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REVIEW

Cellular and regional vulnerability in frontotemporal tauopathies

Shelley L. Forrest[1] · Jillian J. Kril[1] · Glenda M. Halliday[2]

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Abstract
The frontotemporal tauopathies all deposit abnormal tau protein aggregates, but often of only certain isoforms and in distinguishing pathologies of five main types (neuronal Pick bodies, neurofibrillary tangles, astrocytic plaques, tufted astrocytes, globular glial inclusions and argyrophilic grains). In those with isoform specific tau aggregates glial pathologies are substantial, even though there is limited evidence that these cells normally produce tau protein. This review will assess the differentiating features and clinicopathological correlations of the frontotemporal tauopathies, the genetic predisposition for these different pathologies, their neuroanatomical selectivity, current observations on how they spread through the brain, and any potential contributing cellular and molecular changes. The findings show that diverse clinical phenotypes relate most to the brain region degenerating rather than the type of pathology involved, that different regions on the *MAPT* gene and novel risk genes are associated with specific tau pathologies, that the 4-repeat glial tauopathies do not follow individual patterns of spreading as identified for neuronal pathologies, and that genetic and pathological data indicate that neuroinflammatory mechanisms are involved. Each pathological frontotemporal tauopathy subtype with their distinct pathological features differ substantially in the cell type affected, morphology, biochemical and anatomical distribution of inclusions, a fundamental concept central to future success in understanding the disease mechanisms required for developing therapeutic interventions. Tau directed therapies targeting genetic mechanisms, tau aggregation and pathological spread are being trialled, although biomarkers that differentiate these diseases are required. Suggested areas of future research to address the regional and cellular vulnerabilities in frontotemporal tauopathies are discussed.

Keywords Argyrophilic grain disease · Corticobasal degeneration · Globular glial tauopathy · Neurofibrillary tangle predominant dementia · Pick's disease · Primary age-related tauopathy · Progressive supranuclear palsy

Introduction

Frontotemporal tauopathies are a clinically, biochemically and morphologically heterogeneous group of neurodegenerative diseases characterised by the deposition of phosphorylated tau protein in neurons and glia [84]. Unlike Alzheimer's disease (AD) and Parkinson's disease, the clinical heterogeneity in frontotemporal dementia (FTD) syndromes is caused by neurodegenerative changes that converge on the different brain regions, giving rise to specific patterns of behavioural, linguistic and motor deficits observed in a variety of syndromes, and discriminatory patterns of brain atrophy, rather than the type of protein abnormality occurring or the major cell type involved (both also being heterogeneous in any brain region affected). The frontotemporal tauopathies are considered a subset of FTD syndromes united by depositing abnormal forms of tau protein in the brain (FTLD-tau). While this review focuses on frontotemporal tauopathies and their regional and cellular vulnerabilities, it is well-established that these pathological entities can also be associated with diverse non-FTD cognitive and motor clinical phenotypes e.g. pathological PSP is associated with seven clinical phenotypes [122]. Based on the anatomical involvement, cell type and cellular compartment affected, a number of frontotemporal tauopathy phenotypes are recognised; Pick's disease (PiD) characterised by 3-repeat tau in neuronal

✉ Glenda M. Halliday
glenda.halliday@sydney.edu.au

[1] Charles Perkins Centre and Discipline of Pathology, Faculty of Medicine and Health, University of Sydney, Sydney, Australia

[2] Brain and Mind Centre and Central Clinical School, Faculty of Medicine and Health, University of Sydney, 94 Mallet Street, Camperdown, Sydney, NSW 2050, Australia

inclusions; corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), globular glial tauopathy (GGT) and argyrophilic grain disease (AGD) characterised by 4-repeat tau in morphologically diverse neuronal and glial inclusions; and the recently described primary age-related tauopathy (PART), which includes neurofibrillary tangle predominant dementia (NFTPD) and is characterised by 3-repeat and 4-repeat tau-immunopositive inclusions predominantly in neurons. Recent studies demonstrate that mutations in the microtubule associated protein tau (*MAPT*) are a strong predictor of FTLD-tau pathology although the pathological phenotype is heterogeneous. *MAPT* mutations were originally described in large families with FTD and clinical parkinsonism linked to chromosome 17 (FTDP-17) [117], and many advances in understanding the pathogenesis of neurodegenerative disorders have arisen from studying these cases.

Normal tau function

Tau is normally expressed in human neurons as a soluble microtubule-associated protein that has important functions in binding, stabilising the cytoskeleton of cell processes and regulating transport. It is only expressed in mature human glia at trace levels (http://www.brainrnaseq.org). Tau may also interact with other cellular structures including cytoplasmic organelles, plasma membrane, the actin cytoskeleton and nucleus [24, 70]. Six tau isoforms are expressed in the adult human brain from alternate splicing of exons 2, 3 and 10 of the *MAPT* gene on chromosome 17q21-22 [14]. The isoforms differ from each other by the presence or absence of a 29- or 58- amino acid insert located on the amino-terminal half, and by the inclusion of a 31-amino acid repeat encoded by exon 10. Inclusion of exon 10 produces three isoforms with four microtubule repeat domains (4-repeat tau), and exclusion of exon 10 produces three isoforms with three microtubule repeat domains (3-repeat tau) [14, 137]. The nomenclature for the domain structure of the six tau isoforms are expressed as 0N3R, 0N4R, 1N3R, 1N4R, 2N3R and 2N4R. Although the six isoforms are thought to have similar functions, it is possible that each isoform has distinct physiological roles since they are differentially expressed during development [14, 24]. However, in the healthy adult human brain there are equal amounts of 3-repeat and 4-repeat tau isoforms expressed, although potentially not in all cell types. As introduced above, the dominant biochemical composition of tau deposited in distinct brain regions forms the basis of the molecular classification of the tauopathies, in which three subtypes are recognised comprising 3-repeat or 4-repeat tau, or both 3-repeat and 4-repeat tau [84].

Abnormal tau aggregation

In FTLD-tau, tau becomes phosphorylated at both physiological and pathological sites making it unable to bind to and interact with microtubules [24, 137]. Consequently, tau detaches from microtubules and becomes insoluble. The transition from normal tau bound to microtubules in neurons to large pathological insoluble and fibrillar aggregates is thought to be initiated by phosphorylation, but why this occurs is unknown, and how it impacts on glia is still poorly understood, although extracellular tau rapidly accumulates in astrocytes [115]. Increasing the concentration of tau may increase its aggregation into non-fibrillar cytoplasmic aggregates in different cellular compartment/s [14]. Eventually tau forms insoluble fibrillar aggregates that accumulate in neurons and glia, contributing to neurodegeneration. Although hyperphosphorylation is an early characteristic of tau aggregation, other post-translational modifications including tau acetylation, glycation, nitration, cis/trans isomerisation, ubiquitination, oligomerisation and C-terminal truncation have been described for FTLD-tau and other tauopathies [14, 137]. The differences in tau phosphorylation and other post-translational modifications may contribute, at least in part, to the distinct tau deposits in FTLD-tau and vulnerability of certain neuronal populations [45]. Different conformational forms or strains can be made from the same recombinant tau protein [104] and these are currently thought to underlie the distinct pathological and genetic phenotypes observed both clinically and in cellular and animal models.

Understanding the selective regional and cellular vulnerabilities to abnormal tau aggregation in FTLD-tau is an emerging research focus that this review will explore. In particular, the concept that genetic diversity in the *MAPT* gene predisposes to certain tau strains and gives rise to the morphologically distinct neuropathological features in each FTLD-tau subtype will be assessed. Comparison between the different anatomical and pathogenic spread of pathology and the emerging evidence of the cellular and molecular basis for neuroanatomical selectivity is presented. Finally, future directions for methods assessing clinical phenotypic diversity, biomarker development and animal modelling are explored. Understanding the selective regional and cellular vulnerabilities in the diverse types of FTLD-tau is a necessary first step to facilitate their accurate identification and progression during life.

Differentiating features and clinicopathological correlations in FTLD-tau

A large number of studies have examined the correlations between FTLD-tau pathologies and FTD clinical

syndromes (see review [76]). In the majority of these studies, case ascertainment is at postmortem and the relationship to clinical features examined retrospectively. These studies have shown the following:

- In those with cognitive syndromes like behavioural variant FTD (bvFTD) or primary progressive aphasia (PPA), the FTLD-tau pathology is most severe in the cortex and limbic regions with more limited involvement of the basal ganglia and brainstem.
- In those with atypical parkinsonism syndromes like corticobasal syndrome or progressive supranuclear palsy, the FTLD-tau pathology is shifted away from the cortex to be more intense in the basal ganglia and brainstem.

