies; MAF = minor allele frequency; MSA = multiple system atrophy; NA = not applicable; OR = odds ratio; p value = p value associated with a logistic regression; PD = Parkinson disease.

^aA total of 72 samples, including one carrier, are part of both the DLB and Lewy body disease series.

^bp Value associated with a Fisher exact test.

The screening of our DLB series (442 patients) identified 6 patients with the p.152T allele, which translates into a MAF of 0.68% (one of these 6 patients is also included in the LBD series). Comparing this frequency to the MAF of the US controls (0.12%) results in an OR of 5.76 ($p = 0.007$), suggesting that p.152T is a significant risk factor for DLB (table 2). Additionally, we detected 2 carriers in our MSA series, one of which is a pathologically confirmed case (of mixed clinical presentation with cerebellar and parkinsonian phenotype) and one is a clinical case (MSA with predominant parkinsonism). The MAF in the MSA series is 0.55%, which results in an OR of 4.68 when compared to US controls ($p = 0.08$) (table 2). It is important to point out that this finding is not statistically significant and therefore should be interpreted with caution; however, the high OR supports further study of MAPT p.A152T as a risk factor for MSA.

As part of the previous study, 176 patients with LBD had been screened for p.A152T and the p.152T allele had not been detected. We screened

the variant in our new expanded LBD series (832 cases, of which 115 samples were part of the first study, and 72 samples overlap with the DLB series, including one p.152T carrier) stratified according to the CDLB classification. The results of the association tests (compared to US clinical controls) are presented in table 3. Our results suggest a significantly increased frequency in total LBD, where a MAF 0.42% was observed in LBD cases compared to 0.12% in US controls (OR 3.55, $p = 0.04$). The risk is significantly increased in LBD cases with intermediate CDLB (OR 4.99, $p = 0.04$). The frequency of p.A152T was also higher in the high CDLB group, but this was not statistically significant and should therefore be viewed cautiously (OR 3.61, $p = 0.09$). No notable difference in the frequency of p.A152T was observed between the low CDLB patients and controls (OR 1.86, $p = 0.58$). Although Braak tangle stage is used along with neuroanatomical predominance of Lewy body pathology to formulate the CDLB likelihood,¹⁴ we did not observe differences in

Table 3 Frequency of MAPT p.A152T variant in LBD series^a

	Cases	Controls	Minor alleles, MAF cases, n (%)	Minor alleles, MAF controls, n (%)	OR (95% CI)	p Value
CDLB low	226	1,679	1 (0.22)	4 (0.12)	1.86 (0.21-16.72)	0.58
CDLB intermediate	255	1,679	3 (0.59)	4 (0.12)	4.99 (1.11-22.4)	0.04
CDLB high	351	1,679	3 (0.43)	4 (0.12)	3.61 (0.80-16.2)	0.09
LBD, total	832	1,679	7 (0.42)	4 (0.12)	3.55 (1.04-12.17)	0.04

Abbreviations: CDLB = Consortium on Dementia with Lewy Bodies pathologic criteria¹⁴; CI = confidence interval; LBD = Lewy body disease; MAF = minor allele frequency; OR = odds ratio; p value = p value associated with a logistic regression.

^aA total of 72 samples, including one carrier, are part of both the dementia with Lewy bodies and LBD series.

hippocampal and cortical density measures of neurofibrillary tangles, amyloid- β plaques, or Lewy body counts between total LBD carriers and noncarriers. We also compared different demographic and neuropathologic characteristics between LBD carriers and noncarriers of p.152T but did not observe any significant differences. Results of these analyses are presented in table e-1 on the *Neurology*[®] Web site at Neurology.org.

As previously mentioned, we did not adjust our regression models for age or sex given that this additional model complexity would be questionable for a rare variant with our sample size. However, in order to address the possibility that differences in age and sex between case and control groups could have influenced our results, we examined descriptive summaries of allele frequencies when stratifying by age and sex in the 2 disease groups for which a significantly different frequency of p.A152T was observed in comparison to controls (DLB and LBD). As shown in table e-2, the aforementioned increased frequencies of MAPT p.A152T in DLB and LBD were generally consistent across age and sex subgroups.

