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Retiring the term FTDP-17 as *MAPT* mutations are genetic forms of sporadic frontotemporal tauopathies

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In many neurodegenerative disorders, familial forms have provided important insights into the pathogenesis of their corresponding sporadic forms. The first mutations associated with frontotemporal lobar degeneration (FTLD) were found in the microtubule-associated protein tau (*MAPT*) gene on chromosome 17 in families with frontotemporal degeneration and parkinsonism (FTDP-17). However, it was soon discovered that 50% of these families had a nearby mutation in progranulin. Regardless, the original FTDP-17 nomenclature has been retained for patients with *MAPT* mutations, with such patients currently classified independently from the different sporadic forms of FTLD with tau-immunoreactive inclusions (FTLD-tau). The separate classification of familial FTLD with *MAPT* mutations implies that familial forms cannot inform on the pathogenesis of the different sporadic forms of FTLD-tau. To test this assumption, this study pathologically assessed all FTLD-tau cases with a known *MAPT* mutation held by the Sydney and Cambridge Brain Banks, and compared them to four cases of four subtypes of sporadic FTLD-tau, in addition to published case reports. Ten FTLD-tau cases with a *MAPT* mutation (K257T, S305S, P301L, IVS10+16, R406W) were screened for the core differentiating neuropathological features used to diagnose the different sporadic FTLD-tau subtypes to determine whether the categorical separation of *MAPT* mutations from sporadic FTLD-tau is valid. Compared with sporadic cases, FTLD-tau cases with *MAPT* mutations had similar mean disease duration but were younger at age of symptom onset (55 $\pm$ 4 years versus 70 $\pm$ 6 years). Interestingly, FTLD-tau cases with *MAPT* mutations had similar patterns and severity of neuropathological features to sporadic FTLD-tau subtypes and could be classified into: Pick's disease (K257T), corticobasal degeneration (S305S, IVS10+16, R406W), progressive supranuclear palsy (S305S) or globular glial tauopathy (P301L, IVS10+16). The finding that the S305S mutation could be classified into two tauopathies suggests additional modifying factors. Assessment of our cases and previous reports suggests that distinct *MAPT* mutations result in particular FTLD-tau subtypes, supporting the concept that they are likely to inform on the varied cellular mechanisms involved in distinctive forms of sporadic FTLD-tau. As such, FTLD-tau cases with *MAPT* mutations should be considered familial forms of FTLD-tau subtypes rather than a separate FTDP-17 category, and continued research on the effects of different mutations more focused on modelling their impact to produce the very different sporadic FTLD-tau pathologies in animal and cellular models.

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Abbreviations: 3R-tau = tau protein with three microtubule binding domains; 4R-tau = tau protein with four microtubule binding domains; CBD = corticobasal degeneration; FTDP-17 = frontotemporal dementia and parkinsonism linked to chromosome 17; FTLD = frontotemporal lobar degeneration; FTLD-tau = FTLD with tau-immunopositive inclusions; GGT = globular glial tauopathy; PSP = progressive supranuclear palsy

Introduction

Frontotemporal lobar degeneration (FTLD) is a clinically, genetically and pathologically diverse group of disorders, with up to 40% of cases having a family history of dementia and/or a movement disorder (Rohrer *et al.*, 2009). The first mutations associated with FTLD were found in the microtubule-associated protein tau (*MAPT*) gene on chromosome 17 in families with familial frontotemporal degeneration and parkinsonism (FTDP-17) (Hutton *et al.*, 1998; Poorkaj *et al.*, 1998; Spillantini *et al.*, 1998). In 2006, the discovery of mutations in the progranulin (*GRN*) gene linked to a similar region on chromosome 17 was identified as the second cause of FTDP-17 (Baker *et al.*, 2006; Cruts *et al.*, 2006). Despite the widespread use of this nomenclature and its usefulness in informing on chromosomal linkage, FTDP-17 is not informative for discriminating between *MAPT* and *GRN* mutations, nor for describing the underlying proteinopathy seen in the disease. Pathologically, patients with mutations in *GRN* show FTLD with TAR DNA binding protein 43-immunopositive inclusions (FTLD-TDP) and are subtyped into the same pathological categories as sporadic FTLD-TDP (Rademakers *et al.*, 2013; Lee *et al.*, 2017). The pathogenic mechanisms underlying sporadic and familial FTLD-TDP are thought to be similar, with the four well-described FTLD-TDP pathological subtypes associated with three different genetic abnormalities, including *GRN* (Rademakers *et al.*, 2013) (Fig. 1). In contrast, some authors have retained the original FTDP-17 nomenclature for patients with mutations in *MAPT* and these are currently classified separately from the sporadic forms of FTLD with tau-immunoreactive inclusions (FTLD-tau, Fig. 1) (Rohrer *et al.*, 2011; Rademakers *et al.*, 2013; Kovacs, 2015; Lashley *et al.*, 2015; Arendt *et al.*, 2016). Separating FTLD-tau cases with a mutation in *MAPT* from sporadic cases suggests they have independent pathogenic mechanisms.

Characterized by the morphology, distribution and biochemical composition of phosphorylated tau in neurons and glia, sporadic FTLD-tau is subdivided into four main pathological subtypes: Pick's disease, corticobasal degeneration (CBD), progressive supranuclear palsy (PSP) and globular glial tauopathy (GGT) (Fig. 1). Argyrophilic grain disease (AGD) and neurofibrillary tangle predominant dementia (NFTPD), which includes primary age-related tauopathy (PART) (Crary *et al.*, 2014) are further recognized subtypes, but comprise a small proportion of FTLD-tau cases (Jellinger and Attems, 2007; Josephs *et al.*, 2011). The neuropathological phenotypes of FTLD-tau associated with *MAPT* mutations are heterogeneous and vary between and within family members with the same mutation (Stanford *et al.*, 2000; Halliday *et al.*, 2006; Skoglund *et al.*, 2008). In addition, the cell types involved and the cellular compartments that aggregate tau are heterogeneous, and many cases have neuropathological features additional to those of sporadic FTLD-tau (Ghetti *et al.*, 2015; Kovacs, 2015; Lashley *et al.*, 2015). Only recently has there been increased recognition that *MAPT* mutations may be associated with neuropathological phenotypes of sporadic FTLD-tau (Kovacs, 2015); however, most of these observations are confined to single case reports (Table 1). These studies suggest that FTLD-tau cases with a *MAPT* mutation have pathological similarities to sporadic FTLD-tau and by identifying subtype-specific features, could be classified into and considered comparable to their sporadic diagnostic counterparts.

To determine whether similar pathologies cluster with different *MAPT* mutations, an experimental design similar to clinicogenetic associations was used to identify pathogenetic associations. This differs significantly from previous studies using case report designs. By assessing pathological correlations to clustered *MAPT* mutations in a cohort of pathologically confirmed FTLD cases with *MAPT* mutations, and by directly comparing their pathologies to those with sporadic FTLD-tau, clear associations can be determined. Similar neuropathological features in both sporadic and FTLD-tau cases with a *MAPT* mutation would suggest that these cases could be considered as familial forms of the different subtypes of FTLD-tau and on a disease continuum with these sporadic forms, potentially simplifying neuropathological criteria. This may have important implications for the recent study by the Genetic Frontotemporal Dementia Initiative (GENFI) demonstrating that structural imaging changes occur in pre-symptomatic *MAPT* mutation carriers 15 years before their estimated symptom onset (Rohrer *et al.*, 2015). Subtype analysis of those with different *MAPT* mutations associated with different sporadic FTLD-tau forms may be more informative for the larger populations of FTLD-tau patients.