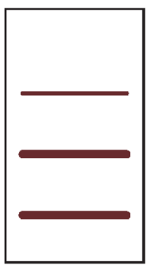
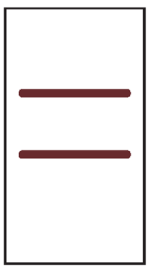
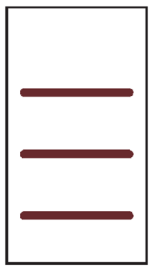
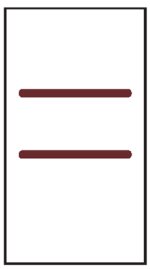
While the distribution and severity of neuronal loss in FTD underlies the different clinical phenotypes, the contribution of astrocytes and oligodendroglia, which play vital roles in maintaining neural function, are underappreciated and are of particular importance to FTLD-tau [84]. In particular, the 4-repeat tauopathies primarily affect these glial cells, a concept well-known pathologically [84] but rarely intellectualised in clinical, biomarker and animal modelling studies. Furthermore, astrocytic cellular compartmentalisation of the abnormally accumulating 4-repeat tau differs substantially to produce the distinct pathological subtypes of FTLD-tau [1, 31]. These distinctive cellular pathologies underlying each of the FTLD-tau subtypes support the concept that distinct pathomechanisms influence tau even if the same tau isoform is deposited into distinct strains (Table 1).

3-repeat frontotemporal tauopathy: Pick's disease

The 3-repeat tauopathy PiD is biochemically and morphologically distinct from all other FTLD-tau subtypes. Western blot of insoluble tau in PiD show two major bands at 58 or 60 kDa and 64 kDa [9, 43] corresponding to 0N3R and 1N3R isoforms, and a minor band at 68 kDa [26] corresponding to 2N3R isoform (Table 1).

First described by Alois Alzheimer, PiD was originally considered a rare neuropathology. It has now been reported in 30% of FTLD-tau cases in five large autopsy cohorts [76]. PiD is characterised by marked neuronal loss in frontal and temporal cortices and 3-repeat tau-immunopositive

Table 1 Molecular and pathological features of FTLD-tau subtypes and ARTAG

Pathological subtype	PiD	CBD	PSP	GGT	AGD	PART/NFTPD	ARTAG
Molecular classification	3R (4R astrocytes)	4R	4R	4R	4R	3R and 4R	4R
Molecular bands (kDa)							
Filament type	15 – 18nm straight tubules and 22 – 24nm twisted. Novel tau protein fold	20 – 24nm twisted ribbons in neurons, tubular and amorphous profiles in astrocytes, oligodendroglial twisted tubules	15 – 18nm straight filaments and compact tubules in tangles, tubular and straight profiles in glia	Granular material and twisted filaments	Tightly aggregated 13 – 18 nm straight filaments or smooth tubules	Paired helical filaments	
Hallmark pathological lesion/s	Pick bodies +/- ramified astrocytes	Astrocytic plaques and white matter threads	Argyrophilic tufted astrocytes and globose tangles	Globular astrocytic and oligodendroglial inclusions	Argyrophilic grains +/- tau-immunopositive astrocytes	Neurofibrillary tangles and no/few beta-amyloid plaques	Granular fuzzy and thorn-shaped astrocytes
Region/s	Frontal and temporal cortices, hippocampus	Frontal and temporal cortices	Precentral cortex, subcortex (globus pallidus, substantia nigra, pontine nuclei, subthalamic nuclei)	Frontal, precentral and/or temporal cortices	Medial temporal lobe	Entorhinal cortex, hippocampus	Grey and/or white matter, perivascular, subpial, subependymal

3R 3-repeat tau, *4R* 4-repeat tau

Pick bodies predominantly located in granular neurons in the hippocampal dentate gyrus, hippocampal CA1 pyramidal neurons, and layer II of frontal and temporal cortices (Fig. 1a) [38, 90]. Pick bodies are argyrophilic on some silver stains including modified Bielschowsky silver, but are not observed with Gallyas silver (Fig. 1a–d). Ramified astrocytes in PiD are characterised by tau-immunopositive deposits in the proximal astrocytic processes usually localised to one side of the astrocyte giving rise to the appearance of an eccentrically placed nucleus (Fig. 1b) [38, 45]. Ramified astrocytes are argyrophilic on modified Bielschowsky and Gallyas silver stains. However, unlike Pick bodies, ramified astrocytes are not the hallmark neuropathological feature of PiD and their prevalence varies between cases [31]. In contrast to Pick bodies, ramified astrocytes contain 4-repeat tau and variable immunoreactivity to 3-repeat tau [45]. Balloon neurons, threads and oligodendroglial globular cytoplasmic inclusions and

