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Genetic Disorders with Tau Pathology: A Review of the Literature and Report of Two Patients with Tauopathy and Positive Family Histories

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Key Words
Tauopathies · Genetics · Tau pathology · Microtubule-associated protein tau gene

Abstract
Background: Tauopathies are a group of neurodegenerative disorders characterized by the pathological accumulation of hyperphosphorylated and insoluble tau protein within neurons and glia. Although most cases are sporadic, hereditary tauopathies have also been reported. ***Summary:*** In this article, we review genetic disorders in which tau pathology has been reported and present two novel families with primary tauopathies. Mutations in the microtubule-associated protein tau gene *(MAPT)* cause a small subset of primary tauopathies. Mutations in 21 other genes and an 18q deletion syndrome have also been reported to be associated with tau pathology reminiscent of Alzheimer's disease, corticobasal degeneration, progressive supranuclear palsy, argyrophilic grain disease or Pick's disease. In 8 of the 21 genes, tau pathology was only seen in cases with some 'specific' mutations. In the remaining genes, tau pathology, often in the form of Alzheimer-type neurofibrillary lesions, was a common finding but was 'not mutation specific'. The probands of the two families were diagnosed with progressive supranuclear palsy based on clinicopathological evaluation. Their family histories were relevant for parkinsonism in 3 siblings of family 1 and 1 brother and the father from family 2, but these were not autopsy-confirmed. DNA from the brains of the probands from these families was screened for *MAPT* and leucine-rich repeat kinase 2 gene mutations, but no mutations were identified. ***Key Messages:*** *MAPT* mutations are a cause of familial tauopathies, but other genes have also been associated with tau pathology. Novel genes still await discovery.

Introduction

Tauopathies are a group of neurodegenerative disorders with pathological accumulation of hyperphosphorylated and insoluble tau protein within neurons and glia [1]. In primary tauopathies tau inclusions are the major neuropathological abnormality, whereas in secondary tauopathies tau pathology occurs in association with other more specific pathology [2].

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The tau protein promotes tubulin polymerization and stabilizes microtubules. Tau is encoded by the microtubule-associated protein tau gene *(MAPT)* on chromosome 17 [3]. Of 14 *MAPT* exons, exons 2, 3 and 10 undergo alternative splicing, and therefore, the mature tau proteins vary in size from 352 to 441 amino acids. Alternative splicing of exon 10 leads to two functionally different isoforms that contain either three or four 31-amino acid repeats depending on whether exon 10 is included (4R tau) or not (3R tau) [3]. Exon 10 encodes 1 of 4 tau microtubule-binding repeat regions; the remaining 3 are encoded by exons 9, 11 and 12. In normal adult human brains, the level of 3R isoforms is approximately equal to that of 4R isoforms [4]. Morphological and biochemical heterogeneity of the primary tauopathies is associated with the predominance of tau isoforms. This and the proportion of tau deposits within neurons or glial cells, together with the areas of the brain affected influence the clinical phenotype. The classical phenotypes of primary tauopathies correspond with the modern classification of frontotemporal lobar degeneration (FTLD) [5] and thus the term FTLD-tau can be applied [4]. These phenotypes include progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Pick's disease (PiD), globular glial tauopathies (GGTs), argyrophilic grain disease (AGD), primary age-related tauopathy (PART), chronic traumatic encephalopathy (CTE), and frontotemporal dementia (FTD) with parkinsonism linked to chromosome 17 (FTDP-17) [4, 6, 7].

Based on the predominance of 3R/4R isoforms, tauopathies can be grouped into 4R tauopathies, including PSP, CBD, AGD, GGT and some forms of FTDP-17, while 3R tauopathies include PiD and some forms of FTDP-17 [4, 7]. In PART, CTE, and some other forms of FTDP-17, there is a mixture of 3R and 4R tau pathology [7]. Neuronal lesions predominate in 3R tauopathies, while 4R tau accumulates in both neurons and glial cells [4, 7]. Tau pathology can also differ depending on the conformational state of tau in neuronal Alzheimer-type paired helical filaments or Pick-type straight filaments [6].