DISCUSSION The MAPT p.A152T substitution has been recognized to confer an increased risk to tauopathies and the common *MAPT* H1 haplotype has been associated with increased risk of synucleinopathies.^{9,17} We screened a series of patients with clinical PD, DLB, MSA, and controls (over 5,000 subjects), as well as 832 LBD cases, for the MAPT p.A152T substitution. We did not detect any significant effect of the p.152T allele in clinical PD but our results show that the variant is associated with DLB (OR = 5.76) and LBD (OR = 3.55). We did not observe a statistically significant difference in the frequency of p.A152T between patients with MSA and controls, but the high estimated OR suggests that further study of the role of MAPT p.A152T in risk of MSA is warranted.

The frequencies between our different clinical PD series appear to vary with a substantial 5-fold difference in MAF between Irish and US controls. This might be due to sampling bias but could also reflect population-specific heterogeneity at the *MAPT* locus; additional studies are warranted to study this phenomenon. The p.A152T variant sits on the *MAPT* H1 haplotype, which is associated with PD.¹⁷ The OR of the H1 haplotype in the largest PD genome-wide association study meta-analysis is 1.3,³ which is typical for an individual locus in complex disease. The risk at the *MAPT* locus could be explained by the cumulative effect of several rare coding alleles such as p.152T or by common low penetrance small effect variants located most likely in less explored genomic regions such as intergenic or intronic sequences. Our

results suggest that MAPT p.A152T is not directly involved in the risk of clinical PD. However, we cannot exclude a true risk effect based on 95% confidence limits for the OR estimate in the overall PD case-control sample, and therefore larger studies are needed to further elucidate the role of this rare variant in susceptibility to PD.

We detected 6 carriers in our DLB series (n = 442) and 7 carriers in our LBD series (n = 832) compared to 4/1,679 in our US controls, which shows an increased risk. The proportion of carriers was also higher in our MSA series compared to controls, but this was not significant and requires confirmation in larger series. Our CDLB-stratified analysis suggests that the risk is increased in intermediate and also potentially in high CDLB. These findings would appear to support the association with clinical DLB, and may in part be influenced by the interrelationship of coexisting LBD and AD pathology. A recent candidate gene association study in DLB failed to find a statistically significant association with the common *MAPT* H1 haplotype, although nominal association was observed.¹⁸

Our previous study including 61 patients with pathologically confirmed MSA suggests that MAPT H1 haplotype is associated with disease risk.¹⁹ These findings and the present study further suggest that there are distinct genetic risk factors between the synucleinopathies, PD, DLB, and MSA. Due to the low frequency of the MAPT p.A152T variant, the possibility of type II error (i.e., a false-negative association) is important to consider, and emphasis is best placed on 95% confidence limits when interpreting the results of comparisons between controls and the different disease groups with regard to the frequency of p.A152T. Larger studies and meta-analytic approaches will be needed to evaluate the role of this rare variant in susceptibility to α -synucleinopathies with more precision.

The functional consequences of the p.A152T substitution are not completely understood. MAPT has a threonine phosphorylation site at position 153. It has been speculated that p.152T creates a new phosphorylation site that contributes to tau hyperphosphorylation.²⁰ The increased phosphorylation could explain the observed reduction in microtubule assembly in p.A152T mutants.⁹ Beyond some overlapping clinical presentation between tauopathies, such as AD, and synucleinopathies, such as PD and DLB—dementia, for example, can be a feature of PD (PD dementia) and DLB—it is increasingly acknowledged that an overlap exists between the pathologic presentations of these disorders. Proteins tau and α -synuclein have both been observed in brain inclusions in the 2 types of diseases.²¹ Phosphorylated tau has been detected in synaptic enriched fractions of frontal cortex from patients with LBD²² and tau-positive inclusions have

been reported in families with dominantly inherited PD caused by mutations in the α -synuclein gene (*SNCA*).²³ Furthermore, it has been shown that tau and α -synuclein synergistically promote the polymerization of each other in vitro.²⁴ The overlapping pathologies could be interpreted as an indication that some molecular pathways involved in these disease pathogenesises are the same and that MAPT p.A152T is a risk factor in several neurodegenerative diseases and acts to influence cell death through promotion of protein aggregation, a toxic gain of function.

We show that the MAPT p.152T allele confers risk to specific synucleinopathies but additional studies are warranted to clarify the role of *MAPT* variation in clinical PD and to further characterize the role of MAPT p.152T in risk of DLB, MSA, and LBD.