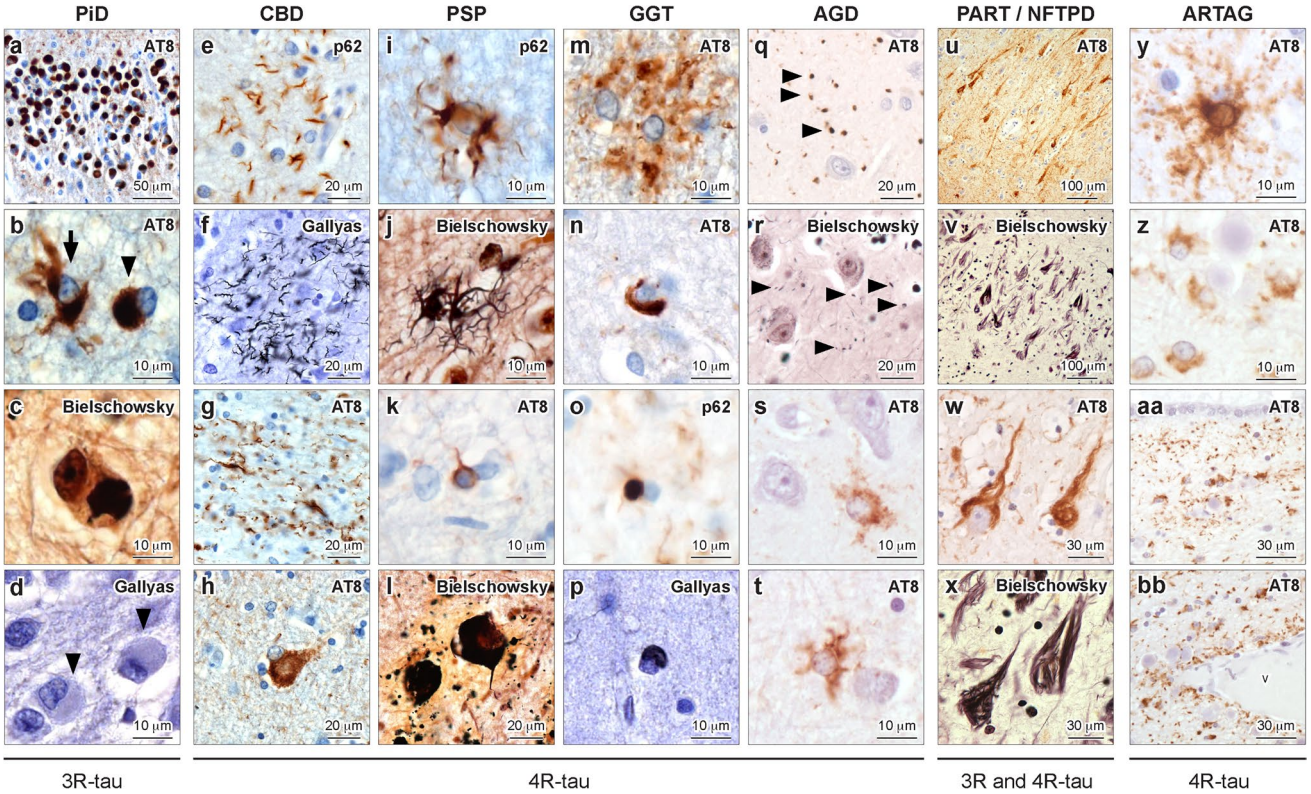


Fig. 1 Characteristic neuropathological features of each FTLD-tau subtype and ARTAG. Each column represents neuropathological features from the different FTLD-tau subtypes and ARTAG, and their corresponding molecular classification (3-repeat tau or 4-repeat tau, or 3-repeat and 4-repeat tau). Sections were immunostained with phosphorylated tau (AT8) or p62, or stained with modified Bielschowsky or Gallyas Silver. Pick bodies in the hippocampal dentate gyrus (**a**), ramified astrocyte (arrow) and Pick body (arrowhead) labelled with AT8 (**b**) and modified Bielschowsky Silver (**c**) in the superior frontal cortex in a case with Pick's disease (PiD). Pick bodies contain 3-repeat tau and are non-argyrophilic on the Gallyas Silver stain although the outline of Pick bodies are observed in the haematoxylin counterstain, shown here in the hippocampal dentate gyrus (**d**). Ramified astrocytes in PiD contain 4-repeat tau and variable immunoreactivity to 3-repeat tau. Astrocytic plaques (**e**) are argyrophilic on Gallyas Silver (**f**) and widespread AT8-immunopositive white matter threads (**g**) in the superior frontal cortex are hallmark features of corticobasal degeneration (CBD). Balloon neurons (**h**) are commonly observed in CBD and PiD. Tufted astrocytes in the precentral cortex (**i**) that are argyrophilic on modified Bielschowsky Silver (**j**) and Gallyas Silver stains are characteristic astrocytic inclusions in progressive supranuclear palsy (PSP). AT8-immunopositive coiled bodies (**k**) are also observed in PSP and other FTLD-tau subtypes and are not differentiating neuropathological features. Globose tangle formation in the substantia nigra pars compacta (**l**) is one of the four hallmark subcortical brain regions affected in PSP. Globular astrocytic inclusions (**m**), swollen coiled bodies (**n**) and globular oligodendroglial inclusions (**o**) are neuropathological features of globular glial tauopathy (GGT). Oligodendroglial inclusions in GGT are argyrophilic on Gallyas Silver (**p**). AT8-immunopositive (**q**) and argyrophilic (**r**) grains (arrowheads) in the medial temporal lobe are characteristic neuropathological features of argyrophilic grain disease (AGD). Granular fuzzy (**s**) and thorn-shaped astrocytes (**t**) are also observed in AGD. Severe neurofibrillary tangle (**u**–**x**) formation in the hippocampus in the absence of beta-amyloid plaques are observed in neurofibrillary tangle predominant dementia/primary age-related tauopathy (NFTPD/PART). Many neurofibrillary tangles are extracellular and do not contain AT8-immunoreactivity (compare panels U and V). Granular fuzzy (**y**) and thorn-shaped (**z**) astrocytes are the hallmark astrocytic inclusions observed in ageing-related tau astrogliopathy (ARTAG). Different types of ARTAG are recognised including grey and white matter, subependymal (**aa**), perivascular (**bb**), and subpial. v in panel (**bb**) indicates vessel

coiled bodies are also found in PiD, although these are not differentiating pathological features and are common to a number of FTLD-tau subtypes.

Tau filaments in PiD are characterised by 15–18 nm diameter straight tubules and 22–24 nm diameter twisted filaments [10]. A recent study reports that the majority (93%) of filaments in PiD are narrow and a small proportion are wide (7%), referred to as narrow and wide Pick filaments [43]. Importantly, this study identified a novel tau protein fold, which is not observed in tau filaments characteristic of AD [43].

Of the clinical phenotypes associated with PiD pathology (Fig. 2), bvFTD is the most common at clinical presentation (in up to 84% of cases) and also with follow-up (in up to 62% of cases), followed by the semantic variant of PPA (svPPA) [69, 90, 116, 164]. In addition, bvFTD patients mainly have FTLD-tau pathology (42%) rather than the other FTD proteinopathies (30% with TDP-43, 6% with FUS) [32] with PiD the most common FTLD-tau subtype (55–70%) followed by CBD (20–30%) and then PSP and GGT (10-15%) [27, 76]. svPPA differs substantially from bvFTD as it is characterised by severe anomia, impaired single word

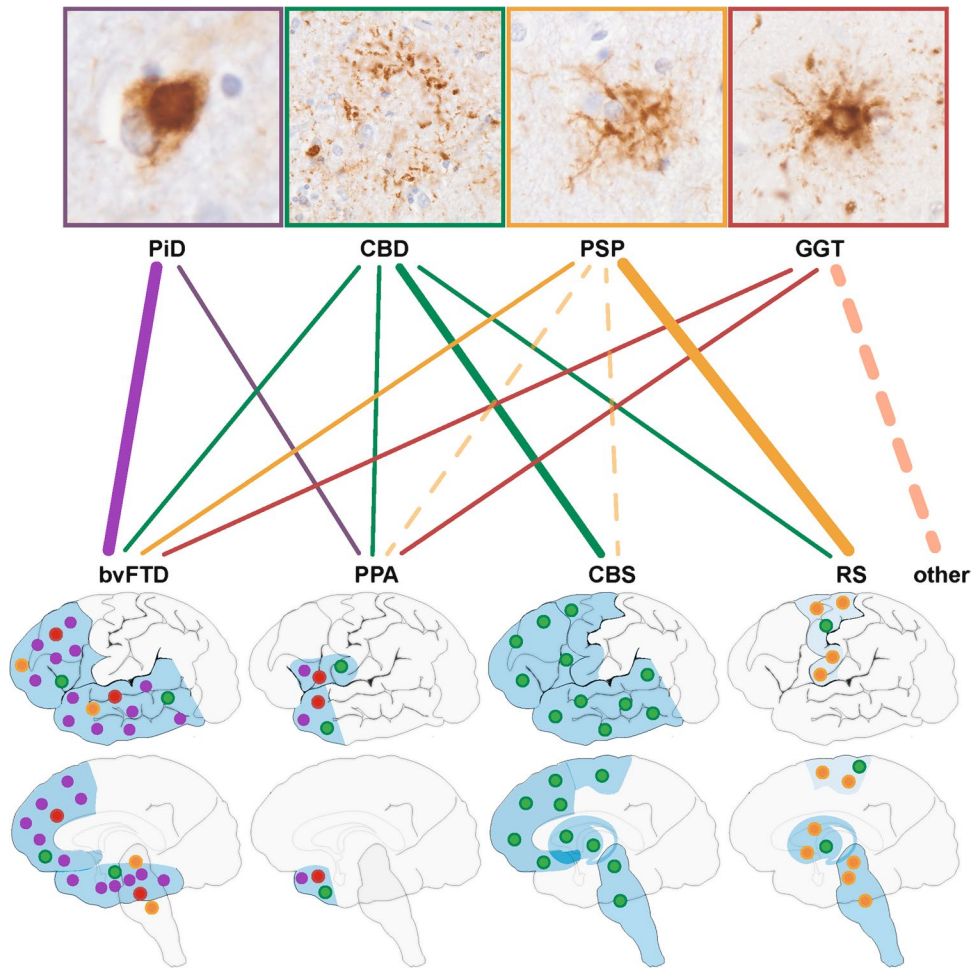


Fig. 2 Clinical phenotypes and regional distribution of FTLD-tau pathology. Diagrammatic representation demonstrating the main clinical phenotypes associated with the four main pathologically confirmed FTLD-tau subtypes. The regional distribution of these pathologies are mapped to the distinct patterns of atrophy associated with each clinical phenotype. Weighting of coloured lines represent the approximate proportion of cases of each pathological subtype associated with each clinical phenotype (total 100%). Pick's disease (PiD, colour coded purple) is most commonly associated with behavioural-variant frontotemporal dementia (bvFTD) and a smaller proportion of cases are associated with primary progressive aphasia (PPA). Corticobasal degeneration (CBD, colour coded green) is mainly associated with corticobasal syndrome (CBS), bvFTD, PPA and Richardson's syndrome (RS). Progressive supranuclear palsy (PSP, colour coded yellow) is most commonly associated with RS, followed by bvFTD. A number of globular glial tauopathy (GGT, colour coded red) pathological subtypes are recognised and are associated with bvFTD and PPA, although the majority of GGT cases described are associated with other movement and/or cognitive syndromes including Alzheimer's disease. The diverse clinical phenotypes relate most to the brain region degenerating rather than the type of pathology. Note that the pathological diagnosis of PSP still requires the presence of neuronal loss and neurofibrillary tangle formation in three out of four hallmark subcortical regions (globus pallidus, substantia nigra, pontine nuclei and the subthalamic nucleus)

comprehension and difficulty recognising words, objects and faces, with speech remaining relatively fluent and without phonological or syntactic errors [64]. Most cases with svPPA have TDP-43 pathology, but of the 10–30% of cases that do not, half have FTLD-tau pathology [32] including PiD and GGT [138], and these patients are more likely to develop prominent bvFTD features in their disease course such as executive impairment, severe behavioural symptoms, disinhibition and apathy [32, 138]. While the number of PiD cases reported with svPPA is small compared to those with bvFTD [76, 116, 120, 138], this diversity in clinical phenotype suggests that the initial vulnerability to PiD targets different brain regions in affected individuals.

4-repeat frontotemporal tauopathies

The 4-repeat tauopathies are a clinically, genetically and pathologically diverse group of disorders, despite all being characterised by the predominant deposition of 4-repeat tau isoforms in neurons, astrocytes and oligodendroglia. Western blot of insoluble tau fractions in the 4-repeat tauopathies show two prominent bands at 64 kD and 68 kDa corresponding to 0N4R and 1N4R isoforms (Table 1), and a minor band at 72 kDa corresponding to the 2N4R isoform. Soluble tau fractions show all six tau isoforms suggesting only 4-repeat tau isoforms aggregate into filaments [25]. Although they have this biochemical similarity, the distinct cellular pathologies suggest diverse pathogenic mechanisms must occur, mechanisms that await elucidation.