The overwhelming majority of tauopathies occur sporadically, but tauopathies linked to *MAPT* mutations (i.e. FTDP-17) frequently share pathological and biochemical features with sporadic tauopathies [6, 8]. Additionally, tau pathology has been reported in mutations in other genes. We review the genetics of tauopathies and describe two previously unpublished families with primary tauopathies.

Methods

We searched the PubMed database for all papers published in English that contained the words 'familial' or 'hereditary' and 'tauopathies', 'progressive supranuclear palsy', 'corticobasal degeneration', 'Pick's disease', 'globular glial tauopathies', 'argyrophilic grain disease' and 'tauopathy-associated disorders'.

Genealogical, clinical and laboratory investigations were performed by means of medical chart review and telephone interviews with members of the two families. The probands of each family were neuropathologically diagnosed with tauopathy by an experienced neuropathologist (D.W.D.). DNA from the brains of the probands, which were stored in the Mayo Clinic Florida brain bank, was screened for mutations in all *MAPT* exons expressed in human brains (0–5, 7, 9–13) and *LRRK2* exons 31 and 41, and flanking intronic regions using the Sanger sequencing method. The clinical study protocols were approved by the Mayo Clinic Institutional Review Board, and the autopsies were performed after approval by the next of kin or an individual with legal power of attorney.

Results and Discussion

Literature Review

More than 50 *MAPT* mutations have been reported in about 150 families with primary tauopathies (see http://www.molgen.ua.ac.be/ADMutations) [6], whereas the overwhelming majority of tauopathies occurs sporadically. This is also true for PSP, the most common primary tauopathy, which has an estimated prevalence of 5–6/100,000. Of all *MAPT* mutations, 10 have been associated with the phenotype of PSP, and 9 of these 10 mutations affected exon 10, increasing the expression of 4R tau isoforms [10].

Apart from *MAPT* mutations, deletion of part of the long arm of chromosome 18 as well as mutations in 21 other genes have been reported to occur with tau pathology. The tau pathology in these cases was reminiscent of that seen in Alzheimer's disease (AD), CBD, PSP, AGD or PiD and was often accompanied by deposition of other proteins, including α-synuclein, β-amyloid or TDP-43 (table 1). Tau protein has been reported to interact with some of these proteins, but the nature and type of these interactions are still a matter of debate. Results from some cellular research and animal models suggest that hyperphosphorylated tau protein is causally related with the activation of β-amyloid-induced microtubule disassembly and cell death. Other authors proposed alternative ways of interaction and suggested either the causative role of β-amyloid in tau pathology or synergistic toxic effects of both proteins [11]. β-Amyloid-induced oxidative stress is considered

Table 1. Genetic disorders with tau pathology (except for tauopathies linked to *MAPT* mutations)

