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

Shelley L. Forrest,1 Jillian J. Kril,1 Claire H. Stevens,2 John B. Kwok,3,4,5 Marianne Hallupp,3 Woojin S. Kim,3,4,5 Yue Huang,5 Ciara V. McGinley,1 Hellen Werka,1 Matthew C. Kiernan,3 Jürgen Götz,6 Maria Grazia Spillantini,7 John R. Hodges,3,4,5 Lars M. Ittner,2,4 and Glenda M. Halliday3,4,5

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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 ± 4 years versus 70 ± 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.

1 Charles Perkins Centre and Discipline of Pathology, Sydney Medical School, University of Sydney, Australia
2 Dementia Research Unit, School of Medical Sciences, University of New South Wales, Australia
3 Brain and Mind Centre and Central Clinical School, Sydney Medical School, University of Sydney, Australia
4 Neuroscience Research Australia, Sydney, Australia
5 School of Medical Sciences, University of New South Wales, Australia
6 Clem Jones Centre for Ageing Dementia Research, Queensland Brain Institute, The University of Queensland, Australia
7 Department of Clinical Neurosciences, University of Cambridge, UK

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Correspondence to: Professor Glenda M. Halliday,
Brain and Mind Centre, 94 Mallett St, Camperdown, NSW 2050 Australia
E-mail: glenda.halliday@sydney.edu.au

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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 andparkinsonism 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-immuneactive 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 pathogenic 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.
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 = 6/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

<table>
<thead>
<tr>
<th>Genetic position</th>
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<th>Subtype</th>
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<th>Filament type</th>
<th>Age at onset</th>
<th>Disease duration (y)</th>
<th>Main clinical diagnosis</th>
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*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.
astrogial cells 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 neuronal pathological 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) 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...
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 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, mid-brain, 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-immunonegative 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-immunopositive 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-immunopositive 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 \( 55 \pm 4 \) years, 95% confidence interval (CI) 52.0–58.0 versus FTLD-tau \( 70 \pm 6 \) 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 \( 55 \pm 3 \) years, 95% CI 50.6–59.0 versus FTLD-tau CBD \( 67 \pm 4 \) years, 95% CI 61.6–74.4. GGT: \( P = 0.029; \) MAPT mutation \( 55 \pm 2 \) years, 95% CI 52.9–55.8 versus FTLD-tau GGT \( 74 \pm 8 \) 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...
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 amyloid-β1-42 (Schellenberg and Montine,
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). Clinico-pathological 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’ splice 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., 2011; Ouchi et al., 2009, 2010; Ling 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., 2011b; 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., 2011a, b; Chahine et al., 2014; Grijalvo-Perez and Litvan, 2014; Ouchi et al., 2014; Malhte, 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 (Scarravilli 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., 2011a, b; Chahine et al., 2014; Grijalvo-Perez and Litvan, 2014; Ouchi et al., 2014; Malhte, 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 mechanisms.

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., 2015b). This mutation has a reduced ability to promote tubulin polymerization, and decreases 3R-tau binding thereby increasing 4R-tau assembly (Tacik et al., 2015b). An earlier study reported a missense RSH mutation in exon 1 in a case with widespread globular oligodendrogial 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. (2017b) 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.

References


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.