		FTLD-tau				FTDP-17	FTLD-TDP			
Pathological subtype		PiD	CBD	PSP	GGT	FTLD-tau or FTLD-TDP	Type A	Type B	Type C	Type D
Molecular classification		3R	4R	4R	4R	3R +/or 4R* or phospho-TDP	Phospho-TDP	Phospho-TDP	Phospho-TDP	Phospho-TDP
Current	Genetic status	Sporadic	Sporadic	Sporadic	Sporadic	Familial	Sporadic or familial	Sporadic or familial	Sporadic	Familial
Current	Main gene associated	-	-	-	-	*MAPT** or *GRN*	*GRN, C9orf72*	*GRN, C9orf72*	-	*VCP*
Suggested	Genetic status	Sporadic or familial	Sporadic or familial	Sporadic or familial	Sporadic or familial	-	No change	No change	No change	No change
Suggested	Main gene associated	*MAPT*	*MAPT*	*MAPT*	*MAPT*	-	No change	No change	No change	No change
Pathological features		Pick bodies 20 µm	Astrocytic plaque 40 µm	Tufted astrocyte 20 µm	GAI 20 µm	Refer to text and figures for *MAPT*	NCIs + neurites 50 µm	NCIs 50 µm	Long neurites 50 µm	NIIs 20 µm

Figure 1 Comparison between the main pathological subtypes of FTLD and known gene associations. For FTLD-TDP subtypes, there is an association between specific gene abnormalities and the morphological type of inclusion pathology, suggesting that specific intracellular processes are involved. For FTLD-tau subtypes, genetic forms are considered as a separate group (FTDP-17). We suggest that different mutations in the *MAPT* gene could inform more about the specific intracellular processes involved in forming the different morphological types of inclusions observed in FTLD-tau. 3R = 3-repeat tau; 4R = 4-repeat tau; GAI = globular astrocytic inclusion; NCIs = neuronal cytoplasmic inclusions; NNIs = neuronal intranuclear inclusions. *Refer to Table 1.

Materials and methods

Cohort

The Sydney-Cambridge cohort ($n = 188$) was used to identify all *MAPT* gene mutation cases ($n = 10$ of 173 FTLD-tau cases in which definitive genetic data could be obtained) and were compared with 16 sporadic FTLD-tau cases with Pick's disease ($n = 4$), CBD ($n = 4$), PSP ($n = 4$) and GGT ($n = 4$) subtypes. No other age-related primary tauopathies were used for comparison in this study. Ethical approval, recruitment processes and genetic screening techniques are provided in the Supplementary material, and demographic details for cases included in this study are shown in Table 2. Due to the recent changes to the reference *MAPT* transcripts used to annotate the position and nature of the nucleotide substitutions described in this study, their corresponding reference SNP (rs) numbers and updated exonic positions are listed in Supplementary Table 1. However, in the text and figures we will use the traditional nomenclature for clear comparisons.

Analyses

All FTLD cases were classified into pathological subtypes throughout the collection period using standardized diagnostic procedures and assigned a family history score using Goldman criteria (Goldman *et al.*, 2005). *MAPT* mutations were identified in eight independent families and included P301L (exon 10; $n = 1$), IVS10+16 (intron 10; $n = 4$, unrelated) and R406W (exon 13; $n = 1$), K257T (exon 9; $n = 1$) and S305S [exon 10; $n = 3$, all siblings from the same family and two have been reported previously (Stanford *et al.*, 2000; Halliday *et al.*, 2006)]. The pattern and severity of neuronal loss and neuropathological features immunostained for phosphorylated tau (AT8), and for tau with three (3R-tau) or four (4R-tau) microtubule binding sites were recorded in *MAPT* mutation cases and compared to FTLD-tau cases with no or low heritability ($n = 4$/subtype). Selection of brain regions of interest was based on key areas routinely sampled for standard FTLD neuropathological assessment (Table 2) (Hauw *et al.*, 1994; Dickson *et al.*, 2002; Cairns *et al.*, 2007; Ahmed *et al.*, 2013).

See Supplementary material for more details on the analyses used in this study.

Results

Cases with specific *MAPT* mutation have the same characteristic pathologies as particular sporadic FTLD-tau subtypes

Pick's disease

The FTLD-tau case with a K257T *MAPT* mutation had the same hallmark neuropathological features (AT8-immunopositive Pick bodies, ballooned neurons, ramified astrocytes, threads, coiled bodies and globular oligodendroglial inclusions) as sporadic Pick's disease cases (Cairns *et al.*, 2007) (Tables 2, 3 and Supplementary Fig. 1). Immunostaining with 3R-tau labelled a similar number of neuropathological features as those labelled with AT8, except ramified astrocytes that were only immunoreactive for 4R-tau. In addition, there was a similar pattern and severity of neuronal loss and gliosis as observed in sporadic Pick's disease cases (Table 2 and Supplementary Fig. 1E). AT8-immunopositive astrocytic plaques and tufted

