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MAPT p.V363I mutation

A rare cause of corticobasal degeneration

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Abstract

Objective

Patients with corticobasal syndrome (CBS) present with heterogeneous clinical features, including asymmetric parkinsonism, dyspraxia, aphasia, and cognitive impairment; to better understand the genetic etiology of this rare disease, we undertook a genetic analysis of microtubule-associated protein tau (*MAPT*).

Methods

We performed a genetic evaluation of *MAPT* mutations in 826 neurologically healthy controls and 173 cases with CBS using the Illumina NeuroChip genotyping array.

Results

We identified 2 patients with CBS heterozygous for a rare mutation in *MAPT* (p.V363I) that is located in the highly conserved microtubule-binding domain. One patient was pathologically confirmed and demonstrated extensive 4-repeat-tau-positive thread pathology, achromatic neurons, and astrocytic plaques consistent with corticobasal degeneration (CBD).

Conclusions

We report 2 CBS cases carrying the rare p.V363I *MAPT* mutation, one of which was pathologically confirmed as CBD. Our findings support the notion that this rare coding change is pathogenic.

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Glossary

CBD = corticobasal degeneration; **CBS** = corticobasal syndrome; **FTD** = frontotemporal dementia; ***MAPT*** = microtubule-associated protein tau; ***PGRN*** = progranulin; **PSP** = progressive supranuclear palsy.

Corticobasal syndrome (CBS) is a rare neurologic disease that presents with heterogeneous motor symptoms and cognitive impairment.[1] A high misdiagnosis rate due to clinical heterogeneity limits efforts to extend disease-modifying therapy trials to this patient population. Improving the diagnostic accuracy of complex neurodegenerative syndromes is an important, yet unmet need in the research community.

Although understanding of the genetic underpinnings of CBS is limited, rare mutations in the microtubule-associated protein tau (*MAPT*) gene are implicated as a cause of CBS and related tauopathy spectrum disorders.[2–6] One of these *MAPT* mutations is the variant p.V363I (rs63750869; c.1087G>A: NM_005910.5), located in the *MAPT* microtubule-binding domain. Previously described in a small number of patients with clinical tauopathy phenotypes (table 1), the mutation is present at a very low frequency in population databases and is hypothesized to be a disease-causing mutation with decreased penetrance rather than a rare polymorphism.[6–10] The rare nature of the mutation makes it difficult to demonstrate disease segregation, and in silico prediction algorithms of this mutation are inconclusive (table e-1, links.lww.com/NXG/A162).

We describe 2 CBS cases who were found to carry the rare p.V363I *MAPT* mutation. In addition, we summarize the clinicopathologic features of previously reported cases with a coding mutation at the *MAPT* p.V363 residue. One of our CBS cases had postmortem confirmation, which found abundant four-repeat tau accumulations consistent with corticobasal degeneration (CBD). As a pathologically confirmed case with this rare missense mutation, this case provides supporting evidence for the pathogenic nature of the p.V363I *MAPT* mutation.

Methods

Study population

Case 1 is a 73-year-old, right-handed, white woman who presented to the NIH Clinical Center in Bethesda, MD, for participation in genetic research. She was diagnosed with probable CBS based on the consensus criteria.[11] A commercial genetic panel (Invitae, San Francisco, CA) that included screening of the genes *CHCHD10, DCTN, FUS, GRN, TARDBP, VCP, UBQLN2, TBK1, PSEN1, PSEN2, APP,* and *MAPT* had previously identified that she was a carrier of the *MAPT* p.V363I variant. Case 2 was identified by querying a research database for the presence of the *MAPT* p.V363I variant. This database contains genotype information on European-ancestry individuals, including 826 neurologically healthy controls and 961 patients with frontotemporal dementia (FTD) spectrum disorders (n = 772 cases with progressive supranuclear palsy [PSP], n = 173 patients with CBS/CBD, n = 41 patients with FTD; sample characteristics are summarized in table e-2 [links.lww.com/NXG/A162]; source of samples and number of samples per disease are described in table e-3). Case 2 was clinically diagnosed with hemiparkinsonism, primary progressive aphasia, and probable CBS.

Standard protocol approvals, registrations, and patient consents

The study was approved by the respective institutional review boards. Written informed consent for research participation was obtained from all participants.