Corticobasal degeneration

Astrocytic plaques characterised by 4-repeat tau-immunopositive deposits in distal astrocytic processes with flat feet-like or annular structures are the hallmark astrocytic lesion of CBD (Fig. 1e, f). Unlike astrocytic inclusions in PiD and PSP, astrocytic plaques are argyrophilic on some silver stains for example Gallyas silver, but not the modified Bielshowsky silver [84, 85], and only rarely with Bodian silver [151, 153]. Argyrophilic features identified with the main silver stains are reviewed by Uchihara [150]. Widespread tau-immunopositive white and grey matter threads are the other hallmark feature of CBD (Fig. 1g). Unlike tau-immunoreactive neurites in AD, thread pathology in CBD and other frontotemporal tauopathies is predominantly astrocytic rather than neuronal [38]. Similar to astrocytic plaques, thread pathology is argyrophilic on Gallyas silver, but not modified Bielschowsky silver. Balloon neurons (Fig. 1h), coiled bodies and neurofibrillary inclusions are common in CBD, but are not distinguishing pathological features. The greatest density of neuronal and non-neuronal pathology is in affected cortical regions, followed by the basal ganglia, thalamus and brain stem [38]. Neuronal tau filaments in CBD are characterised by 20–24 nm twisted ribbons, tubular structures and amorphous profiles in astrocytes, and twisted tubules in oligodendroglia [10].

CBD pathology was originally described as a separate clinicopathological entity from FTD in patients with corticobasal syndrome, however, CBD is associated with a number of cognitive and motor syndromes [76, 82]. The main clinical phenotypes at final diagnosis associated with CBD pathology are corticobasal syndrome (37% of cases) followed by Richardson syndrome (23%), FTD (14% bvFTD and 5% PPA), and AD-like dementia (8%) [11] (Fig. 2). Although now part of the FTD clinical syndromes, corticobasal syndrome and Richardson syndrome are considered asymmetric movement disorders rather than primary dementias, and therefore are often excluded from consideration in clinical studies of dementia phenotypes. However, cognitive features of corticobasal syndrome include aphasia and frontal executive dysfunction, occurring in addition to the extrapyramidal rigidity, dystonia, apraxia and alien limb phenomenon that characterise this syndrome [28, 101]. Corticobasal syndrome is typically associated with FTLD-tau of the CBD subtype. For bvFTD, 20-30% have CBD at autopsy [27, 76] again highlighting the diversity in the initial site of vulnerability to CBD in affected individuals.

Progressive supranuclear palsy

The neuropathological diagnostic hallmarks of PSP include the presence of neuronal loss and tangle formation in three out of four cardinal brain regions (globus pallidus, substantia nigra, pontine nuclei and the subthalamic nucleus) in combination with tau-immunoreactive tufted astrocytes, neuropil threads and oligodendroglial coiled bodies (Fig. 1i–l). Neuronal tangles made of 4-repeat tau are the predominant neuronal pathological feature in PSP and contrast to those in AD, which are comprised of both 3-repeat tau and 4-repeat tau [25, 152]. However, 3-repeat tau- and 4-repeat tau-immunoreactivity has been reported in neuronal tangles confined to the basal ganglia and substantia nigra in PSP in a small number of studies, in contrast to cortical tangles that contain only 4-repeat tau-immunoreactivity [152, 168]. Other 3-repeat tau immunostaining in PSP is largely confined to age-related neurofibrillary tangles.

Argyrophilic tufted astrocytes are the hallmark astrocytic lesion in PSP [31, 99], which are characterised by tau-immunopositive deposits in the proximal astrocytic processes with a tuft-like morphology (Fig. 1i, J). Both tufted astrocytes and coiled bodies are argyrophilic on modified Bielschowsky and Gallyas silver stains. The argyrophilic properties of tufted astrocytes and coiled bodies in PSP prove informative in distinguishing tufted astrocytes in PSP from globular astrocytic inclusions in GGT, and astrocytic plaques in CBD [84]. Similar to neuropil threads, coiled bodies are common

to multiple FTLD-tau subtypes and are not considered a hallmark neuropathological feature of PSP. Tau filaments in PSP are characterised by 15-18 nm straight filaments, compact accumulations of 14 nm straight tubules in neuronal tangles, and tubular profiles and straight filaments in glia [10].

Similar to CBD, PSP pathology was originally described as a clinicopathological entity in patients with Richardson syndrome, but is also associated with a range of motor and cognitive phenotypes [37, 67, 76, 160] (Fig. 2). Richardson syndrome is a movement disorder characterised by extrapyramidal features, postural instability or unexpected falls, and vertical supranuclear gaze palsy with limited to no response to levodopa therapy [98]. Richardson syndrome is associated with PSP pathology in approximately 90% of cases [112]. In contrast, a recent retrospective multicentre study of 100 pathologically confirmed PSP cases [122] found that only 24% had Richardson syndrome in the first 2 years, while 19% had parkinsonism, 7% had oculomotor dysfunction only, 18% had postural instability, and 13% had postural instability with additional bulbar signs. Early cognitive dysfunction was observed in the remaining 19% of cases, including corticobasal syndrome and bvFTD. In patients with bvFTD associated with FTLD-tau, PSP pathology accounts for 10–15% of cases [27, 76]. These data highlight the diversity of clinical phenotypes associated with PSP pathology, again suggesting that there is a diversity of sites of initial vulnerability in affected individuals.

The diversity of clinical phenotypes in cases with pathological PSP and the clinical overlap with CBD are well-established [92], and for these reasons, there has been debate on whether the two pathological entities should be grouped together or not. While this might improve clinical identification of these FTLD-tau pathologies, the distinctive hallmark pathological lesions in separate cellular compartments in CBD and PSP suggest distinct pathomechanisms, and recent studies show that they are associated with distinct tau strains [84].

Globular glial tauopathy

GGT is the most recently described subtype comprising < 10% of all FTLD-tau cases [27], with neuropathological diagnostic consensus recommendations published in 2013 [1]. It is a rarer form of FTLD-tau, and has unique globular tau-immunopositive inclusions. Cases with GGT were originally classified as atypical pathological PSP and CBD, or unclassifiable tauopathy [1, 77] with the rarity of the pathology contributing to it being unrecognised as a FTLD-tau subtype for so long.

GGT is characterised by 4-repeat tau-immunopositive globular astrocytic and oligodendroglial inclusions [1, 3]. Globular astrocytic inclusions contain tau-immunopositive cytoplasmic globules and 1-5 µm tau-immunopositive deposits in proximal astrocytic processes (Fig. 1m). They are non-argyrophilic with modified Bielschowsky silver and largely non-argyrophilic with Gallyas silver [3, 84], which facilitates their differentiation from tufted astrocytes in PSP. Oligodendroglial inclusions in GGT comprise swollen coiled bodies (Fig. 1n) and globular oligodendroglial inclusions characterised by globular cytoplasmic inclusions larger than the size of the nucleus (Fig. 1o) [1]. Unlike astrocytic inclusions in GGT, oligodendroglial inclusions are argyrophilic on Gallyas silver (Fig. 1p) [1].

A number of GGT subtypes are recognised, corresponding to a different density and regional involvement of pathology, which are proposed to stratify different clinical phenotypes [1]. GGT-Type I has pathological involvement of frontal and temporal cortices without corticospinal tract involvement, and is proposed to have a bvFTD clinical phenotype. GGT-Type II cases show motor cortex involvement and/or corticospinal tract involvement and/or extrapyramidal features; and is proposed to have motor neuron disease and/or clinical parkinsonism including Richardson and corticobasal syndromes. GGT-Type III cases show pathological involvement of frontal, temporal and motor cortices and/or corticospinal involvement and/or extrapyramidal features, and is proposed to have bvFTD combined with motor neuron disease and/or parkinsonism including Richardson and corticobasal syndromes [1]. However, recent studies indicate that this further subtyping of GGT does not improve clinicopathological correlations [27]. The most common clinical phenotype associated with GGT pathology is bvFTD, and less commonly the non-fluent variant of PPA (nfvPPA), clinical AD and atypical parkinsonian disorders (Fig. 2) [27]. 10–15% of patients with bvFTD have GGT (10–15%) [27, 76].