Gene	Cytogenetic location	Disorders	Inheritance	Primary molecular pathology (CNS)	Tau pathology findings (seen with multiple mutations unless specified)	Ref. No.
TARDBP	1p36.22	ALS with or without FTD	Autosomal dominant	Ubiquitylated TDP-43 deposits	p.I383V: NFT, pretangles, neuropil threads, 4R positive rings in granular neurons of dentate gyrus, bush-like, tufted and thorn-shaped astrocytes in the amygdala	7, 26
PSEN2	1q42.13	Familial AD4	Autosomal dominant	Deposits of Aβ (and also tau)	AD	14
CYP27A1	2q35	Cerebrotendinous xanthomatosis	Autosomal recessive	Cholestanol and cholesterol deposits	p.R127W (c.379C>T): AGD-like, predominantly 4R, Braak stage III	7, 24
CNBP	3q21	DM2 (PROMM, Ricker syndrome)	Autosomal dominant	Deposits of RNA nuclear inclusions (foci)	AD-like (NFTs, Braak stage III–IV)	27
SNCA	4q22.1	PD/PARK1	Autosomal dominant	α-Synuclein deposits	p.G51D, p.A53T, p.A30P, *SNCA* duplication in heterozygous and homozygous state: AD-like with 3R and 4R NFTs (Braak stage 0–IV), pre-tangles, neuropil threads	28
SLC17A5	6q13	Sialic acid storage disease	Autosomal recessive	Storage of free sialic acid	AD-like (NFTs)	29
PRKN	6q26	PD/PARK2	Autosomal recessive	α-Synuclein deposits (infrequently)	p.C212Y: PSP-like with globose-type NFTs and ‹tufted astrocytes›, no Lewy bodies; exon 3 deletion and p.K211N: tau-positive thorn-shaped astrocytes, tau-positive astrocytes, no NFTs, no α-synuclein, no Lewy bodies	21, 30
C9ORF72	9p21.2	ALS and/or FTD	Autosomal dominant	Deposits of dipeptide repeat, RNA nuclear inclusions (foci), sometimes TDP-43	AD-like with NFTs (Braak stage II–III); *C9ORF72* and *MAPT* p.A239T variant: 3R PBli	25, 31
LRRK2	12q12	PD/PARK8	Autosomal dominant	α-Synuclein deposits	p.G2019S: PSP-like, predominantly 4R (no α-synuclein); p.R1441C: PSP-like predominantly 4R (no α-synuclein)	18, 19
ITM2B	13q14.3	Hereditary cerebral amyloid angiopathy (familial British dementia and familial Danish dementia)	Autosomal dominant	Aβ deposits	AD-like with amyloid-Bri or amyloid-Dan deposition with tau-positive NFTs (Braak stage V–VI), neuropil threads and dystrophic neurites	7, 32
PSEN1	14q24.2	Familial AD3	Autosomal dominant	Deposits of Aβ (and also tau)	AD; in addition 3 mutations with FTD phenotype: p.G183V (PBli, no extracellular Aβ), p.M146L (PBli, Aβ, NFTs), p.M146V (PBli, Aβ, NFTs)	14–17
NPC2	14q24.3	Niemann-Pick disease, type C	Autosomal recessive	Accumulation of cholesterol	AD-like (NFTs)	7, 29
NPC1	18q11.2					

Table 1 (continued)

Gene	Cytogenetic location	Disorders	Inheritance	Primary molecular pathology (CNS)	Tau pathology findings (seen with multiple mutations unless specified)	Ref. No.
CLN6	15q23	Kufs disease	Autosomal recessive	Accumulation of lipopigments	AD-like (NFTs)	29
GRN	17q21.32	FTLD with ubiquitin-positive inclusions	Autosomal dominant	Ubiquitylated TDP-43 deposits	IVS709-2A4G (c.709-2A4G): AD-like (NFTs, Braak stage 0–II)	33
	18q11–21	18q deletion syndrome (De Grouchy syndrome 2)	Few inherited cases reported (from carriers of chromosomal rearrangement)	Not given	AD-like (NFTs)	29
DMPK	19q13.3	DM1 (Curschmann-Steinert myotonic dystrophy)	Autosomal dominant	Deposits of RNA nuclear inclusions (foci)	AD-like (NFTs, Braak stage III–IV)	27
PRNP	20p13	Familial prion diseases (fCJD, GSS, FFI)	Autosomal dominant	Prion protein deposits	AD-like (NFTs are not uncommon in *PRNP* mutations, may reach Braak stage VI in p.Q160X and p.Y145X mutations, especially in cases of long disease duration)	7, 34
PANK2	20p13	Neuro-degeneration with brain iron accumulation	Autosomal recessive	Iron deposition	AD-like with NFTs (in 1 case Braak stage V), neuropil threads, tau-positive glia; presence of α-synuclein	35
APP	21q21.3	Familial AD1	Autosomal dominant	Deposits of Aβ (and also tau)	AD	14
SLC9A6	Xq26.3	Christianson syndrome	X-linked recessive	Impaired pH regulation of endosomes (few autopsy cases reported)	c.1012_1020del: CBD-like, 4R (no α-synuclein, no TDP-43, no amyloid)	22
ATP6AP2	Xp11.4	XPDS[1]	X-linked recessive	SQSTM1 deposits	p.S115S: CBD-like with 4R plaque-like structures and NFTs (Braak stage III)	23