Table 1 ***MAPT*** **mutations associated with FTLD-tau pathological subtypes**

Genetic position	Mutation	Subtype	Tau isoform deposited	Filament type	Age at onset	Disease duration (y)	Main clinical diagnosis	Reference
Exon 1	R5L	PSP	4R	Straight	57	5	PSP-RS	Poorkaj *et al.*, 2002
	R5H	GGT	4R	Straight tubules	75	6	Dementia NS	Hayashi *et al.*, 2002
Exon 9	K257T	PiD	3R	Twisted ribbons	47	4	bvFTD	Rizzini *et al.*, 2000
		PiD	3R		N/A	N/A	N/A	Pickering-Brown *et al.*, 2000
		PiD	3R		64	4	bvFTD	Current study
	L266V	PiD	3R	Straight	33	3.5	bvFTD	Hogg *et al.*, 2003
		PiD	3R		31	3	bvFTD	Van Deerlin *et al.*, 2007
		PiD	3R		24	7	bvFTD	Irwin *et al.*, 2016
	G272V	PiD	3R	Twisted ribbons	45	9		Bronner *et al.*, 2005
		PiD	3R	Twisted ribbons	52	15		Bronner *et al.*, 2005
Intron 9	IVS9-15*	PiD	3R		46	9	bvFTD	Anfossi *et al.*, 2011
Exon 10	ΔK280	PiD	3R	Twisted	53	10	bvFTD	van Swieten *et al.*, 2007
	N279K	PSP	4R?	Twisted ribbons	40	7	PSP	Delisle *et al.*, 1999
	S285R	PSP	4R		40	4	PPSP	Fujioka *et al.*, 2015
		PSP	4R		41	9	PSP	Fujioka *et al.*, 2015
	P301L	GGT	4R		54	9	bvFTD	Current study
		GGT	4R		53	12	bvFTD	Current study
		GGT	4R		66	17	bvFTD	Current study
		GGT	4R		53	12	bvFTD	Tacik *et al.*, 2017*b*
	S303S	PSP	4R		37	8	PSP	Ros *et al.*, 2005
		PSP	4R		41	4	PSP	Ros *et al.*, 2005
		PSP	4R		Late 30s	41 (died)	PSP	Ros *et al.*, 2005
	S305S	PSP	4R	Twisted + straight	49	2	PSP	Stanford *et al.*, 2000; current study
		CBD	4R		55	1	bvFTD	
		CBD	4R		56	7	FT	Current study
	N296H	GGT	4R		57	5	FTD	Halliday *et al.*, 2006; current study
	S305I	AGD	4R	Straight tubules	39	1.5	bvFTD	Iseki *et al.*, 2001
				Straight tubules				Kovacs *et al.*, 2008
Intron 10	IVS10+4*	PiD	3R		Above	Above	Above	Anfossi *et al.*, 2011
	IVS10+16	CBD	4R		57	5	AD	Current study
		CBD	4R		49	14	bvFTD	Current study
		GGT	4R		55	3	bvFTD	Current study
		PSP	4R?		40	5	PSP	Morris *et al.*, 2003
Exon 11	L315A	PiD	3R > 4R		25	8	PPA	van Herpen *et al.*, 2003
		PiD	3R > 4R	Twisted + straight	53	8	bvFTD	van Herpen *et al.*, 2003
	S320F	PiD	3R + 4R	Straight + twisted	38	15	bvFTD	Rosso *et al.*, 2002
	P332S	PiD	3R > 4R		60	15	Anarthria + opercular syndrome	Deramecourt *et al.*, 2012
	K317N	GGT	4R	Straight	64	5	FTD-MND	Tacik *et al.*, 2015*b*
Exon 12	Q336R	PiD	3R + 4R	Straight	58	10	FTD	Pickering-Brown *et al.*, 2004
	Q336H	PiD	3R > 4R	Straight	55	8	Atypical AD	Tacik *et al.*, 2015*a*
	K369I	PiD	3R + 4R	Twisted	52	9	bvFTD	Neumann *et al.*, 2001
	G342V	PiD	4R > 3R	Helical	48	7	PNFA	Lippa *et al.*, 2000
Exon 13	E372G	PiD	3R + 4R		40	18	bvFTD	Tacik *et al.*, 2017*a*
	G389R	PiD	3R + 4R		24	7	PNFA/bvFTD	Tacik *et al.*, 2017*a*
		PiD	3R + 4R		53	7	bvFTD/CBS	Tacik *et al.*, 2017*a*
		PiD	3R + 4R		17	7	bvFTD	Chaunu *et al.*, 2013
		PiD	3R + 4R		38	5	FTD	Ghetti *et al.*, 2000; Murrell *et al.*, 1999
	R406W	PiD	3R + 4R		32	5	bvFTD	Pickering-Brown *et al.*, 2000
	N410H	CBD	4R		57	17	bvFTD	Current study
		CBD	4R		63	4	PSP/CBS	Kouri *et al.*, 2014

*Two intronic mutations in *MAPT* were identified in this patient.

3R = 3-repeat tau; 4R = 4-repeat tau; AD = Alzheimer's disease; bvFTD = behavioural variant frontotemporal dementia; CBS = corticobasal syndrome; IR = immunoreactive; NFT = neurofibrillary tangle; NS = not specified; PNFA = progressive non-fluent aphasia; PPA = primary progressive aphasia; RS = Richardson's syndrome.

Table 2 Demographic details and distribution of neuronal loss associated with FTLD-tau cases with a *MAPT* mutation and FTLD-tau subtypes

	Cases													
	1	2	3[a]	4[b]	5	6	7	8	9	10	PiD[c]	CBD[c]	PSP[c]	GGT[c]
Gender	M	M	F	F	F	M	M	M	M	F	2:2	3:1	3:1	3:1
Age at diagnosis (y)	64	55	56	49	57	57	49	55	54	54	70 ± 5	67 ± 4	67 ± 7	74 ± 8
Disease duration (y)	4	1	7	2	17	5	14	3	4	9	8 ± 3	5 ± 3	4 ± 2	5 ± 3
***MAPT* mutation**	K257T	S305S	S305S	S305S	R406W	+16	+16	+16	+16	P301L				
FTLD-tau subtype	PiD	CBD	CBD	PSP	CBD	CBD	CBD	GGT	GGT	GGT				
Neuronal loss														
Superior frontal cortex	+ +	+ +	+ +	+	+	+	+	+ +	+ +	+ +	0,0,1,3	0,3,1,0	2,2,0,0	0,2,1,1
Precentral cortex	–	+ + +	+	+ +	–	–	–	–	–	–	2,2,0,0	2,1,0,0[d]	2,2,0,0	2,1,1,0
Inferior temporal cortex	+ +	+ + +	+	+	+	+	+	+ +	+ + +	+ + +	0,0,1,3	0,3,0,1	2,2,0,0	0,2,2,0
Entorhinal cortex	+	+	+	+	+	+ +	+	+ +	+ +	+	0,0,0,4	2,0,1,1	2,2,0,0	1,2,0,1
Hippocampus														
Dentate gyrus	–	+	+	–	+	+	+	–	–	–	3,0,0,1	2,2,0,0	3,1,0,0	4,0,0,0
CA1	+ +	+	+ +	+	+ + +	+ +	+	+	+ +	+	0,2,0,2	2,0,0,2	2,1,1,0	2,1,0,1
Basal ganglia	–	+	+	+ +	–	+	–	+ +	+	+ +	1,1,1,1	1,2,0,0[d]	1,2,1,0	1,2,1,0
Midbrain	+ +	+ + +	+ + +	+ +	+	+	+	+ + +	+ +	+ +	1,2,1,0	0,0,2,2	0,1,1,2	1,1,2,0
Pons	–	+ + +	–	+	–	–	–	+ + +	+ + +	–	1,3,0,0	3,0,1,0	2,2,0,0	1,3,0,0
STN			–	+ +		–							0,1,2,1	4,0,0,0
Medulla	–	–	–	–	–	–	–	–	–	–	2,2,0,0	4,0,0,0	3,1,0,0	4,0,0,0

CA1 = hippocampal CA1 region; CBD = corticobasal degeneration; PiD = Picks disease; STN = subthalamic nucleus.
Severity of neuronal loss in FTLD-tau cases with a MAPT mutation was graded as none (–), mild (+), moderate (+ +) or severe (+ + +).
[a,b]S305S siblings previously reported in Halliday *et al.*, 2006[a] and Stanford *et al.*, 2000[b].
[c]For FTLD-tau cases with PiD (n = 4), CBD (n = 4), PSP (n = 4) and GGT (n = 4) subtypes, gender is expressed as the number of males and females (M:F). Age at symptom onset and disease duration are expressed as the mean ± SD. Severity of neuronal loss is expressed as the number of cases within each subtype with no, mild, moderate or severe neuronal loss.
[d]The precentral cortex and basal ganglia were unavailable for one CBD case.

astrocytes characteristic of CBD and PSP, respectively, were not observed.

Corticobasal degeneration

Five FTLD-tau cases with a mutation in *MAPT* (S305S, R406W, IVS10+16) had characteristic neuropathological features of sporadic CBD (moderate-to-severe number of AT8-immunostained astrocytic plaques and thread pathology) (Dickson *et al.*, 2002; Cairns *et al.*, 2007) (Tables 2, 3 and Supplementary Fig. 2). Immunostaining with 4R-tau labelled a similar number of neuropathological features as those labelled with AT8. Immunostaining with 3R-tau was absent or rare in sporadic CBD cases, confined to occasional neurofibrillary tangles and neurites in one case.