Argyrophilic grain disease

AGD is a rare FTLD-tau subtype comprising < 5% of all cases with FTD syndromes. It is differentiated from other subtypes by the widespread and distinct spindle-shaped, argyrophilic and 4-repeat tau-immunopositive grains (Fig. 1q, r) [19, 31, 147]. The medial temporal lobe, predominantly the entorhinal cortex, hippocampal CA1 region and amygdala are the most severely affected areas. Two types of tau-immunopositive astrocytic inclusions have been described in AGD, thorn-shaped and fuzzy or bush-like astrocytes [18, 128]. Both types of astrocytic inclusions are characterised by 4-repeat tau-immunoreactivity and are predominantly non-argyrophilic on Gallyas silver and modified Bielschowsky silver stains. Bush-like astrocytes are characterised by tau-immunoreactivity in all cellular compartments, extending to the distal astrocytic processes (Fig. 1s), and are most prevalent in the medial temporal lobe. Thorn-shaped astrocytes are characterised by tau-immunoreactivity

in the cytoplasm and short, stubby tau-immunoreactive deposits in proximal processes (Fig. 1t), and unlike astrocytic inclusions in other FTLD-tau subtypes, are largely confined to the white matter and perivascular regions in the medial temporal lobe [45, 86]. Interestingly, the astrocytic inclusions in AGD show morphological, biochemical and regional similarities to thorn shaped astrocytes and granular fuzzy astrocytes described in ageing-related tau astrogliopathy (ARTAG) [86]. This suggests that astrocytic inclusions previously described in AGD are likely to represent thorn shaped astrocytes in white matter and perivascular ARTAG and granular fuzzy astrocytes characteristic of grey matter ARTAG [89]. Argyrophilic tau-immunopositive coiled bodies are also a pathological feature of AGD, most commonly observed in the white matter underlying the medial temporal lobe [19]. Tau filaments in AGD comprise tightly aggregated 13-18 nm straight filaments or smooth tubules, with 1.5-4 µm diameter [148].

Although a recognised FTLD-tau subtype of clinical FTD, AGD can also occur as an age-related pathology that increases in prevalence with advancing age. The presence of AGD in non-demented elderly individuals has been suggested to decrease the threshold for developing dementia [78]. AGD is found in approximately 40% of cognitively normal individuals and can co-exist as an age-related pathology in a number of neurodegenerative diseases including pathologically confirmed CBD, PSP and AD [127, 147]. Concomitant AGD has been reported in 41% of CBD cases and as well as in many PSP cases [57]. These studies indicate that AGD occurs on a clinical spectrum from cognitively normal, through to cognitive impairment. Since clinical FTD with an FTLD-tau AGD subtype is a rare disorder, a large pathologically confirmed cohort has not been reported making clinicopathological correlations difficult, although some studies have reported cases with cognitive decline and memory disturbances [57, 59, 76, 123, 148].

3-repeat and 4-repeat frontotemporal tauopathies–—Neurofibrillary tangle predominant dementia (NFTPD) and Primary Age-Related Tauopathy (PART)

NFTPD is a rare pathological subtype comprising < 5% of all FTLD-tau cases [27, 76] characterised by neurofibrillary tangles similar to AD that contain 3-repeat and 4-repeat tau but with few, or lack of, beta-amyloid plaques (Fig. 1u-x) [31, 74]. Many of the tangles in NFTPD are extracellular and show limited phosphorylated-tau-immunoreactivity (compare Fig. 1u and 1v). For this reason they are better assessed with silver stains. Although the distribution of neurofibrillary tangles in NFTPD is similar to that in AD, the density of tangles in the hippocampus is more severe and their cortical involvement more limited than that observed in AD [34]. For this reason, NFTPD does not fit the Braak neurofibrillary staging criteria for AD [20] where cortical pathology is required. NFTPD is most commonly observed in elderly females > 80 years with a short disease duration of cognitive decline, disorientation and depression [74].

NFTPD also fulfils neuropathological criteria for primary age-related tauopathy (PART), a common age-related tauopathy that occurs in individuals that range from being neurologically normal through to having cognitive impairment [34], as seen in NFTPD. PART is characterised by a Braak neurofibrillary stage of < IV (severe hippocampal involvement) in the absence of beta-amyloid plaques, therefore not fulfilling AD criteria [34]. In addition, slightly different patterns of neurofibrillary tangle formation are observed in the hippocampus in PART and AD, with a higher density of neurofibrillary tangles in the CA2 hippocampal region in PART [72]. PART is one of the most common age-related pathologies, and there is controversy as to whether those with PART progress to AD, which is the most common dementia, or to the very rare NFTPD [40, 73, 157]. A number of recent studies have demonstrated that AD neuropathological change is not increased in FTLD-tau compared to controls [146], suggesting that many of those with PART are unlikely to transition to FTLD-tau.

Genetic predisposition to differential vulnerability

Emerging studies suggest that the genetic abnormalities in *MAPT* can be used to inform on the mechanisms leading to the unique cellular compartments affected in FTLD-tau that give rise to the distinct astrocytic (astrocytic plaque, tufted and fibrous astrocytes, and globular inclusions) morphologies and cellular phenotypic diversity. Although there is less heterogeneity in oligodendroglial and neuronal inclusions in FTLD-tau, similar studies investigating certain regions on the *MAPT* gene might also prove informative for discriminating the mechanisms underlying the diversity of oligodendroglial (coiled bodies and globular oligodendroglial inclusions) and neuronal (Pick bodies, globose and neurofibrillary tangles, and ballooned neurons) inclusions in FTLD-tau.

Familial FTLD-tau

Autosomal dominant mutations in the *MAPT* gene account for 20% of all familial FTD cases with a strong family history (approximately 50% of all FTD have FTLD-tau pathology, [76]), and all cases with *MAPT* mutations have FTLD-tau pathology. In cases with FTLD-tau pathology, a positive family history of FTD, ALS, parkinsonism or dementia occurs in up 40% of which approximately one-third have a strong family history associated with an autosomal dominant pattern of inheritance [47, 161], with significant differences between the heritability of the different pathological

subtypes [47]. The possibility of finding a mutation in *MAPT* in FTLD-tau cases with low or no family history is small [161], so in general these cases would not be screened for mutations in *MAPT*. The clinical syndromes and underlying FTLD-tau pathology vary within and between family members with the same mutation, suggesting additional modifying factors are likely to contribute to disease pathogenesis [17, 47, 48]. Currently, phenotypical differences in vertical transmission of mutations in *MAPT* through maternal versus paternal inheritance have not been investigated in the frontotemporal tauopathies.

Similar to AD, there is likely to be a long prodromal period in FTD between the formation of tau inclusions and the emergence of clinical symptoms. The Genetic FTD Initiative (GENFI) has identified structural imaging changes in *MAPT* mutation carriers 15 years before estimated symptom onset [125] with early disruption to white matter integrity on diffusion tensor imaging [75]. These studies indicate that a window of therapeutic intervention exits prior to symptom onset and that prevention of tau spreading is a potential avenue to halt progression of clinical symptoms.

Mutations in *MAPT* follow an autosomal dominant pattern of inheritance with high disease penetrance defined as the presence of at least three affected family members across two generations, and one affected individual being a first degree relative of the other two [60]. Most mutations in *MAPT* are found in exons 9-13, with the majority clustering around the microtubule binding domain on exon ten. Two broad categories of *MAPT* mutations are recognised based on whether the mutation has a primary affect at the protein level or whether the mutation influences alternative splicing of tau pre-messenger RNA [137].

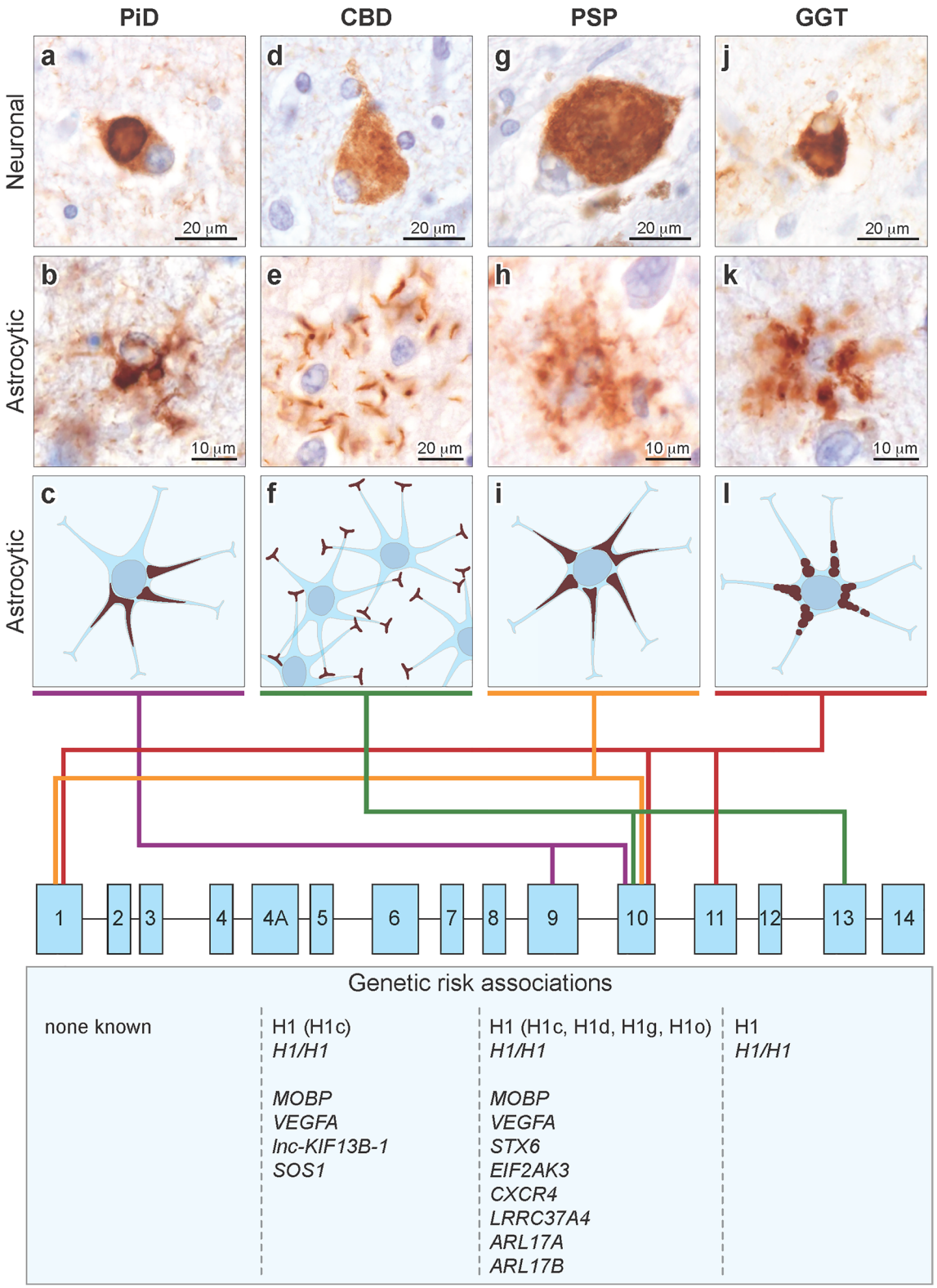
Pathologies in cases with MAPT mutations