Genetic analysis and validation

For each participant, DNA was extracted from blood or brain tissue using standard methods and followed by genotyping on the NeuroChip platform (Illumina, San Diego, CA). This affordable genotyping array contains a tagging single nucleotide polymorphism backbone combined with high-yield custom content that allows for rapid screening of ~180,000 mutations and risk variants previously implicated in neurologic diseases, including the *MAPT* p.V363I variant. The detailed contents of this versatile genotyping platform have been described elsewhere.[12] The *MAPT* p.V363I mutation was only present in 2 patients (henceforth referred to as case 1 and case 2), and we validated the mutation via direct Sanger sequencing using the following primers: forward 5′-GTGGCCAGGTGGAAGTAAAA, reverse 5′-ACATCCAGCCAGTCAACACA. To rule out other possible pathogenic mutations in these 2 patients, we assessed the NeuroChip data for damaging progranulin (*PGRN*) gene mutations. We also performed repeat-primed PCR screening of the *C9orf72* repeat using methods described elsewhere.[13] *APOE* genotypes were determined by extracting rs7412 and rs429358 as previously described.[12] *MAPT* haplotype status was determined by imputation of the polymorphism rs1052553 (R^2 = 0.99494), with the "A" allele determining the H1 haplotype and the "G" allele segregating with the H2 haplotype.[14]

Bioinformatic analysis

To better understand the effects of the p.V363I variant, a systematic literature review was conducted and summarized in table 1. In silico predictive tools (SIFT, PolyPhen2, FATHMM-XF, M-CAP, MutationTaster, CADD, ClinVar, and ClinPred) were applied to classify the *MAPT* p.V363I mutation.[15–21] Sequence conservation analyses were performed in T-Coffee.[22] A previously described, cryo-electron microscopy structure of the tau protofibril was used for 3-dimensional protein modeling (figure 1).[23] Allele frequency differences between CBS cases and neurologically healthy

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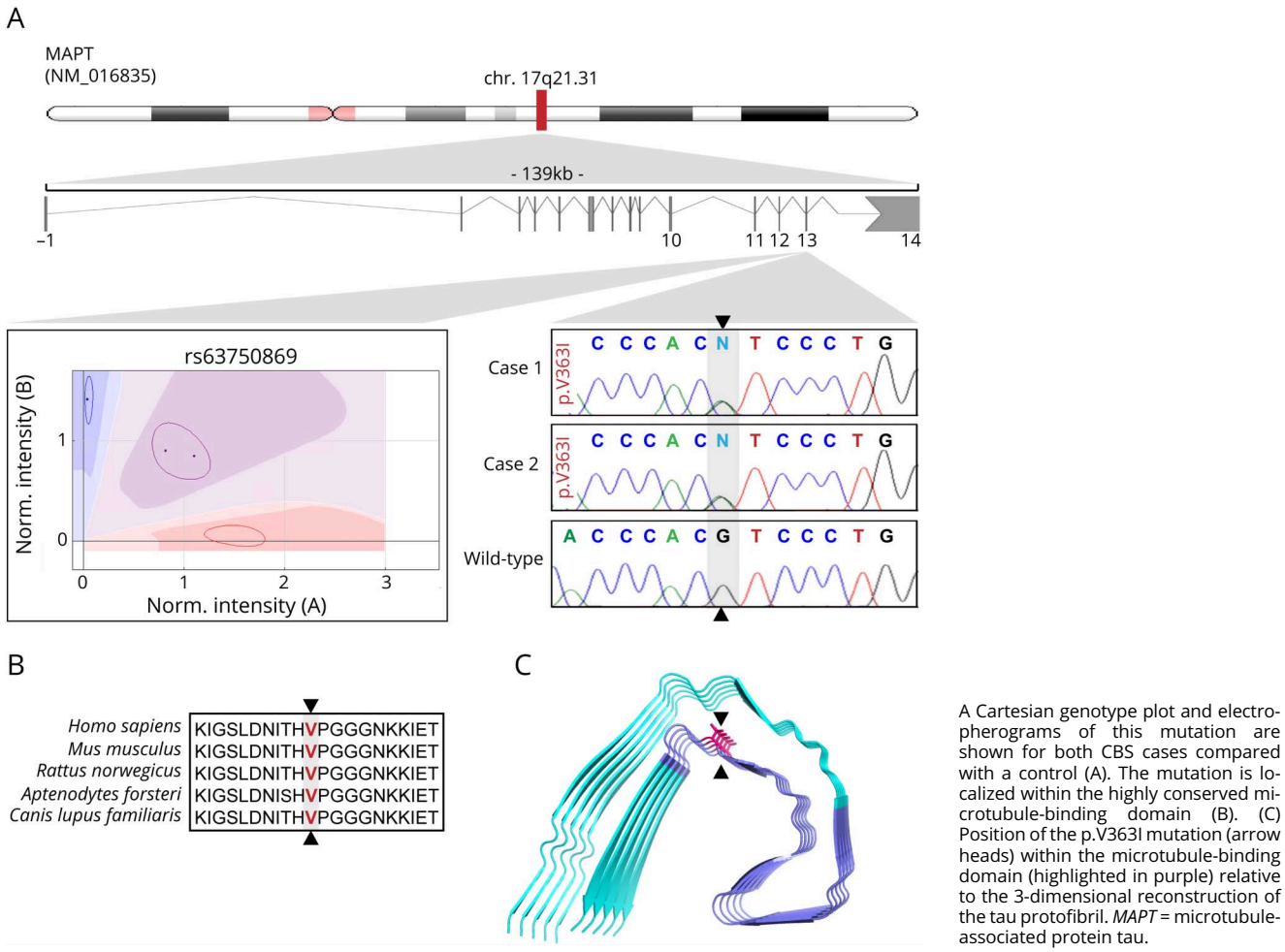
Table 1 Clinicopathologic features of patients with a mutation at the highly conserved p.V363 residue of *MAPT*