Two of the three siblings from the Sydney S305S family have been reported previously and demonstrate that the neuropathology associated with *MAPT* mutations can be heterogeneous, even between family members with the same mutation. Although both reported cases had a similar distribution of neuronal loss (Table 2), one case had pathologically confirmed CBD (Case 3) (Halliday *et al.*, 2006), and the other pathologically confirmed PSP with associated subcortical neuronal loss and neurofibrillary tangle formation (Case 4) (Stanford *et al.*, 2000). The third S305S sibling had pathologically confirmed CBD (Case 2), reported for the first time in this study, with the shortest disease duration and the most widespread and greatest severity of neuronal loss of all siblings (Table 2). The severity of neuropathological features immunostained with AT8 was heterogeneous between siblings but was most similar in the two siblings with CBD, which had a similar distribution and severity of AT8-immunopositive ballooned neurons, astrocytic plaques, grey and white matter thread pathology, coiled bodies and globular oligodendroglial inclusions (Table 3 and Supplementary Fig. 2F–J). The distribution of neuronal loss and these neuropathological features immunostained with AT8 was similar to all sporadic CBD cases. Argyrophilic AT8-immunopositive tufted astrocytes were also observed in affected cortical regions of both siblings with CBD pathology. In addition, both siblings had AT8-immunopositive perinuclear rings in all cortical regions examined and AT8-immunopositive grain-like structures in cortical regions and the hippocampus. These grain-like structures were non-argyrophilic on Gallyas and modified Bielschowsky silver stains and did not resemble the spindle-shaped grains observed in argyrophilic grain disease. All neuropathological features in both siblings were 4R-tau-immunoreactive. 3R-tau immunostaining was not observed.

The FTLD-tau case with an R406W mutation (Case 5) had limited cortical and subcortical neuronal loss (Table 2), although the pattern and distribution of neuronal loss, gliosis and neuropathological features immunostained with AT8 was similar to all sporadic CBD cases (Supplementary Fig. 2K–O). These neuropathological

Table 3 Severity of neuropathological features in the superior frontal cortex immunostained with phosphorylated tau in FTLD-tau cases with a *MAPT* mutation and in Pick's disease, CBD, PSP and GGT subtypes

	Cases													
	1	2	3[a]	4[b]	5	6	7	8	9	10	PiD[c]	CBD[c]	PSP[c]	GGT[c]
***MAPT* mutation**	K257T	S305S	S305S	S305S	R406W	+16	+16	+16	+16	P301L				
FTLD-tau subtype	PiD	CBD	CBD	PSP	CBD	CBD	CBD	GGT	GGT	GGT				
Neuronal														
Pick bodies	+ + +	–	–	–	–	–	–	–	–	–	0,1,1,2	4,0,0,0	4,0,0,0	4,0,0,0
Balloon neurons	+ +	+	+	+ +	+	+ +	+	+	–	+	1,1,2,0	0,3,1,0	4,0,0,0	4,0,0,0
Peri-nuclear rings	–	+	+	+	–	–	–	–	–	–	4,0,0,0	4,0,0,0	4,0,0,0	4,0,0,0
Astrocytic														
Ramified astrocytes	+	–	–	–	–	–	–	–	–	–	0,1,2,1	4,0,0,0	4,0,0,0	4,0,0,0
Astrocytic plaques	–	+	+	+ +	+	+	+	–	–	–	4,0,0,0	0,0,1,3	4,0,0,0	4,0,0,0
Tufted astrocytes	–	+	+	+	–	–	–	–	–	–	4,0,0,0	4,0,0,0	0,2,2,0	4,0,0,0
GAIs	–	–	–	–	–	–	–	+ +	+ + +	+ +	4,0,0,0	4,0,0,0	4,0,0,0	0,2,1,1
Threads - GM	+ +	+	+	+ + +	+	+ +	+ +	+ +	+ + +	+ +	1,1,2,0	0,1,1,2	2,2,0,0	2,0,2,0
Threads - WM	+ +	+ + +	+ + +	+ +	+	+ + +	+ + +	+ + +	+ + +	+ +	0,4,0,0	0,0,3,1	0,4,0,0	1,2,0,1
Oligodendroglial														
Coiled bodies - GM	+	+ +	+	+ +	+	+	+ +	+ + +	+ + +	+	0,3,1,0	0,2,2,0	0,1,3,0	0,3,1,0
Coiled bodies - WM	+ +	+ + +	+ + +	+ +	–	+ + +	+ + +	+ + +	+ + +	+ +	0,2,2,0	0,0,4,0	0,0,2,2	0,0,3,1
GOIs - GM	+ +	+	+ +	+ + +	+	+ +	+	+ + +	+ + +	+	0,2,2,0	0,1,3,0	3,1,0,0	0,2,2,0
GOIs - WM	+	+	+ +	+ +	–	+ +	+ +	+ + +	+ + +	+ +	0,4,0,0	0,2,2,0	4,0,0,0	0,2,1,1

CBD = corticobasal degeneration; GAIs = globular astrocytic inclusions; GM = grey matter; GOIs = globular oligodendroglial inclusions; PiD = Picks disease; WM = white matter. Severity of neuropathological features immunostained with phosphorylated tau in FTLD-tau cases with a MAPT mutation was graded as none (–), mild (+), moderate (+ +) or severe (+ + +).

[a,b]S305S siblings previously reported in Halliday *et al.*, 2006[a] and Stanford *et al.*, 2000[b].

[c]For FTLD-tau cases with PiD (n = 4), CBD (n = 4), PSP (n = 4) and GGT (n = 4) subtypes, severity of neuropathological features immunostained with phosphorylated tau is expressed as the number of cases within each subtype with no, mild, moderate or severe pathological lesions.

features were 4R-tau-immunopositive and negative for 3R-tau-immunoreactivity. In addition, occasional argyrophilic and AT8-immunopositive round neuronal cytoplasmic inclusions were observed in granular neurons in the hippocampal dentate gyrus. These neuronal inclusions closely resembled the morphology of Pick bodies in Pick's disease except they were 4R-tau-immunoreactive and did not contain 3R-tau-immunoreactivity. Numerous neurofibrillary tangles were also present in the hippocampal dentate gyrus but they had a limited distribution cortically and subcortically.

Both unrelated FTLD-tau cases with an IVS10+16 mutation (Cases 6 and 7) had limited neuronal loss and gliosis although the pattern and distribution was similar to sporadic FTLD-tau cases with CBD subtype (Table 3 and Supplementary Fig. 2P–T). Similar AT8-immunopositive neuropathological features were observed in both cases. The severity of neuropathological features immunostained with AT8 was similar in both cases; however, fewer AT8-immunopositive astrocytic plaques were observed than in sporadic CBD cases (Table 3). Immunostaining with 4R-tau in both cases labelled a similar number of neuropathological features immunostained with AT8, which did not contain 3R-tau-immunoreactivity.

Progressive supranuclear palsy

One sibling with the S305S mutation had similar hallmark neuropathological features of PSP, which were present in all sporadic cases (Hauw *et al.*, 1994; Cairns *et al.*, 2007) (Tables 2, 3 and Supplementary Fig. 3). Immunostaining for 4R-tau in sporadic PSP cases labelled a similar number of neuropathological features as those labelled with AT8. Immunostaining with 3R-tau was limited to some neurofibrillary tangles.