Until recently, FTLD-tau cases with a mutation in *MAPT* were considered to have a completely separate subtype of pathology from other FTLD-tau cases and retained their original FTDP-17 nomenclature [93, 119]. The separate classification of these genetic cases suggested an independent mechanism that could not inform on other sporadic or familial FTLD-tau cases. This contrasted with genetic concepts for all other forms of neurodegenerative diseases, for example, genes identified in Parkinson's disease, AD and amyotrophic lateral sclerosis have been used to inform on the pathogenesis of the pathologies in these diseases and are not pathologically separated. Similar developments have also been made for FTLD-TDP associated with genetic abnormalities in the progranulin (*GRN*) and chromosome 9 open reading frame 72 (*C9orf72*) genes, including the most recently proposed FTLD-TDP pathological subtype (Type E) [94]. Despite these advances, FTLD-tau cases with a mutation in *MAPT* have until recently remained classified as a separate pathological entity. A recent study reported ten FTLD-tau cases with a mutation in *MAPT* gene identified in a large pathologically confirmed FTD cohort and found that the cases had the same core differentiating neuropathological features as one of the sporadic FTLD-tau subtypes and could be classified into a comparable diagnostic category [48]. The authors proposed that FTLD-tau cases with a mutation in *MAPT* be classified as familial forms of the sporadic FTLD-tau subtypes, aligning with the classification of FTLD-TDP with a mutation in *GRN* as well as with genetic forms of other neurodegenerative diseases. This will allow for a better understanding of the molecular mechanisms responsible for FTLD-tau and the development of appropriate animal and cellular models.

Recent studies suggest that there are certain regions on the *MAPT* gene that are associated with certain pathological subtypes, with particular morphological and biochemical signatures [48]. Depending on the type and location of the mutation in *MAPT*, they can result in an abnormal ratio of 3-repeat or 4-repeat tau isoforms deposited, or both, with tau pathology predominantly confined to neurons, or both neurons and glia [56]. To date, 3-repeat PiD is only associated with mutations in *MAPT* on exons and introns 9 and 10. There is considerable overlap in mutations associated with 4-repeat subtypes clustered around exon and intron 10 with additional modifying factors likely to be involved [48]. Modifying factors are likely to be particularly important for the very distinctive pathologies observed with mutations giving rise to 4-repeat frontotemporal tauopathies (Fig. 3). The identification that mutations in certain amino acids in *MAPT* allows for the potential to learn about the cellular pathogenesis of sporadic forms of FTLD-tau and develop animal models to allow a better understanding of the mechanisms involved, as has been done for other neurodegenerative diseases.

MAPT mutations and PiD pathology

The majority of mutations in *MAPT* have been reported with PiD pathology [48]. However, pathological descriptions of FTLD-tau cases with a mutation in *MAPT* reported in the literature need to be considered conservatively if thorough immunohistochemical characterisation using 3-repeat tau and 4-repeat tau antibodies have not been performed. For example, a large number of mutations in *MAPT* have been reported with PiD pathology that show both 3-repeat and 4-repeat tau in protein extracts obtained from dissociated tissue (summarised in [48]). Many of these studies are difficult to interpret as minor deviation away from the 3-repeat tau-immunopositive Pick bodies suggest a different disorder [90]. Whether the 4-repeat tau in protein extracts represent fibrous astrocytes (4-repeat



tau-immunopositive) or age-related neurofibrillary tangles (both 3-repeat and 4-repeat tau-immunopositive) needs to be reconciled in these cases.

Three missense mutations in exon 9 (L257T, L226 V and G272 V), one mutation in intron 9 (IVS9-15), one deletion mutation in exon 10 (ΔK280), and one mutation in intron 10 (IVS10+4) and exon 12 (P364S) have been reported with

◂**Fig. 3** Pathological and genetic correlations in the main FTLD-tau subtypes. Each column represents neuronal and astrocytic neuropathological features, and genetic associations from the four main FTLD-tau subtypes. 3-repeat tau Pick's disease (PiD) neuropathology is associated with mutations on exons and introns 9 and 10 of the microtubule associate protein tau (*MAPT*) gene (purple). 4-repeat tau corticobasal degeneration (CBD) is associated with mutations on exon and intron 10 and exon 13 of the *MAPT* gene (green). 4-repeat tau progressive supranuclear palsy (PSP) is associated with mutations on exon 1, exon and intron 10 of the *MAPT* gene (yellow). 4-repeat tau globular glial tauopathy (GGT) is associated with mutations on exons 1, 10 and 11 (red). *MAPT* risk haplotypes/genotypes and other genetic risk associations for each FTLD-tau subtype are shown. Pick bodies (**a**) are the characteristic neuronal feature of PiD. Ramified astrocytes (**b**) are also observed in PiD, characterised by asymmetric tau-immunopositive inclusions in proximal astrocytic processes (**c**). Tau-immunopositive balloon neurons (**d**) are a common neuronal pathology in CBD and tau-immunopositive astrocytic plaques (**e**) are the distinguishing pathological inclusion, which are characterised by tau-immunopositive inclusions in distal astrocytic processes and endfeet with a central clearing (**f**). Globose tangles are the predominant neuronal inclusion in PSP and commonly observed in the substantia nigra (**g**). Tufted astrocytes (**h**) are characterised by symmetric tau-immunopositive astrocytic inclusions in proximal astrocytic processes (**i**) and are the hallmark pathological lesion in PSP. Tau-immunopositive globular neuronal cytoplasmic inclusions (**j**) are frequently observed in the cortex in GGT cases. Globular astrocytic inclusions (**k**) are a distinguishing neuropathological feature of GGT and are characterised by tau-immunopositive globular inclusions in proximal astrocytic processes (**l**)

3-repeat PiD ([141] and reviewed in [48]). The exon 9 missense mutations reduce the binding of tau to microtubules enhancing 3-repeat tau but not 4-repeat tau assembly, while the deletion in exon 10 and mutations in intron 10 disrupt exon 10 splicing to decrease 4-repeat tau mRNA transcripts and increase of 3-repeat tau [48, 141].

MAPT mutations and CBD and PSP pathologies

The clinical and genetic overlap between CBD and PSP is well-established [132], although PSP pathology is more rarely associated with mutations in *MAPT* (< 10% of PSP versus > 20% of CBD) [47]. 4-repeat CBD pathology is associated with *MAPT* mutations in exon 10 (S305S), intron 10 (IVS10 + 16) and exon 13 (R406 W, N410H), while 4-repeat PSP pathology is associated with *MAPT* mutations mainly in exon 10 (N297 K, S285S, S303S, S305S) but also occasionally in exon 1 (R5L) and intron 10 (IVS10 + 16) [48]. A recent study reporting two sibling pairs with late onset pathologically confirmed PSP are not associated with a known *MAPT* mutation [52], indicating a dominant genetic cause for PSP awaits discovery.