	Clinical features						Genetics				
No.	**Clinical diagnosis**	**Sex**	**AAO**	**AAD**	**FH**	**Neuroimaging finding(s)**	**Mutation**	**Haplotype**	**Pathology**	**Country**	**Reference**
1	CBS	F	70	NA	+	MRI: bilateral parietal atrophy	p.V363I	H1/H1	NA	United States	This report
2	CBS and PPA	F	Late 50s	62	−	NA	p.V363I	H1/H1	CBD	Spain	This report
3	PPA (nonfluent variant)	F	69	NA	+	SPECT: bilateral Sylvian hypoperfusion	p.V363I	H1/H1	NA	Spain	Munoz et al.[9]
4	FTD (behavioral variant)	F	53	61	+	MRI: bilateral frontotemporal atrophy	p.V363I	H1/H1	NA	Italy	Anfossi et al.[8]
5	PPA (semantic variant)	F	46	NA	−	MRI: asymmetric temporopolar atrophy	p.V363I	NA	NA	Italy	Bessi et al.[6]
6	FTD and PPA (nonfluent variant)	F	55	NA	NA	SPECT: bilateral Sylvian hypoperfusion	p.V363I	NA	NA	Italy	Rossi et al.[7]
7	PCA	F	54	NA	NA	NA	p.V363I	NA	NA	Italy	Rossi et al.[7]
8	FTD, PPA (nonfluent variant), and CBS	F	55	NA	NA	MRI: mild left frontal atrophy SPECT: left frontotemporal predominant hypoperfusion FDG-PET: left parietal hypometabolism	p.V363I	H1/H1	NA	Italy	Rossi et al.[10]
9	PCA	F	51	N/A	+	MRI: slight, asymmetric atrophy of posterior temporoparietal and occipital lobes; white matter abnormalities FDG-PET: bilateral posterior temporo-occipital and right posterior frontoparietal hypometabolism	p.V363I	H1/H1	N/A	Italy	Rossi et al.[10]
10	PSP	M	53	NA	+	MRI: midbrain atrophy DAT scan: bilateral dopaminergic denervation	p.V363A	H1/H1	NA	Italy	Rossi et al.[10]

Abbreviations: AAD = age at death; AAO = age at onset; CBS = corticobasal syndrome; CBD = corticobasal degeneration; DAT scan = dopamine transporter scan; FDG = fluorodeoxyglucose PET; FH = family history; +/− = present/absent; FTD = frontotemporal dementia; *MAPT* = microtubule-associated protein tau; NA = not available or not applicable; PCA = posterior cortical atrophy; PPA = primary progressive aphasia; PSP = progressive supranuclear palsy; SPECT = single-photon emission computed tomography.