The S305S sibling with PSP (Case 4) described here and in Stanford *et al.* (2000) had a similar distribution of neuronal loss as the other S305S siblings, but additional neuronal loss in the subthalamic nucleus (Table 2). This sibling had argyrophilic AT8-immunopositive tufted astrocytes and coiled bodies in affected cortical regions, neuronal loss and neurofibrillary tangle formation in the basal ganglia, midbrain, pons and subthalamic nucleus (Supplementary Fig. 3D–F), consistent with sporadic PSP. Other AT8-immunopositive neuropathological features, including ballooned neurons, astrocytic plaques, threads and globular oligodendroglial inclusions, were observed (Supplementary Fig. 3G–I). Interestingly, a greater number of astrocytic plaques was observed in this sibling in comparison to the two CBD siblings (Table 3). Similar to the CBD siblings, this sibling had AT8-immunopositive perinuclear rings and grain-like structures in the same brain regions as described above. Immunostaining with 4R-tau labelled a similar number of neuropathological features as observed with AT8 immunostaining. 3R-tau immunostaining was restricted to some neurofibrillary tangles.

Globular glial tauopathy

Three cases with a mutation in *MAPT* (P301L, IVS10+16) had characteristic neuropathological features of sporadic GGT (Ahmed *et al.*, 2013), similar to all other GGT cases (Tables 2, 3 and Supplementary Fig. 4). The distribution and severity of globular glial inclusions was heterogeneous between sporadic cases (Table 3) and varied between the grey and white matter of affected cortical regions, which is likely to reflect different pathological GGT subtypes (Ahmed *et al.*, 2013). Immunostaining with 4R-tau labelled a similar number of neuropathological features as those labelled with AT8. Immunostaining with 3R-tau was absent in all sporadic GGT cases.

The FTLD-tau cases with an IVS10+16 mutation (Cases 8 and 9) were associated with the most widespread and the greatest severity of neuronal loss (Table 2). Neuropathological features resembling sporadic FTLD-tau with GGT subtype were observed including AT8-immunopositive globular astrocytic inclusions and globular oligodendroglial inclusions (Tables 2, 3 and Supplementary Fig. 4D and E). AT8-immunopositive ballooned neurons, threads and coiled bodies were also observed (Supplementary Fig. 4F). All neuropathological features were immunostained with 4R-tau, which labelled a similar number of neuropathological features as AT8. Immunostaining with 3R-tau, and AT8-immunuopositive astrocytic plaques and tufted astrocytes were absent.

The FTLD-tau case with a P301L mutation (Case 10) had a similar distribution and severity of neuronal loss and neuropathological features as sporadic FTLD-tau cases with GGT subtype (Tables 2 and 3, Supplementary Fig. 4G–I). Immunostaining with 4R-tau labelled a similar number of neuropathological features immunostained with AT8, which did not contain 3R-tau-immunoreactivity. AT8-immnopositive astrocytic plaques or tufted astrocytes were not observed.

Analysis of pathogenetic correlations

Assessment of data from the literature (Table 1) and our cases show that different regions of the *MAPT* gene appear to associate with only certain pathological FTLD-tau subtypes, with particular molecular and morphological signatures. The regions around exon and intron 10 associated with all pathological subtypes depositing 4R-tau (Fig. 2). While there is considerable overlap in the exon and intron 10 mutations associated with 4R-tau subtypes CBD, PSP and GGT, CBD pathology is consistently associated with the exon 13 R406W mutation (Fig. 2). Also, 3R-tau Pick's disease is most associated with mutations in exon and intron 9 (Fig. 2), although there seems to be Pick's disease cases with both 3R-tau and 4R-tau with mutations in exons 11 to 13 that require reanalyses. It would be important to know if the neuronal tau inclusions in these cases were composed of only 3R-tau, as observed in sporadic Pick's disease cases, as glial tau is often 4R-tau. Of importance in the present study, each FTLD-tau case with a *MAPT* mutation had similar hallmark neuropathological features, both molecularly and morphologically, to one of the sporadic FTLD-tau subtypes (Fig. 2).

Assessment of demographic differences between *MAPT* mutations and sporadic FTLD-tau

The FTLD-tau cases with *MAPT* mutations were significantly younger at age of symptom onset compared with the sporadic FTLD-tau cases [$P < 0.001$; *MAPT* mutation 55 ± 4 years, 95% confidence interval (CI) 52.0–58.0 versus FTLD-tau 70 ± 6 years, 95% CI 66.2–72.9]. Disease duration varied widely across the FTLD-tau cases ranging from 1 to 17 years (mean for cohort = 6 ± 5 years) with no difference in duration between sporadic (6 ± 3 years) and *MAPT* mutation (6 ± 5 years) FTLD-tau cases. The difference in age of symptom onset in FTLD-tau cases with *MAPT* mutations was confirmed in cases with CBD and GGT subtypes. CBD and GGT cases with a *MAPT* mutation were significantly younger at age of symptom onset compared with sporadic FTLD-tau CBD and sporadic FTLD-tau GGT subtypes (CBD: $P = 0.016$; *MAPT* mutation 55 ± 3 years, 95% CI 50.6–59.0 versus FTLD-tau CBD 67 ± 4 years, 95% CI 61.6–74.4. GGT: $P = 0.029$; *MAPT* mutation 55 ± 2 years, 95% CI 52.9–55.8 versus FTLD-tau GGT 74 ± 8 years, 95% CI 59.5–87.0).

Discussion

The present study illustrates the similarities in the hallmark neuropathological features of FTLD-tau cases with specific *MAPT* mutations and the varied subtypes of sporadic FTLD-tau, and demonstrates that *MAPT* mutation status also influences age of symptom onset. In any classification scheme the identification of differentiating neuropathological features is important, with a necessary emphasis on overlapping or additional pathologies. While age-related and incidental pathologies occur in sporadic and genetic forms of FTLD-tau, additional secondary pathologies reaching neuropathological diagnostic criteria are thought to be rare and comprise a small proportion of cases. Although FTLD-tau cases with mutations in *MAPT* are considered independently in FTLD-tau consensus criteria (Cairns *et al.*, 2007; Kovacs, 2015), the same core differentiating neuropathological features present in defined sporadic FTLD-tau subtypes were easily identified in each case. Importantly, the data indicate that abnormalities in different regions of the *MAPT* gene are likely to associate with different types of FTLD-tau pathologies, while those around exon 10 and intron 10 impact on all FTLD-tau subtypes with additional modifying factors likely to be involved.