These *MAPT* genetic mutations mainly predispose to increased 4-repeat tau isoforms that are available to aggregate rather than changing the protein structure [48]. The *MAPT* mutations in exon 13 that give rise to CBD pathology are thought to abolish tau's membrane binding rather than impacting on microtubules [55], a finding likely to impact most on astrocytic endfeet predisposing to CBD pathology. The R5L mutation in exon 1 found in a single PSP family is at the N-terminus rather than the C-terminus exon 13 CBD-causing mutation. 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 [33]. In this context additional differentiating genetic influences have been observed to associate more with either PSP or CBD [7, 44, 66, 83], which are likely to influence more the hairpin conformation of tau to enhance the characteristic filaments of 4-repeat tau found in the tufted astrocytes and globose tangles of PSP, or tau's membrane binding to predispose 4-repeat tau aggregation found in the endfeet of astrocytes in the astrocytic plaques in CBD.

MAPT mutations and GGT pathology

While rarer than CBD or PSP, GGT represents the main pathological subtype associated with mutations in *MAPT* as most of the previously unclassifiable cases with a mutation in *MAPT* fulfil criteria for GGT, a finding contributing to the previous under-recognition of this pathological subtype [47, 48]. *MAPT* mutations associated with 4-repeat GGT pathology occur in exon 1 (R5H), exon 10 (P301L, N296H) and exon 11 (K317 N) [48, 144]. The exon 10 *MAPT* mutations are currently the most prevalent *MAPT* mutations (http://www.molgen.ua.ac.be/ADMutations/) causing aggregates of mixed short and long filaments [166], as the protein is more prone to increased phosphorylation [33] which perturb its chaperone-assisted stabilisation [61]. The R5H *MAPT* mutation in exon 1 may also affect tau's chaperone-assisted stabilisation by alterations in the global hairpin conformation of tau, while the *MAPT* mutation in exon 11 reduces the ability of tau to promote tubulin polymerisation, decreasing 3-repeat tau binding thereby increasing 4-repeat tau assembly [143]. This suggests that pathological globular 4-repeat tau cellular structures are likely to occur through several mechanisms, which give rise to a mixture of highly phosphorylated 4-repeat tau filament lengths. Whether particular GGT subtypes (I-III) are more likely associated with these different mutations in *MAPT*, as suggested by Tacik et al. [143], or whether these mutations are more likely to influence certain brain cell types to aggregate globular 4-repeat tau, requires further investigation.

MAPT mutations and rarer FTLD-tau subtype pathologies

NFTPD is a rare FTLD-tau subtype and to date has not been associated with mutations in *MAPT*. However, the relatively common R406W mutation on exon 13 can lead to abnormal

3-repeat tau and 4-repeat tau accumulation predominantly in neurons [56, 68, 136]. Many studies report both 3-repeat tau and 4-repeat tau isoforms in protein extracts from dissociated tissue or associated with neurofibrillary tangles in a pattern similar to AD or PART/NFTPD [154] or associated with inclusions with similar morphology to Pick bodies [162]. Unless immunohistochemistry using antibodies against 3-repeat tau and 4-repeat tau is used to clarify the molecular properties of inclusions, the pathology of these cases can be difficult to interpret. Rather than having an effect on microtubule assembly [121, 154], the R406W mutation is thought to abolish tau's membrane binding [55] and is often associated with limited neuronal loss and longer disease duration in cases [48, 154].

A single case report has described a missense mutation in *MAPT* in exon 10 (S305I, [88]) associated with 4-repeat tau AGD. However, the distribution of pathology in this case is more widespread than has been previously described for AGD. Located two base pairs before the end of exon 10, close to the exon/intron 10 splice-junction and the stem loop structure, the mutation is thought to have a dual effect, influencing both exon 10 splicing and aggregation of 4-repeat tau isoforms. The altered amino acid (AGT to ATT) and Ile substitution with this mutation is thought to increase the aggregation of mutant 4-repeat tau and due to its hydrophobic side chain, will impair tau's binding to microtubules and promote microtubule assembly [88]. Underlying AGD pathology is predominantly neuronal and oligodendroglial, with only rare thorn shaped astrocytes. It remains to be determined why this *MAPT* mutation has a preferential effect on neurons and oligodendroglia over astrocytes. Another study has described two siblings with the silent S305S mutation on exon 10 [126], as reported above with CBD and PSP.

Other genetic variations associated with FTLD-tau pathologies

In addition to the highly penetrant mutations in *MAPT*, common variants in *MAPT* increase the population risk of 4-repeat frontotemporal tauopathies (and not 3-repeat PiD, [107]) and might contribute directly or indirectly to the pathogenesis of the 4-repeat FTLD-tau subtypes by increasing the transcription of 4-repeat tau [149]. In populations of European decent, the *MAPT* gene has two divergent haplotypes that separated approximately 3 million years ago. The H1 haplotype is the more common *MAPT* variant, representing approximately 80% of the population which have a 900-kb inversion in the gene (H1) compared with non-inversion in the H2 haplotype [140, 149]. It is now well established that the H1 haplotype and the H1/H1 genotype are associated with increased risk of 4-repeat FTLD-tau subtypes, with differences in the H1 haplotype predisposing to the different subtypes [1, 130, 149, 172], whereas the H2 haplotype appears protective due to the inclusion of exon 3 in the tau protein [30, 149]. In addition to the previously reported and well-established associations with PSP risk for H1c and H2 haplotypes, a recent study has identified novel associations with PSP risk for three H1 subhaplotypes (H1d, H1g and H1o) and identified potential associations with the severity of tau pathology [62].

While *MAPT* haplotype influences risk of a 4-repeat FTLD-tau pathology, both H1 and H2 haplotypes do not influence the pathological or biochemical phenotype [149], nor disease duration, symptom severity or survival [54, 58]. The association of the H1/H1 genotype is on age of symptom onset and is heterogeneous between the clinicopathological entity [54, 58]. This relationship and the relative high prevalence of the H1 haplotype in healthy controls (77%) [66] and other neurodegenerative diseases confirms that the H1 haplotype is a predisposing mechanism. Additional disease modifying or risk factors are likely to differentiate the different 4-repeat frontotemporal tauopathies, as discussed above.

Genome-wide association studies

In addition to confirming the two independent *MAPT* variants, rs8070723 and rs242557 that map directly or closely to H1/H2 haplotypes, the first PSP genome wide association study (GWAS) [66] identified single nucleotide polymorphisms clustered at three different non-*MAPT* susceptibility loci at *STX6* (1q25.3), *EIF2AK3* (2p11.2) and *MOBP* (3p22.1) that modify risk of PSP (Fig. 3) [44, 66]. In 2015, a GWAS identified a novel association of the *MOBP* locus also modifies risk of CBD [83] and identified novel risk loci on chromosome 2 (*SOS1*) and chromosome 8 (*Inc-KIF13B-1*) that confer risk of CBD rather than PSP [83]. Although the single nucleotide polymorphism at *MOBP* was found to confer greater risk of CBD than it does PSP, it was the first non-*MAPT* genetic risk factor identified that is shared between 4-repeat FTLD-tau subtypes [83] and encodes a myelin structural component in oligodendroglia [44, 66]. Of note, the *MAPT* and *MOBP* region risk alleles also associated with higher levels of 4-repeat tau neuropathology [7]. Further assessment of overlapping genetic risk confirmed associations with these genes and identified CXCR4, EGFR, and GLDC as well [165]. CXCR4 encodes a chemokine receptor important in vascularization and cerebellar development, and has broad regulatory functions in the immune system and neurodevelopment, regulating neuronal guidance and apoptosis through astroglial and microglial activation [16]. The physical interactions of *CXCR4* and four microglial-related genes, *CXCL12, TLR2, RALB* and *CCR5*, are perturbed in a transgenic mouse model of tauopathy [16]. EGFR encodes the epidermal growth factor receptor and GLDC encodes glycine dehydrogenase, a critical enzyme required

for glycine degradation, and both are highly expressed in mature astrocytes [165]. The epidermal growth factor receptor shows an increase in expression in astrocytes after injury, and can promote their transformation into reactive astrocytes [163]. This data suggests that a variety of genes interact with tau mechanisms to predispose to 4-repeat tau aggregation in neurons and glia in 4-repeat FTLD-tau subtypes.

The non-overlapping genes identified in GWAS studies to date may be more related to the distinctive neuropathologies observed in these FTLD-tau subtypes. These genes encode proteins involved in intracellular membrane trafficking (*STX6*), the endoplasmic reticulum unfolded protein response (*EIF2AK3*) [44, 66], membrane signal transduction through a guanine nucleotide exchange factor for Ras (*SOS1*) and a large intergenic non-coding RNA (*Inc-KIF13B-1*) that may regulate peripheral protein transcription in astrocytes [129]. The first risk alleles *ARL17A/ARL17B* associated with a distinctive 4-repeat tau pathology, tufted astrocytes in PSP, has been identified [7], confirming the concept that genetic variation predisposes to the distinctive neuropathologies observed in these disorders. More recently it has been shown that the tufted astrocytes in PSP are associated with decreased levels of synaptic genes (including *MAPT, STX6* and *ARL17A/ARL17B*) and increased levels of immune system transcripts (highly enriched in microglial genes, note *ARL17* is also associated with antibody response) [8]. More information on how membrane signal transduction and potentially peripheral protein transcription (see above) are involved in the astrocytic plaques observed in CBD, and some insight into pathways involved in the other distinct pathways for the differentiating tau pathologies, are now needed.