Genetic disorders with tau pathology (except for tauopathies linked to *MAPT* mutations). Aβ = β-Amyloid peptide; AD = Alzheimer's disease; AD4 = Alzheimer's disease type 4; AGD = argyrophilic grain disease; ALS = amyotrophic lateral sclerosis; *APP* = amyloid precursor protein gene; *ATP6AP2* = ATPase, H+ transporting, lysosomal accessory protein 2 gene; *C9ORF72* = chromosome 9 open reading frame 72 gene; CBD = corticobasal degeneration; *CNBP* = CCHC-type zinc finger, nucleic acid binding protein gene; CNS = central nervous system; *CYP27A1* = cytochrome P450, family 27, subfamily A, polypeptide 1 gene; DM1 = myotonic dystrophy type 1; DM2 (PROMM) = myotonic dystrophy type 2 (proximal myotonic myopathy); *DMPK* = dystrophia myotonica protein kinase gene; fCJD = familial Creutzfeldt-Jacob disease; FFI = fatal familial insomnia; FTLD = frontotemporal lobar degeneration; FTD = frontotemporal dementia; *GRN* = progranulin gene; GSS = Gerstmann-Sträussler-Scheinker syndrome; *ITM2B* = integral membrane protein 2B gene; *LRRK2* = leucine-rich repeat kinase 2 gene; NFTs = neurofibrillary tangles; *NPC1* = Niemann-Pick disease, type C1, gene; *NPC2* = Niemann-Pick disease, type C2, gene; *PANK2* = pantothenate kinase 2 gene; PARK1 = autosomal dominant Parkinson's disease 1; PARK2 = juvenile, autosomal recessive Parkinson's disease type 2; PARK8 = autosomal dominant Parkinson's disease 8; PD = Parkinson's disease; PBli = Pick body-like inclusions; *PRKN* = parkin gene; *PRNP* = prion protein gene; *PSEN1* = presenilin-1 gene; PSP = progressive supranuclear palsy; *SLC9A6* = solute carrier family 9, subfamily A (NHE6, cation proton antiporter 6), member 6 gene; *SLC17A5* = solute carrier family 17 (acidic sugar transporter), member 5 gene; SNCA = α-synuclein gene; SQSTM1 = sequestosome 1; TARDBP = transactivationresponse DNA binding protein gene; *TRPM7* = transient receptor potential cation channel, subfamily M, member 7 gene; XPDS = X-linked parkinsonism with spasticity; 3R = 3-repeat tau isoform; 4R = 4-repeat tau isoform.

to be essential for tau hyperphosphorylation and subsequent neurofibrillary tangle (NFT) formation [12]. According to the tau axis hypothesis, progressively increasing concentrations of hyperphosphorylated tau in dendrites make neurons vulnerable to lesions caused by β-amyloid at the postsynaptic compartment. However, the process of tau hyperphosphorylation is driven by β-amyloid [11, 12]. Tau has also been reported to interact with α-synuclein. Both proteins share some similarities. They are heat-stable, unfolded, contain characteristic repeats, and tau can also be present in Lewy bodies. Recent reports have shown that α-synuclein stimulates kinase-mediated phosphorylation of tau initiated by oxidative stress [12]. Prion proteins can also interact with tau by binding directly to tubulin and inhibiting tubulin oligomerization and, as a consequence, microtubule assembly [13].

In 8 of the 21 genes, tau pathology was detected in patients only with some 'specific' mutations. In the remaining 12 genes *(PSEN2, CNBP, SLC17A5, C9ORF72, ITM2B, NPC2, NPC1, CLN6, DMPK, PRNP, PANK2, APP)*, tau pathology in the form of Alzheimer-type NFTs was a common finding (table 1). Therefore we attributed this tauopathy to a nonspecific result of these mutations. Mutations of one gene, presenilin-1 *(PSEN1)*, comprise both 'specific' and 'nonspecific' mutations with two different tauopathy phenotypes: AD and FTD. In the majority of the cases, it remains unclear what impact the primary mutation has on aggregation of tau protein and whether tau pathology is directly linked to these mutations or only an incidental finding.