While FTLD-tau cases with mutations in *MAPT* have been associated previously with the neuropathological

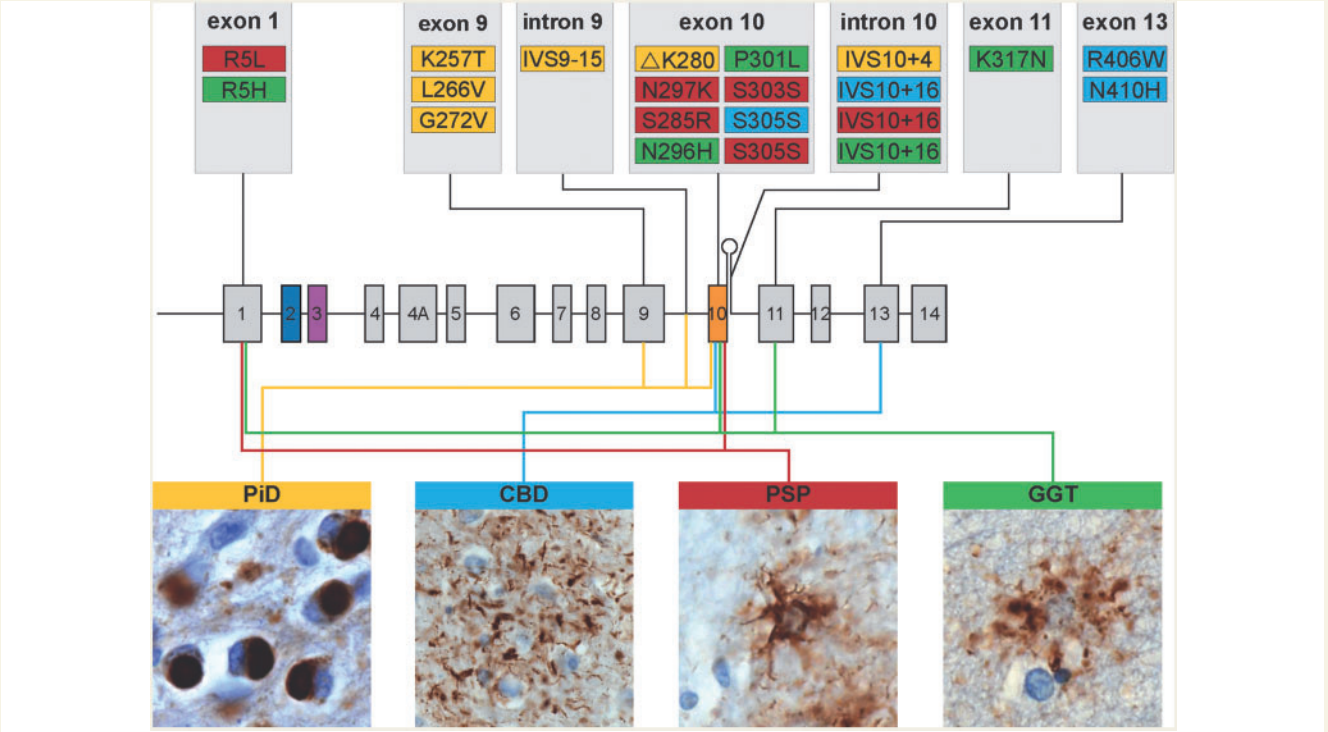

Figure 2 Diagrammatic representation of the location of different mutations in the *MAPT* gene associated with the diagnostic pathologies for sporadic FTLD-tau. Those exons not highlighted may contribute to subtype specific neuropathology, but at present require reassessment to confirm. Point mutations in exon 9 and intron 9, and a deletion in exon 10, give rise to more 3R-tau which accumulates in Pick bodies found in Pick's disease (PiD, colour-coded yellow). Point mutations in exon 13 cause dysfunction of membrane associated 4R-tau, which accumulates in the endfeet of astrocytic plaques in CBD (colour-coded blue). A point mutation in exon 11 gives rise to both short and long 4R-tau filaments that accumulate in globules in GGT (colour-coded green). A point mutation in exon 1 has been associated with longer filaments that accumulate in tufted astrocytes and neurofibrillary tangles in PSP (colour-coded red). Point mutations in exon 10 and intron 10 give rise to increased 4R-tau and CBD, GGT or PSP, suggesting that additional modifying factors can influence the processes producing these pathologies.

features similar to sporadic Pick's disease, CBD, PSP, AGD and GGT (Table 1), pathological phenotype to genotype associations have not been systematically characterized. Analysis of these data suggests that 27 different *MAPT* mutations out of the reported 44 mutations in 134 families on the Alzheimer Disease and Frontotemporal Dementia Mutation Database (AD&FTD) describe a characteristic pathology similar to the different sporadic FTLD-tau subtypes, indicating 59% of *MAPT* cases are associated with a particular sporadic FTLD-tau subtype (Table 1 and Fig. 2). By identifying subtype-specific pathologies in FTLD-tau cases with known mutations in *MAPT*, these associations can be made and cases classified into similar diagnostic FTLD-tau categories (Hauw *et al.*, 1994; Dickson *et al.*, 2002; Cairns *et al.*, 2007; Ahmed *et al.*, 2013) to identify familial forms of these FTLD-tau subtypes and assist with genetic modelling of these different tau pathologies. That such modelling can replicate mutation-specific pathologies has been shown by Ittner and colleagues (Ittner *et al.*, 2008) in their K369I mouse model of the *MAPT* mutation identified by Neumann *et al.* (2001). While several features common to more than one FTLD-tau subtype are found in most *MAPT* cases (for example ballooned neurons, coiled bodies, globular oligodendroglial inclusions) (Ferrer *et al.*, 2014), the unique and characteristic neuropathological features for each subtype were easily identified in affected cortical regions immunostained with the AT8 antibody. This has important implications for pathogenetic correlations and animal modelling of these different forms of sporadic FTLD-tau.

The impact of heritability and known genetic mutations, including *MAPT*, on patient survival and age of symptom onset is heterogeneous in frontotemporal dementia (Hodges *et al.*, 2003; van Swieten and Spillantini, 2007; Rohrer *et al.*, 2009; Chiu *et al.*, 2010; Po *et al.*, 2014; Domoto-Reilly *et al.*, 2017). This study demonstrates that FTLD-tau cases with a mutation in *MAPT* are significantly younger at age of symptom onset than sporadic FTLD-tau cases, and also than other genetic forms of frontotemporal dementia (Le Ber *et al.*, 2013; Rohrer *et al.*, 2015; Gasca-Salas *et al.*, 2016). In this aspect, *MAPT* mutations are similar for FTLD-tau as the early-onset familial Alzheimer's disease due to mutations in the presenilin-encoding *PSEN 1* and 2 genes (Schellenberg and Montine, 2012). While the mechanism of an earlier onset for presenilin gene mutations is known [they make more damaging amlyloid-$\beta_{1\text{-}42}$ (Schellenberg and Montine,

2012)], the mechanism/s for an earlier onset of symptoms in *MAPT* mutation carriers is less obvious. However, as additional functions of tau beyond microtubule stability grows [e.g. nuclear and dendritic functions (Frost *et al.*, 2014; Ittner *et al.*, 2016)], new insights into variations in pathogenesis are likely to be revealed. Not surprisingly, since FTLD-tau cases with a mutation in *MAPT* reported in this study have a wide variation in disease duration (range 1 to 17 years), no difference in survival was found compared to sporadic FTLD-tau cases. This suggests that the disease course is likely to be similar for FTLD-tau cases with and without mutations in *MAPT*.

As expected, the FTLD-tau pathologies depositing 4R-tau isoforms can have similar intron 10 mutations (Fig. 2). These mutations do not change the tau protein structure but increase the concentration of 4R-tau by causing a more frequent usage of the 5′ splice site and an increased inclusion of exon 10 and 4R-tau that is seen in three of the four main FTLD-tau subtypes (Ahmed *et al.*, 2013; Spillantini and Goedert, 2013; Kovacs, 2015). We suggest that more attention should be paid to the similar *MAPT* mutations that can produce divergent pathological lesions, as this suggests that environmental and/or genetic modifiers must occur to produce the different 4R-tau FTLD subtypes. Alternatively, significant differences in tau function are likely with the *MAPT* gene variants that associate only with one of the different sporadic forms of FTLD-tau (Fig. 2). Identifying distinctive *MAPT* mechanisms underlying different FTLD-tau pathologies may be important for sporadic forms of these diseases. These differences will be discussed below for each sporadic FTLD-tau subtypes analysed.