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Figure 1 This schematic representation illustrates the location of the *MAPT* p.V363I mutation



A Cartesian genotype plot and electropherograms of this mutation are shown for both CBS cases compared with a control (A). The mutation is localized within the highly conserved microtubule-binding domain (B). (C) Position of the p.V363I mutation (arrow heads) within the microtubule-binding domain (highlighted in purple) relative to the 3-dimensional reconstruction of the tau protofibril. *MAPT* = microtubule-associated protein tau.

controls were determined using a Fisher exact test with a significance threshold of 0.05.

Neuropathology

The brain of case 2 was pathologically evaluated at the Neurological Tissue Bank of the IDIBPAS Biobank in Barcelona, Spain, after obtaining written informed consent from the patient's relatives for use of tissue for diagnostic and research purposes. Hematoxylin and eosin staining was performed after standard formalin fixation and paraffin block sectioning of multiple cortical and subcortical brain areas. Immunohistochemistry was performed using phospho-tau (Ser202 and Thr205) monoclonal antibodies (AT8; 1:2000; Thermo Scientific, Rockford, IL) and anti-4R-tau (RD4) antibodies. In addition, selected areas were stained for ßA4-amyloid (6F/3D 1:400; Dako, Glostrup, Denmark), α-synuclein (KM51 2:200; Novocastra, Newcastle upon Tyne, UK), and TDP43 protein (2E2-E3 1:500; Abnova, Taipei, Taiwan) for identification of concomitant pathologies.

Data availability

Deidentified data are available upon request from qualified investigators.

Results

Genetic characteristics

In a cohort of 173 CBS cases, we identified 2 patients who were heterozygous for the rare p.V363I (c.1087G>A: NM_005910.5) mutation located in the highly conserved microtubule-binding domain of *MAPT* (Fisher exact test comparing CBS cases with neurologically healthy controls $p = 0.0299$). Both patients were homozygous for the H1 *MAPT* haplotype and carried no pathogenic mutations in *PGRN* or *C9orf72*. The patients' *APOE* genotypes were ε3/ε3. The *MAPT* p.V363I mutation was absent in ~1,800 additional samples, including 826 neurologically healthy controls and 984 cases with diverse frontotemporal degeneration spectrum disorders. Bioinformatic predictions demonstrated that SIFT, PolyPhen2, MutationTaster, and ClinPred categorized the variant as tolerated and benign, whereas ClinVar, FATHMM-XF, M-CAP, and CADD predictions suggested a likely pathogenic mutation (table e-1, links.lww.com/NXG/A162).