In familial AD due to mutations in amyloid precursor protein *(APP)*, *PSEN1* or presenilin-2 *(PSEN2)* genes, accumulation of β-amyloid in senile plaques and amyloid angiopathy are considered to be the primary defects, but accumulation of hyperphosphorylated tau in NFTs, neuropil threads and dystrophic neurites in senile plaques is clearly involved in disease pathogenesis, and it is strongly linked to clinical phenotype [14]. Three *PSEN1* mutations (p.M146L, p.M146V and p.G183V) have been reported to present with a clinical phenotype of FTD. At autopsy, the carriers of these mutations had neuronal inclusions reminiscent of Pick bodies [15–17]. Of note, the case with the p.G183V mutation showed only tau pathology but no extracellular amyloid deposits [15].

PSP-like pathology with substantia nigra globose NFTs and tufted astrocytes in the basal ganglia, but no significant neuronal loss in the subthalamic nucleus, was reported in the p.G2019S mutation in the leucine-rich repeat kinase 2 gene *(LRRK2)*. Contrary to other *LRRK2* mutation cases, there was no evidence of abnormal accumulation of α-synuclein, but only tau pathology in these particular patients with p.G2019S or p.R1441C mutations in *LRRK2* (table 1) [18, 19]. Another *LRRK2* mutation, p.R1441H, was reported in a patient with Parkinson's disease (PD) whose clinical manifestation evolved to PSP. However, the neuropathology was not reported [20].

The clinicopathological phenotype reminiscent of PSP was also reported in a patient with parkinsonism and vertical gaze palsy due to a p.C212Y mutation in the parkin *(PRKN)* gene. On autopsy, globose-type NFTs and tufted astrocytes were described but no Lewy bodies were identified. Although *PRKN* mutations have been associated with autosomal recessive, juvenile-onset PD, it is not unusual for there to be a lack of Lewy bodies or α-synuclein staining in cases with *PRKN* mutations [21]. PSP was also seen in four members of a Spanish family, and one of these cases was autopsy confirmed. Genetic testing did not show any MAPT mutations, but PSP was linked to 3.4 cM locus on chromosome 1q31.1 [9].

Tau pathology that resembled CBD was reported in patients with c.1012_1020del mutation of the solute carrier family 9, subfamily A (NHE6, cation proton antiporter 6), member 6 gene *(SLC9A6)*. This included a variable degree of cortical and basal ganglia atrophy, coiled bodies and astrocytic plaques; however, severe degeneration of Purkinje cells and dentate nucleus and an absence of ballooned neurons differed from the classical CBD phenotype in these patients [22].

In a patient with a p.S115S mutation in the ATPase H+ transporting lysosomal accessory protein 2 gene *(ATP6AP2)*, there were plaque-like structures in the striatum consisting of tau-positive glial processes similar to astrocytic plaques [23]. The latter are frequently seen in CBD, but in this patient they were limited in distribution, while more widespread in cortical and basal ganglia in CBD.

In patients with cerebrotendinous xanthomatosis caused by the p.R127W mutation in the cytochrome P450, family 27, subfamily A, polypeptide 1 gene *(CYP27A1)*, tau pathology took the form of grains, tangles and coiled bodies that were predominantly found in the limbic system [24]. This phenotype is similar to that observed in sporadic AGD of the elderly.