AUTHOR CONTRIBUTIONS

Catherine Labbé: drafting/revising the manuscript for content, study concept and design, analysis and interpretation of data. Kotaro Ogaki: drafting/revising the manuscript for content. Oswaldo Lorenzo-Betancor: drafting/revising the manuscript for content. Alexandra I. Soto-Ortolaza: revising the manuscript for content. Ronald L. Walton: revising the manuscript for content. Sruti Rayaprolu: revising the manuscript for content. Shinsuke Fujioka: revising the manuscript for content. Melissa E. Murray: revising the manuscript for content, analysis and interpretation of data. Michael G. Heckman: revising the manuscript for content, analysis and interpretation of data. Andreas Puschmann: drafting/revising the manuscript for content, including medical writing for content; contribution of vital reagents/tools/patents. Allan McCarthy: revising the manuscript for content, acquisition of data. Timothy Lynch: revising the manuscript for content, acquisition of data. Joanna Siuda: revising the manuscript for content, acquisition of data. Grzegorz Opala: revising the manuscript for content, acquisition of data. Monika Rudzinska: revising the manuscript for content, acquisition of data. Anna Krygowska-Wajs: revising the manuscript for content, acquisition of data. Maria Barcikowska: revising the manuscript for content, acquisition of data. Krzysztof Czyzewski: revising the manuscript for content, acquisition of data. Yanosh Sanotsky: revising the manuscript for content, acquisition of data. Irena Rektorová: revising the manuscript for content, acquisition of data. Pamela J. McLean: revising the manuscript for content. Rosa Rademakers: revising the manuscript for content, acquisition of data. Nilüfer Ertekin-Taner: revising the manuscript for content. Anhar Hassan: revising the manuscript for content, acquisition of data. J. Eric Ahlskog: revising the manuscript for content, acquisition of data. Bradley F. Boeve: revising the manuscript for content, acquisition of data. Ronald C. Petersen: revising the manuscript for content, acquisition of data. Dementrius M. Maraganore: revising the manuscript for content, acquisition of data. Charles H. Adler: revising the manuscript for content, acquisition of data. Tanis J. Ferman: revising the manuscript for content, acquisition of data. Joseph E. Parisi: revising the manuscript for content, acquisition of data. Neill R. Graff-Radford: revising the manuscript for content, acquisition of data. Ryan J. Uitti: revising the manuscript for content, acquisition of data. Zbigniew K. Wszolek: revising the manuscript for content, acquisition of data. Dennis W. Dickson: revising the manuscript for content, analysis or interpretation of data, acquisition of data. Owen A. Ross: drafting/revising the manuscript for content, study concept and design, analysis or interpretation of data.

ACKNOWLEDGMENT

The authors thank those who contributed to their research, particularly the patients and families who donated DNA samples and brain tissue for this work.

STUDY FUNDING

The Mayo Clinic Jacksonville is a Morris K. Udall Parkinson's Disease Research Center of Excellence (NINDS P50 #NS072187) and is supported

by The Little Family Foundation and the Mangurian Foundation for Lewy body research. This work is also supported by NINDS R01 NS078086, R01 NS080820, U01 AG046139, and a gift from Carl Edward Bolch, Jr. and Susan Bass Bolch. C.L. is the recipient of a FRSQ postdoctoral fellowship and is a 2015 Yonkin Scholar supported by the Mayo Clinic Alzheimer's Disease and Related Dementias Genetics program.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received February 6, 2015. Accepted in final form July 14, 2015.