Clinicopathologic features

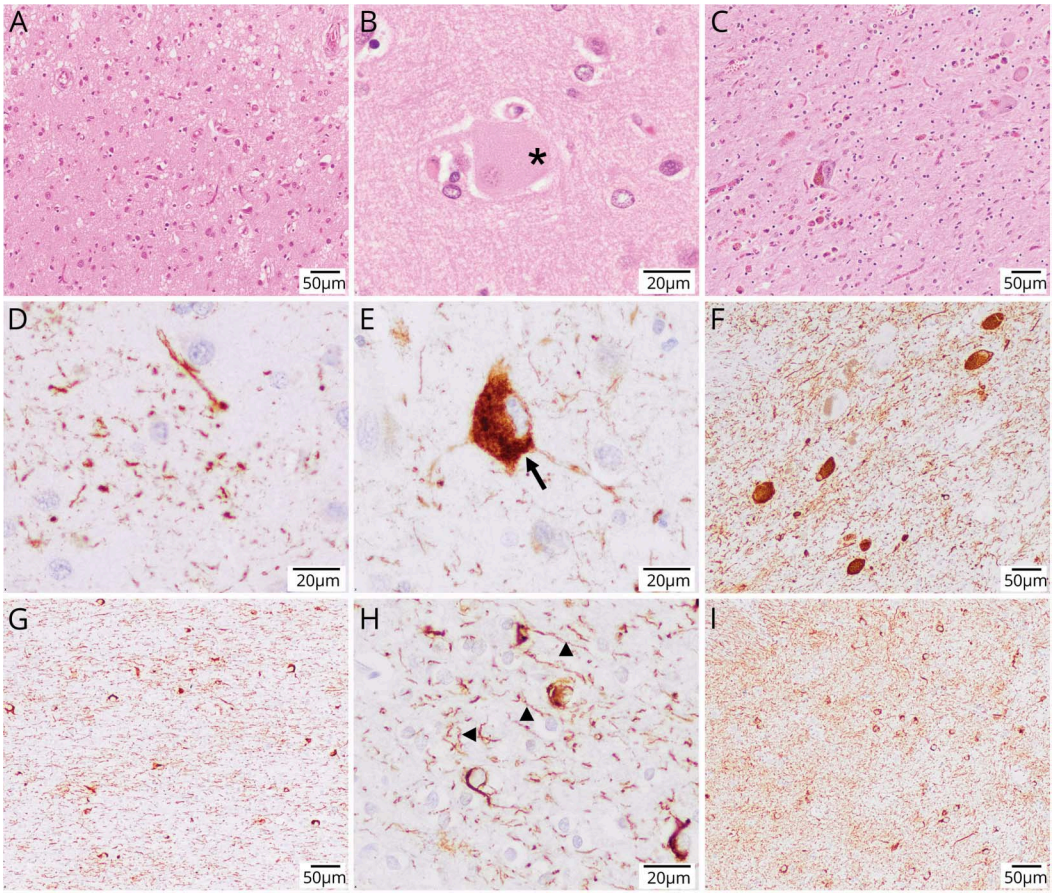
Case 1 is a 73-year-old, right-handed, white woman with a medical history of hypertension, coronary artery disease, an

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old segmental left parietal stroke at age 54 years that resolved without residual neurologic deficits, and major depressive disorder. She was diagnosed with CBS at age 70 years after developing progressive right-sided impairment of her dexterity, slowed gait, and imbalance resulting in backward falls. A levodopa trial up to a maximum dose of 450 mg daily yielded no benefits. Over the course of 3 years, she gradually developed dysarthria, severe gait dysfunction rendering her wheelchair-bound, asymmetric parkinsonism, hand dystonia, apraxia, impaired word retrieval, and executive dysfunction. Her neurologic examination demonstrated bradyphrenia with a tendency to perseverate. She had severe ideomotor apraxia that was more prominent in her dominant hand. She was neglecting her right-sided space. Her speech was moderately dysarthric. Cranial nerve examination showed slowed, hypometric saccades (vertical more than horizontal), severe axial and right-sided rigidity with only mild rigidity on the left, bradykinesia, and dystonia with high-frequency/low-amplitude tremor in her right hand. She had agraphesthesia and astereognosis in her right hand. Reflexes were brisk throughout. Primitive reflexes, including grasp and palmomental reflexes, were present. She was unable to stand without assistance and would spontaneously fall without support. MRI of the brain demonstrated bilateral parietal atrophy with proportional, ex vacuo dilatation of the lateral ventricles. Her family history was notable for parkinsonism in her father (age at onset ~65 years). No DNA was available from her father to test for segregation. The patient is alive after a 3-year disease duration.

Case 2 was a white woman who presented in her late 50s with primary progressive aphasia, left-sided parkinsonism, and CBS. The disease progressed to complete anarthria and severe dysphagia. She died at age 62 years. Clinical data on this case were limited. She had no known family history of dementia. The patient's neuropathologic findings were notable for widespread, 4-repeat-tau-positive inclusions in cortical and subcortical regions, including neurons and glial cells, consistent with CBD (figure 2). Frequent achromatic neurons were detected in frontal, parietal, and cingular cortices. These were

Figure 2 These images showcase the pertinent neuropathologic findings of case 2



Hematoxylin and eosin staining shows superficial spongiosis in the postcentral region (A), a large achromatic or ballooned cell (highlighted by asterisk in B), and prominent nigral degeneration with severe neuronal loss and abundant extracellular neuromelanin pigment (C). (D–I) Abnormal pTau (AT8) and 4-repeat-tau-positive protein deposition on immunohistochemistry. Notable abnormal histopathologic findings included astrocytic plaques (D), frequent pretangles with some focal cytoplasmic condensations (E), tangles, pretangles, and abundant threads in the substantia nigra (F), very abundant threads (arrow heads) and coiled bodies (arrow) in the white matter (G and H), and abundant threads and pretangles in the striatum (I), overall consistent with the neuropathologic findings observed in corticobasal degeneration. Magnification scale bars are indicated in the bottom right corner of each panel.