Coexistence of the p.A239T variant of the *MAPT* gene and hexanucleotide expansions in *C9ORF72* in a patient led to a clinicopathological phenotype of FTD without symptoms of motor neuron disease and with neuronal inclusions that were reminiscent of Pick bodies. The

Table 2. Clinical, genealogical and neuropathological data of two probands

	Proband 1 (family 1)	Proband 2 (family 2)
Sex	F	M
Handedness	Right	Right
Age at death, years	79	69
Disease duration, years	4	9
First symptom	Eye movement impairment	Behavioral changes (disinhibition, agitation, violent outbursts, high libido), parkinsonism
FTD type	PPA	bvFTD, later PPA (impairment of verbal fluency, motor speed and processing speed)
Motor neuron disease sign	Spasticity	No
Parkinsonism	Axial rigidity, backward falls	Gait imbalance, postural instability, shuffling feet, backward falls, axial rigidity
Gaze palsy	Vertical	Vertical
Other signs and symptoms	Retrocollis, dysarthria, dysphagia, alteration of language and cognition, anxiety, nocturia	Mild cognitive impairment, hypophonia, urine incontinence, erectile dysfunction
Brain imaging	CT (at 75 years): no vascular lesions, marked to moderate atrophy of brain, especially cerebellum, prominent ventricles	^{18}F-FDG PET/CT (at 65 years): bilateral asymmetric left > right decreased FDG activity involving the anteromedial portions of the bilateral temporal lobes. No significant cortical atrophy MRI (at 68 years): prominent cerebral sulci and ventricles consistent with volume loss, chronic periventricular microvascular ischemic changes
Family history of movement disorders and dementia	1 brother and 2 sisters with parkinsonism late in life; no autopsy	1 brother with PSP, father parkinsonism; no autopsy
MAPT mutation	No	No
Brain weight, g	1,080	1,280
Cortical atrophy	Moderate atrophy (parasagittal superior frontal and superior parietal convexity)	No
NFT Braak stage	III	II–III
Globus pallidus (gliosis)	Mild	Mild
STN NL	Severe	Severe
SN pig. SN NL	Decreased Marked	Decreased Marked
MTR cortex NL	Mild to moderate	Moderate
Other features	Mild atrophy of callosum, enlargement of lateral ventricle	Atrophy of dentate nucleus, superior cerebellar peduncle (severe) and midbrain, enlargement of fourth ventricle
Clinical-pathological diagnosis	PSP	PSP

bvFTD = Behavioral variant of frontotemporal dementia; CT = computer tomography; F = female; 18F-FDG PET/CT = fluorine-18 fluorodeoxyglucose positron emission tomography/computer tomography; M = male; MTR cortex NL = neuronal loss in the motor cortex; NFTs = neurofibrillary tangles; PPA = primary progressive aphasia; PSP = progressive supranuclear palsy; SN NL = neuronal loss of the substantia nigra; SN pig. = pigmentation of the substantia nigra; STN NL = subthalamic nucleus neuronal loss.

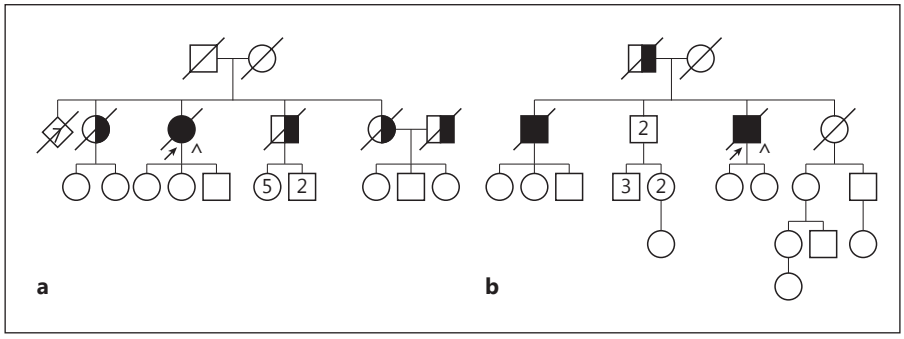

Fig. 1. Pedigrees of family 1 (**a**) and family 2 (**b**). Round symbols indicate women; squares indicate men; figures inside symbols indicate number of children; diagonal lines indicate that the individual is deceased. The arrow indicates the proband. A caret indicates an autopsy was completed. Black symbols indicate individual with PSP; black and white symbols indicate individuals with parkinsonism.