Pick bodies, and mechanisms associated with *MAPT* mutations

Although Pick's disease neuropathology is thought to be rare, it has been documented in 30% of FTLD-tau patients in five large autopsy cohorts (Josephs *et al.*, 2011). It is pathologically characterized by round neuronal cytoplasmic inclusions, most easily found in the dentate gyrus of the hippocampus, that contain 3R-tau and not 4R-tau, and even minor deviations from this pattern suggests a different disorder (Kovacs *et al.*, 2013). Clinicopathological studies of neuropathologically confirmed Pick's disease suggest that survival outcomes can be predicted from clinical features present at initial presentation. With an average age at symptom onset of 57 years and disease duration of around 9 years (Yokota *et al.*, 2009; Irwin *et al.*, 2016), the most common first syndrome in Pick's disease cases is behavioural variant (bv)FTD (comprising 64–86% of cases), followed by primary progressive aphasia (PPA) (Yokota *et al.*, 2009; Piguet *et al.*, 2011; Irwin *et al.*, 2016). A recent study describing four pathological stages of Pick's disease in 21 cases (age at onset 57 ± 13 years, duration 9 ± 4 years) included two Pick's disease cases with a L266V mutation, which were characterized by a very early age of onset (24 and 30 years, respectively) and duration (7 and 5 years, respectively), and severe tau pathology (stage IV) (Irwin *et al.*, 2016). The Pick's disease case with the K257T mutation in the current study differed and had more similar demographic features, distribution and severity of neuronal loss and tau-immunoreactive and biochemical features as sporadic Pick's disease.

Over half of the *MAPT* mutations described with characteristic pathology similar to sporadic FTLD-tau subtypes report Pick's disease pathology (15 out of 27 mutations). These mutations occur in exons 9, 10, 11, 12 and 13, and introns 9 and 10 (Table 1). However, many of these case reports describe both 3R-tau and 4R-tau isoforms often demonstrated in extracts obtained from dissociated tissue (Table 1). Unless immunohistochemistry using antibodies against 3R-tau and 4R-tau is used to determine the molecular characteristics of their neuropathological features (Kovacs *et al.*, 2013), the pathology in these cases is difficult to interpret. Three mutations in exon 9 (L257T, L226V and G272V), one deletion in exon 10 (ΔK280) and two intronic mutations (IVS9-15 and IVS10+4) have Pick's disease pathology characterized by 3R-tau Pick bodies (Fig. 2). It is particularly interesting that mutations in exon 9 and intron 9 give rise to only 3R-tau Pick's disease pathology (Fig. 2). 4R-tau in these cases is confined to ramified astrocytes and rare neurofibrillary tangles (Hogg *et al.*, 2003; Bronner *et al.*, 2005; Anfossi *et al.*, 2011), consistent with descriptions of sporadic Pick's disease (Kovacs *et al.*, 2013). The three missense exon 9 mutations reduce the binding of tau to microtubules, enhancing 3R-tau but not 4R-tau assembly, leading to increased unbound 3R-tau that is available to aggregate into filaments (Pickering-Brown *et al.*, 2000; Rizzini *et al.*, 2000; Hogg *et al.*, 2003; Bronner *et al.*, 2005). The ΔK280 deletion in exon 10 disrupts an exon 10 splicing enhancer, which produces a 2-fold decrease of 4R-tau mRNA transcripts and a corresponding increase of unbound 3R-tau (D'Souza and Schellenberg, 2006; van Swieten *et al.*, 2007). The IVS9-15 mutation is located in the 3' splice site region of exon 10 and little is known about how this mutation leads to the aggregation of 3R-tau. The IVS10+4 mutation is located in the 5′ site region on the stem loop, which is thought to destabilize this structure. The combination of both these mutations in the one patient with Pick's disease characterized by 3R-tau Pick bodies is thought to alter exon 10 splicing mechanisms leading to an increase of 3R-tau, as both mutations are found in regulatory splicing regions (Anfossi *et al.*, 2011).

CBD astrocytic plaques, PSP tufted astrocytes, and mechanisms associated with *MAPT* mutations

It has been known for some time that while the characteristic lesions of CBD (tau-positive astrocytic plaques and thread-like lesions in both the white and grey matter)

discriminates CBD from the other FTLD-tau subtypes, they do not discriminate sporadic CBD cases from those with *MAPT* mutations (Dickson *et al.*, 2002) and therefore recent clinical criteria exclude cases with a family history or *MAPT* mutation from a diagnosis of probable (although not possible) CBD (Armstrong *et al.*, 2013). It has also been long recognized that there is considerable clinical, pathological and genetic overlap between CBD and PSP (Katsuse *et al.*, 2003; Lang, 2003; Tan *et al.*, 2005; Jung *et al.*, 2012) with genome wide association studies showing that common polymorphisms in *MAPT*, *MOBP* and *VEGFA* increase the risk for both CBD and PSP (Borroni *et al.*, 2010; Kouri *et al.*, 2014, 2015). While familial forms of the CBD pathological subtype are recognized (Dickson *et al.*, 2002), familial forms of PSP occur but are considered rare (<10% of cases) (de Yebenes *et al.*, 1995; Rojo *et al.*, 1999; Vanacore *et al.*, 2001; Ros *et al.*, 2005; Donker Kaat *et al.*, 2009; Rohrer *et al.*, 2011; Fujioka *et al.*, 2015), possibly because of the more typical motor phenotype being identified with pathological PSP. Together, CBD and PSP pathologies form the largest proportion of FTLD-tau cases in five large autopsy cohorts (Josephs *et al.*, 2011), with CBD distinguished by 4R-tau astrocytic plaques and PSP by 4R-tau neurofibrillary tangles and tufted astrocytes (Kouri *et al.*, 2011*b*; Ferrer *et al.*, 2014; Kovacs, 2015). The regional pattern rather than type of these pathologies determines the clinical phenotype making clinical prediction of pathology difficult (Dickson *et al.*, 2010; Ling *et al.*, 2010; Boeve, 2011; Kouri *et al.*, 2011*a*, *b*; Chahine *et al.*, 2014; Grijalvo-Perez and Litvan, 2014; Ouchi *et al.*, 2014; Maltete, 2016). Of importance is that in both disorders 4R-tau isoforms deposit in the characteristic lesions in brain astrocytes, but within different cellular compartments (endfeet in the astrocytic plaques of CBD and somatodendritic compartment in the tufted astrocytes of PSP). Because of this significant overlap and targeting of the same cell type with the similar pathogenic tau isoforms, it has been suggested that these disorders should be grouped together rather than split into distinct subtypes (Scaravilli *et al.*, 2005), a concept that may assist significantly with the considerable overlap observed clinically (Dickson *et al.*, 2010; Ling *et al.*, 2010; Boeve, 2011; Kouri *et al.*, 2011*a*, *b*; Chahine *et al.*, 2014; Grijalvo-Perez and Litvan, 2014; Ouchi *et al.*, 2014; Maltete, 2016).