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associated with focal superficial spongiosis, diffuse neuronal loss, astrogliosis, and microglial activation in cortical areas, including the motor cortex, and diffuse gliosis of the underlying white matter. Prominent neuronal loss was noted in the globus pallidus and in the substantia nigra. Immunohistochemistry revealed astrocytic plaques, abundant pretangles, ballooned neurons, and neuropil threads in the cortex, abundant threads and pretangles in her basal ganglia, and prominent white matter pathology with widespread threads and coiled bodies involving also the brainstem. Remarkably, there was also prominent involvement of the hippocampus, including the granule cells of the dentate gyrus, without grain pathology. Co-comitant pathologies included a moderate amount of diffuse ßA4-amyloid deposits and few cored plaques in cortical areas, as well as few neuronal and glial cytoplasmic TDP43 protein inclusions in the globus pallidus, without frontal, temporal, or hippocampal involvement. No α-synuclein aggregates were identified.

Discussion

We describe 2 CBS cases carrying the rare p.V363I *MAPT* mutation located in the conserved microtubule-binding domain. One of the 2 cases was pathologically confirmed, demonstrating widespread, 4-repeat-tau-positive neuronal and glial pathology consistent with CBD. This report describes the pathology present in a p.V363I *MAPT* mutation carrier providing further support for the notion that this variant is likely disease causing. To date, this coding mutation has been described in 7 neurodegenerative disease cases with heterogeneous presentations, including FTD, primary progressive aphasia, and posterior cortical atrophy (table 1).[6,8–10] Another mutation at the same residue (p.V363A) has been described in a single case with clinically diagnosed PSP.[10] Of interest, all cases were female, had ε3/ε3 *APOE* genotypes, and were homozygous for the *MAPT* H1 haplotype. The average age at onset was 57 years, ranging from 46 to 70 years. The 2 CBS cases presented here extend the disease onset. This wide age spectrum is consistent with the pattern seen in tauopathies associated with *MAPT* mutations and could indicate a decreased, age-related penetrance.[24]

Among the cases, the initial disease manifestations were quite varied, including gait disturbances, memory deficits, and personality changes. This heterogeneity is not unusual for patients with *MAPT* mutations.[25] The p.V363I mutation is present in 3 of 62,784 people in the NHLBI TopMed Bravo database (bravo.sph.umich.edu/freeze5/hg38/; allele frequency: 0.0000239; date accessed: October 14, 2018) and in 2 of 60,702 individuals in ExAC (allele frequency: 0.0000167, data accessed: October 14, 2018).[26] The very rare presence within population databases might be explained by incomplete penetrance and late disease onset. In addition, limited in vitro analyses in 1 case demonstrated that this mutation leads to an increased propensity for microtubule polymerization and the formation of tau protein oligomers.[10] Because of the lack of familial genetic data, we were not able to test for disease segregation, and this has not yet been reported by other investigators.

We present a pathologically confirmed patient with a p.V363I *MAPT* mutation. The neuropathologic findings of this case were consistent with CBD. An additional p.V363I carrier was identified with a CBS phenotype. This mutation was absent in neurologically healthy controls. Considering previous reports on mutation carriers with information about sequence conservation, functional studies, and pathologic confirmation, we nominate the *MAPT* p.V363I change as a likely disease-causing mutation. Identifying additional cases with this mutation will be important to understand the natural history and penetrance of this familial disease.

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Disclosure

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Ellen Gelpi, MD, PhD	University of Barcelona-Hospital Clinic	Author	Neuropathologic assessment and critical review
Alexander Pantelyat, MD	Johns Hopkins University Medical Center	Author	Conceptualization and design; clinical/pathologic characterization; and critical review
Sonja W. Scholz, MD, PhD	National Institutes of Health and Johns Hopkins University Medical Center	Author	Drafting of the manuscript; conceptualization and design; clinical/pathologic characterization; and critical review

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