REFERENCES

- McCann H, Stevens CH, Cartwright H, Halliday GM. Alpha-synucleinopathy phenotypes. *Parkinsonism Relat Disord* 2014;20(suppl 1):S62–S67.
- Jenner P, Morris HR, Robbins TW, et al. Parkinson's disease: the debate on the clinical phenomenology, aetiology, pathology and pathogenesis. *J Parkinson Dis* 2013;3:1–11.
- Nalls MA, Pankratz N, Lill CM, et al. Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. *Nat Genet* 2014;46:989–993.
- Lill CM, Roehr JT, McQueen MB, et al. Comprehensive research synopsis and systematic meta-analyses in Parkinson's disease genetics: the PDGene database. *Plos Genet* 2012;8:e1002548.
- Sharma M, Ioannidis JP, Aasly JO, et al. Large-scale replication and heterogeneity in Parkinson disease genetic loci. *Neurology* 2012;79:659–667.
- Hutton M, Lendon CL, Rizzu P, et al. Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. *Nature* 1998;393:702–705.
- Pittman AM, Fung HC, de Silva R. Untangling the tau gene association with neurodegenerative disorders. *Hum Mol Genet* 2006;15(Spec 2):R188–R195.
- Kovacs GG, Wohrer A, Strobel T, Botond G, Attems J, Budka H. Unclassifiable tauopathy associated with an A152T variation in MAPT exon 7. *Clin Neuropathol* 2011;30:3–10.
- Coppola G, Chinnathambi S, Lee JJ, et al. Evidence for a role of the rare p.A152T variant in MAPT in increasing the risk for FTD-spectrum and Alzheimer's diseases. *Hum Mol Genet* 2012;21:3500–3512.
- Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992;55:181–184.
- McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology* 2005;65:1863–1872.
- Gilman S, Wenning GK, Low PA, et al. Second consensus statement on the diagnosis of multiple system atrophy. *Neurology* 2008;71:670–676.
- Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol* 1991;82:239–259.
- McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology* 1996;47:1113–1124.
- Labbe C, Soto-Ortolaza AI, Rayaprolu S, et al. Investigating the role of FUS exonic variants in essential tremor. *Parkinsonism Relat Disord* 2013;19:755–757.

16. Purcell S, Neale B, Todd-Brown K, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet* 2007;81: 559–575.
17. Skipper L, Wilkes K, Toft M, et al. Linkage disequilibrium and association of MAPT H1 in Parkinson disease. *Am J Hum Genet* 2004;75:669–677.
18. Bras J, Guerreiro R, Darwent L, et al. Genetic analysis implicates APOE, SNCA and suggests lysosomal dysfunction in the etiology of dementia with Lewy bodies. *Hum Mol Genet* 2014;23:6139–6146.
19. Vilarino-Guell C, Soto-Ortolaza AI, Rajput A, et al. MAPT H1 haplotype is a risk factor for essential tremor and multiple system atrophy. *Neurology* 2011; 76:670–672.
20. Kara E, Ling H, Pittman AM, et al. The MAPT p.A152T variant is a risk factor associated with tauopathies with atypical clinical and neuropathological features. *Neurobiol Aging* 2012;33:2231.e7–2231.e14.
21. Moussaud S, Jones DR, Moussaud-Lamodiere EL, Delenclos M, Ross OA, McLean PJ. Alpha-synuclein and tau: teammates in neurodegeneration? *Mol Neurodegen* 2014;9:43.
22. Muntane G, Dalfo E, Martinez A, Ferrer I. Phosphorylation of tau and alpha-synuclein in synaptic-enriched fractions of the frontal cortex in Alzheimer's disease, and in Parkinson's disease and related alpha-synucleinopathies. *Neuroscience* 2008;152:913–923.
23. Duda JE, Giasson BI, Mabon ME, et al. Concurrence of alpha-synuclein and tau brain pathology in the Contursi kindred. *Acta Neuropathol* 2002;104:7–11.
24. Giasson BI, Forman MS, Higuchi M, et al. Initiation and synergistic fibrillization of tau and alpha-synuclein. *Science* 2003;300:636–640.

Subspecialty Alerts by E-mail!

Customize your online journal experience by signing up for e-mail alerts related to your subspecialty or area of interest. Access this free service by visiting Neurology.org/site/subscriptions/etoc.xhtml or click on the “E-mail Alerts” link on the home page. An extensive list of subspecialties, methods, and study design choices will be available for you to choose from—allowing you priority alerts to cutting-edge research in your field!

How Do YOU Compare? Access New *Neurology Compensation and Productivity Report*

The AAN's 2015 *Neurology Compensation and Productivity Report* is now available. Based on data from more than 1,300 neurologists and neurology practice managers, this is the most recent and reliable information on the neurology profession.

The *Neurology Compensation and Productivity Report* is a powerful, versatile tool that can help you:

- Compare and customize your individual practice-related data with your colleagues at national and local levels
- Determine if you are being paid fairly relative to your peers
- Use the data in contracting with payers and demonstrating your value
- Discover fair market value based on your subspecialty, region, and practice type
- Create charts and graphs and download them right to your desktop
- Assess patient and practice management principals and implement efficiencies that ultimately can help improve the quality of patient care

Learn more at AAN.com/view/2015NeuroReport.