The assessment of the similarities (and differences) in the genetics of the FTLD-tau subtypes of CBD and PSP has not been focused on, and may prove informative. Of interest is the finding that both pathological subtypes can occur in the same family with the same mutation (present study and Tuite *et al.*, 2005). The significant overlap between clinical, genetic and pathological structures involved in CBD and PSP suggests that additional genetic and/or environmental factors may be important mediators of the different cellular pathologies observed. Of note, the genetic mutations that overlap (e.g. S305S, IVS10+16 in the present cohort) are those that do not change tau protein structure but predispose to increased 4R-tau (Fig. 2). In this context additional genetic influences are likely and have been observed [(Hoglinger *et al.*, 2011; Ferrari *et al.*, 2014; Kouri *et al.*, 2015); *ARL17A/ARL17B* risk alleles associate with more tufted astrocytes in PSP (Allen *et al.*, 2016); polymorphisms in *PARK2* associate with PSP (Sanchez *et al.*, 2002; Ros *et al.*, 2008)]. In addition, different *MAPT* mutations that change tau protein structure have been associated with either CBD or PSP (Fig. 2) suggesting that tau conformation or interactions with binding proteins are important for these different pathological subtypes. In the present series, the case with the R406W missense mutation in exon 13, a relatively common mutation (at least 13 families on http://www.molgen.ua.ac.be/ADMutations/), had CBD pathology. Another close mutation on exon 13 (N410H) has also been identified in patients with CBD pathology (Kouri *et al.*, 2014). Recent data suggest that rather than having an impact on microtubule interactions (van Swieten *et al.*, 1999; Reed *et al.*, 2001), R406W abolishes tau's membrane binding (Gauthier-Kemper *et al.*, 2011). In astrocytes, this may have the largest impact at the membrane-binding endfeet and predispose to CBD pathology. It will be important to determine the degree to which other *MAPT* mutations also disrupt membrane binding and any potential common mechanism/s.

In contrast, *MAPT* mutations associated with PSP pathology occur mainly in exon 10 and in rare instances in exon 1 (Fig. 2). The most common exon 10 mutations appear to increase the binding of exonic splicer enhancers to generate more 4R-tau (Jiang *et al.*, 2003; Kondo *et al.*, 2004; D'Souza and Schellenberg, 2006). The R5L mutation in exon 1 has only been found in a single family and is at the N-terminus rather than the C-terminus that carries the R406W CBD-causing mutation (Fig. 2). The R5L *MAPT* mutation induces fewer albeit longer filaments than wild-type tau protein, with this N-terminal region having an enhancing effect on aggregation most likely due to alterations in the global hairpin conformation of tau (Combs and Gamblin, 2012). It may be that the other *MAPT* mutations may also align to affect the hairpin conformation of tau that enhances the characteristic filaments of 4R-tau found in the tufted astrocytes and globose tangles of PSP.

GGT and mechanisms associated with *MAPT* mutations

The most recently identified pathological subtype of FTLD-tau is the GGT subtype, with pathological consensus on its characteristic globular glial inclusions published only in 2013 (Ahmed *et al.*, 2013). It is a rarer form of FTLD-tau (<10%, Burrell *et al.*, 2016), which has contributed to it only being recently recognized. As a new form of FTLD-tau, its relationship to *MAPT* mutations has not been examined in detail, although a novel mutation in exon 11 (K317N) has already been associated with this

pathological subtype (Tacik *et al.*, 2015*b*). This mutation has a reduced ability to promote tubulin polymerization, and decreases 3R-tau binding thereby increasing 4R-tau assembly (Tacik *et al.*, 2015*b*). An earlier study reported a missense R5H mutation in exon 1 in a case with widespread globular oligodendroglial and astrocytic inclusions, which also increases 4R-tau assembly (Hayashi *et al.*, 2002), and is likely to meet neuropathological criteria for GGT (Ahmed *et al.*, 2013). Of importance is our finding and that of Tacik *et al.* (2017*b*) that cases with the exon 10 P301L *MAPT* mutation, currently the most prevalent *MAPT* mutation (http://www.molgen.ua.ac.be/ADMutations/), can have GGT pathology (Fig. 2). The distinctive but rare GGT pathology in *MAPT* mutation cases may explain why the GGT FTLD-tau subtype was not identified for so long, as most cases may have been considered to be *MAPT* mutation cases with a different morphological pathology to other FTLD-tau subtypes of Pick's disease, CBD and PSP. Of interest is the recent finding that induced pluripotent stem cells carrying the P301L mutation have contorted processes with varicosity-like structures that appear similar to the GGT pathological subtype (Iovino *et al.*, 2015). This may be due to the increased phosphorylation and aggregation properties of the mutant P301L tau protein (Aoyagi *et al.*, 2007; Combs and Gamblin, 2012) that perturbs its chaperone-assisted stabilization (Gunawardana *et al.*, 2015). In addition, exon 10 mutations at position N296H have also been described as having GGT-like pathology (Iseki *et al.*, 2001). Disruption at this site in the *MAPT* gene increases 4R-tau isoform levels and causes aggregates of mixed short and long filaments (Yoshida *et al.*, 2002; Combs and Gamblin, 2012). This suggests that pathological globular 4R-tau cellular structures are likely to occur through several mechanisms which potentially give rise to a mixture of highly phosphorylated 4R-tau filament lengths.

Conclusion

In summary, these results indicate that FTLD-tau cases with different *MAPT* mutations can be considered as familial forms of the different subtypes of sporadic FTLD-tau, including those with 3R-tau isoforms. Understanding the potential mechanisms for the different sporadic forms of FTLD-tau is unlikely to be achieved if familial forms of FTLD-tau are considered independently. As with other neurodegenerative diseases, analysis of genetic cases with similar pathologies has identified important molecular mechanisms and modifiers. Modifying factors are likely to be particularly important for the very distinctive pathologies observed with mutations giving rise to 4R-tauopathies. The classification of FTLD-tau cases with different *MAPT* mutations as familial forms of the different types of sporadic FTLD-tau will allow important insights into the molecular understanding of these distinctive FTLD-tau pathologies. While FTLD-tau cases with *MAPT* mutations are associated with a younger age of symptom onset than sporadic FTLD-tau cases, no differences in disease duration have been identified, suggesting similar disease courses. In combination with distinctive cellular and animal models (Ittner *et al.*, 2015), further functional characterizations of the different *MAPT* mutations is likely to significantly improve the understanding of the pathogenesis of the different forms of sporadic FTLD-tau.

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Supplementary material

Supplementary material is available at *Brain* online.

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CORRIGENDUM

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The authors would like to apologize for an error in the abstract. The sentence:

Ten FTLD-tau cases with a *MAPT* mutation (K257T, S3035S, P301L, IVS10+16, R406W) were screened for the core differentiating neuropathological features used to diagnose the different sporadic FTLD-tau subtypes to determine whether the categorical separation of *MAPT* mutations from sporadic FTLD-tau is valid.

should read as follows:

Ten FTLD-tau cases with a *MAPT* mutation (K257T, S305S, P301L, IVS10+16, R406W) were screened for the core differentiating neuropathological features used to diagnose the different sporadic FTLD-tau subtypes to determine whether the categorical separation of *MAPT* mutations from sporadic FTLD-tau is valid.

This error has been corrected online.

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