Region	NFT & pre-NFT		Coiled bodies		Tufted astrocytes		Tau(+) threads	
Proband:	1	2	1	2	1	2	1	2
Temporal cortex	2	1	1	0	2	0	1	0
Superior frontal	3	2	3	1	3	2	2	1
Motor cortex	3	2	3	3	3	2	3	3
Striatum	2	1	2	3	3	3	2	1
Globus pallidus	3	2	2	3	1	0	3	2
Basal nucleus	2	3	1	2	0	1	2	3
Hypothalamus	3	3	1	1	1	0	2	2
Thalamus	3	3	3	3	2	3	3	3
Subthalamic nucleus	3	3	2	3	3	3	3	3
Red nucleus	3	3	3	3	2	2	3	3
Substantia nigra	3	3	2	2	1	2	3	2
Midbrain tectum	2	3	3	3	2	3	3	3
Locus ceruleus	3	3	1	1	0	0	3	3
Pontine tegmentum	3	3	2	3	0	0	3	3
Pontine base	3	3	2	2	0	0	2	3
Medullary tegmentum	3	3	2	3	0	0	3	3
Inferior olive	2	3	2	2	1	0	2	3
Dentate nucleus	3	2	1	2	0	1	2	1
Cerebellar white matter	0	0	3	3	0	0	2	3

Fig. 2. Semiquantitative assessment of tau pathology in two probands. The pattern of neuronal and glial tau pathology is similar in the probands. Number and shading represent lesion density score: 0 = none; 1 = sparse; 2 = moderate; 3 = frequent.

proband's 2 brothers were carriers of only the *C9ORF72* mutation and developed amyotrophic lateral sclerosis, but not FTD [25].

Clinicopathological, Genealogical and Genetic Analysis of Two Families with Tauopathy

Family 1

The proband was a 79-year-old, right-handed woman with a 4-year history of a motor and cognitive disorder that initially presented with eye movement impairment. Later, she developed speech difficulties that were suggestive of progressive aphasia. She had backward falls, memory problems and episodes of anxiety. Two years before her death, neurological evaluation showed vertical gaze palsy, dysarthria and dysphagia. Motor signs included axial rigidity, retrocollis and limb spasticity. Brain computer tomography scans revealed moderate-to-marked atrophy of the brain, especially of the cerebellum, with

prominent ventricles (table 2). Her family history was remarkable for parkinsonism in a brother and 2 sisters. No postmortem studies were available on other family members (fig. 1a).

The proband's calculated brain weight was 1,080 g. It had moderate cortical atrophy over the parasagittal superior frontal and superior parietal convexities. The subthalamic nucleus was slightly smaller than normal. There was no atrophy of the superior cerebellar peduncle. The substantia nigra had mild decreased pigmentation. Histologically, there was marked neuronal loss in the subthalamic nucleus and the substantia nigra. The motor cortex and the globus pallidus showed mild to moderate neuronal loss and gliosis. The cerebellum revealed patchy Purkinje cell loss and Bergmann gliosis in the vermis. The cerebellar dentate nucleus had focal neuronal loss and gliosis.

Alzheimer-type neurofibrillary pathology assessed with thioflavin S fluorescent microscopy was consistent with Braak NFT stage III (table 2). Neither senile plaques nor Lewy bodies were detected. Tau immunohistochemistry revealed a range of lesions, including pretangles, NFTs, tufted astrocytes, coiled bodies and neuropil threads (fig. 2). There was neither α-synuclein nor TDP-43 immunostaining present.

The overall pathological findings were those of a tauopathy most consistent with PSP, although cortical tau pathology was greater than usual. Involvement of the frontal cortex and the corticobulbar and corticospinal tracts correlated with clinical findings of dementia, dysphagia and limb spasticity.

Family 2

The proband was a right-handed man who died at the age of 69 years following a 9-year disease course. His first symptoms were parkinsonism and behavioral changes, including disinhibition, agitation, violent outbursts and increased libido.

Five years after symptom onset, he had difficulty multitasking, as well as visuoperceptual and visuospatial impairments. His language difficulties included reduced verbal fluency and impairments in motor speed and processing speed. The findings were consistent with primary progressive aphasia. Memory problems were also noted. On neurological examination he had axial rigidity, shuffling gait, postural instability with backward falls and hypophonia. He also had vertical gaze palsy, urinary incontinence and erectile dysfunction. ^{18}F-fluorodeoxyglucose positron emission tomography showed decreased activity in anteromedial portions of both temporal lobes, which was worse on the left. There was no significant cortical atrophy.

Eight years after symptomatic onset he was wheelchair-bound and mute. He scored 22/30 on the Montreal Cognitive Assessment scale. There was no response to 75 mg/300 mg of carbidopa/levodopa therapy. Magnetic resonance imaging showed minimal periventricular white matter changes that were consistent with chronic microvascular ischemic changes. The cerebral sulci and prominent ventricles indicated volume loss. Molecular genetic analysis of transactivation response DNA binding protein *(TARDBP)* gene did not reveal any mutations.

The patient's family history was remarkable for PSP in a brother and parkinsonism in his father (fig. 1b). Neither diagnosis was pathologically confirmed.

The proband's calculated brain weight was 1,280 g. The cerebral hemisphere had a normal configuration, and the sulci and gyri showed no atrophy over the convexity. The periventricular white matter had patchy gray discoloration. The subthalamic nucleus was much smaller than normal. The infratentorial structures showed midbrain atrophy with dilation of the aqueduct, enlargement of the fourth ventricle and severe atrophy of the superior cerebellar peduncle. The substantia nigra had decreased pigmentation. The cerebellar sections showed marked atrophy of the dentate nucleus.

The neocortex had no significant neuronal loss or gliosis, except in the motor cortex where there was subjective neuronal loss. The globus pallidus revealed mild vascular calcification and mild gliosis. The thalamus had gliosis in the ventrolateral region. The subthalamic nucleus showed severe neuronal loss and gliosis, with severe neuronal and glial tau pathology. The thalamic fasciculus and internal capsule had many threads and coiled bodies. The substantia nigra showed marked neuronal loss in the ventrolateral cell group, but less neuronal loss in dorsal and medial cell groups. This was associated with extraneuronal neuromelanin, gliosis and neuronal and glial tau pathology. The cerebellum showed no significant Purkinje cell loss or Bergmann gliosis. The cerebellar dentate nucleus had severe neuronal loss and gliosis with severe grumose degeneration.

The Braak NFT stage was consistent with stage II–III (table 2). No senile plaques were present in the cortex or hippocampus. Tau immunohistochemistry revealed a range of lesions, including pretangles, NFTs, tufted astrocytes, coiled bodies and neuropil threads (fig. 2). There was neither α-synuclein nor TDP-43 immunostaining present.

The overall pathological findings were those of a primary tauopathy consistent with PSP, although oligoden-

droglial pathology was more marked than usual in both the forebrain and hindbrain structures.

Sequence analysis of the entire coding region of the *MAPT* gene identified no mutation in the probands of family 1 and family 2. Additional sequencing of *LRRK2* exons 31 and 41 in both probands revealed no mutation at codons 1441 and 2019. Both probands were homozygous for the H1 *MAPT* haplotype.

Conclusions

MAPT mutations are a cause of familial tauopathies. However, the 18q deletion syndrome and mutations in 21 other genes may present with tau pathology, most frequently in the context of other well-defined pathologies. Importantly, while we aimed to provide a comprehensive overview of familial cases with known gene mutations and tau pathology, it remains unclear whether tau pathology is caused by the reported gene mutations or merely presents an incidental finding.

In our two families, the clinicopathological findings were consistent with primary tauopathies in the form of PSP. Molecular genetic analysis of all coding regions of *MAPT* did not bring clarification. Screening of the *LRRK2* codons 1441 and 2019 that previously had been linked to the PSP phenotype [18, 19] did not reveal any mutations. Despite a positive family history, we conclude that the lack of mutations in *MAPT* and *LRRK2* suggests that unknown genetic factors and possibly mutations in new genes may play a role in the pathogenesis of familial tauopathies.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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