Neuroanatomical selectivity associated with phenotypic diversity

The last decade has seen significant progress in mapping the prediction site of the main underlying proteinopathies in a large proportion of FTD patients primarily through neuroimaging studies [35, 124]. Unfortunately, there are no autopsy-confirmed studies using functional brain imaging, but magnetic resonance imaging (MRI) has been used to asses structural changes in the brain and 18-F fluorodeoxyglucose (FDG) PET has identified anatomical regions of hypometabolism in autopsy-confirmed cases. To date the majority of studies have focused on distinguishing bvFTD from AD [49], although studies focussing on differentiating the main underlying proteinopathies (but not their subtypes) are now more common (e.g. [102]). These analyses are important for the different types of proteins aggregating in FTD syndromes and the future success of protein-targeted therapeutic interventions. Newer studies are targeting cases with genetic forms of FTD, including those with *MAPT* mutations (see papers by the Genetic FTD initiative, GENFI), but analyses are presented as a single gene group which appears relatively uniform [124, 169]. This may suggest that a number of these cases have the P301L *MAPT* mutation, one of the most common mutations in *MAPT*, which predisposes to GGT with bvFTD (see above) and predominantly temporal lobe atrophy [124, 169]. Of course, there are no data for the rarer clinical FTD syndromes where FTLD-tau comprises less than 10% of cases (e.g. sv-PPA).

Only a small number of neuroimaging studies have examined the most common autopsy-confirmed FTLD-tau subtypes of PiD, CBD and PSP. PiD has the greatest cortical atrophy with more rightward ventral and dorsal frontal and anterior temporal atrophy in autopsy confirmed cases [69, 114]. All autopsy confirmed PiD cases have initial knife-edged atrophy on MRI [69, 114] and widespread metabolic abnormalities [108, 159]. CBD has less anterior temporal atrophy and more dorsolateral frontal atrophy with notable focal supplementary motor area atrophy in autopsy confirmed cases [114, 159]. In autopsy confirmed CBD cases metabolic changes are typically asymmetric and involve subcortical structures [108, 110, 159]. PSP has the least cortical atrophy with less anterior temporal and less severe frontal grey atrophy [114] with significant bilateral subcortical atrophy and hypometabolism in autopsy confirmed cases [158, 170].

Whether the clinical variability observed in the FTLD-tau subtypes has been captured sufficiently in these studies requires further assessment. Studies assessing clinical phenotypes have found that no single cortical or subcortical region identified on neuroimaging differentiates a particular pathological subtype [124] confirming that the same brain regions can concentrate diverse neuropathologies to give the same clinical phenotype. PiD is the most common FTLD-tau subtype found in bvFTD [27, 76] and not surprisingly as a group has a neuroimaging phenotype more typical of bvFTD [103, 139]. Cases with PiD pathology and the rarer PPA clinical phenotypes may have a different neuroimaging profile as they have different clinical phenotypes and different clinical courses to bvFTD [64, 116, 164]. The newly recognised diversity of clinical phenotypes in both CBD [5] and PSP [6, 67] may be even more problematic for conceptualising the earliest brain regions affected by these pathologies and their trajectories apart from those clinical syndromes already closely aligned with these pathologies and described above. Over 20% of cases with CBD pathology have Richardson syndrome and around 20% have a FTD clinical syndrome without parkinsonism (note up to 30% of bvFTD with FTLD-tau have the CBD subtype) (see above). Similarly for PSP, ~ 25% have early Richardson syndrome with many having features of Parkinson's disease and ~ 20% having either corticobasal syndrome or bvFTD (see above). These cases are likely to have more diverse brain regions

affected and this has called for a rethinking of whether these syndromes can be clinically separated with certainty at present [65, 97]. For both CBD and PSP subtypes, the patterns of brain atrophy that may relate to PPA clinical phenotypes remain unknown even though FTLD-tau is found in a high proportion of some PPA clinical phenotypes [81, 106, 155]. These difficulties emphasise the need for differential biomarkers for the clinical separation of the different FTLD-tau subtypes.

Spreading of FTLD-tau pathologies

It is now well described using a variety of different approaches that disease progression is characterised by the spreading of localised pathological inclusions in the vulnerable neuronal populations identified (primary vulnerable cells [51]) to an increasing number of brain regions (secondary vulnerable cells [51]) in a stereotypical and hierarchical pattern. This cellular vulnerability hypothesis suggests that the different forms of tau and/or the deposition of other proteins is initiated in a certain population of neurons and each neuron in the network is subsequently involved over time as a result [156]. These network concepts are largely conceived for neuronal networks even though the pathologies in FTLD-tau subtypes are not all (or even dominantly) neuronal, e.g. in CBD astrogliopathy is the earliest tau pathology observed [96] and tau astrogliopathy is often the earliest pathology observed in FTLD-tau [87]. Also, genetic forms of FTLD-tau have cells with mutant tau protein that may more easily explain cell-autonomous mechanisms [156], although the impact on the different brain cell types remains unknown as does their role/s in the spreading of pathology in the brain.

A number of well-established studies suggest that the spread of tau pathology occurs through synaptic and functional connectivity, rather than spatial proximity to pathological inclusions [2], and perhaps astrocytes that are intimately involved in synaptic plasticity (one of the elements of the tripartite synapse) and neuronal network oscillations [39, 131], may play a larger role than currently envisaged. While this concept has not yet been assessed, the concept that hierarchical anatomical distribution of pathological inclusions has been demonstrated now for most of the common FTLD-tau pathologies (except GGT) and suggests that pathological spread occurs between interconnected regions, although this does not seem to be the case for all FTLD-tau subtypes as detailed below.

Four pathological stages have been proposed for PiD suggesting that pathological lesions originate in limbic regions [69], which match somewhat the severity of pathology previously identified [13]. Phase I PiD is characterised by limbic and frontotemporal involvement; Phase II involves subcortical structures including basal ganglia, thalamus and brainstem; Phase III has additional involvement of the primary motor cortex and precerebellar nuclei; and Phase IV involves widespread pathology including the primary visual cortex [69]. These patterns suggest pathological spread via frontotemporal cortices to subcortical sites, then back to primary motor cortex and the cerebellum possibly through the thalamus, prior to more widespread brain involvement potentially also via thalamic relays. Note that the majority of these pathological cases have bvFTD and whether different initiation and core network sites would be the same for those with PPA that potentially impacts on different brain regions still needs to be determined. Also the timing of this trajectory and the potential for identifying an important relay node for PiD pathology need further examination.

Pathological staging and hierarchical anatomical involvement for CBD has yet to be performed in detail in a large series, potentially due to the problems with identifying the many potential clinical phenotypes and their differential progressions (see above). However, the severity of tau pathology in CBD has been determined [13] and follows a similar pattern to that identified in the neuroimaging studies described above. Recently there have been a few case reports of incidental CBD in individuals [100, 105] and comparison to a small number of cases with end-stage CBD [96]. This confirms the other preclinical case reports showing the hallmark astrocytic plaque pathology as the most prominent lesion in the striatum and also in anterior frontal and parietal regions in the absence of significant neuronal loss prior to symptom onset. Notably, the tau pathology prior to symptom onset is widespread and similar to end-stage CBD but less severe [96]. Four stages have been proposed which largely use cell type and lesion load as distinguishing early and late preclinical versus early and late clinical CBD (see Fig. 7 in [96]). Further issues that need to be addressed in larger clinically-diverse autopsy cohorts are whether the variety of clinical phenotypes is due to the initial site of focal neuronal loss or more focal astroglial or tau pathology, and how these may overlay on the widespread tau pathology observed in preclinical CBD.

Pathological staging for progressive regional involvement has been proposed for PSP based on the severity of neuronal tangles, tufted astrocytes, coiled bodies and tau-immunopositive threads and notably differs by clinical phenotype [37, 95, 160]. That the distribution and severity of PSP pathology varies by clinical phenotype suggests a different staging scenario to CBD where widespread pathology occurs preclinically (see above), a scenario where different foci of PSP pathology are initiated and either spread during progression, or remain focal and increase in severity over time. The data on diverse progression of the different clinical phenotypes would suggest the latter concept for PSP [37, 95, 160] and data on incipient cases from forensic and geriatric hospital autopsies confirm this concept [111, 167]. Importantly, in all pathological phenotypes the subthalamic nucleus, substantia

nigra and globus pallidus contain tau pathology, consistent with the subcortical focus observed on imaging (see above). In incipient cases, the dominant tau pathology is astrocytic [167] with the variability in coiled bodies and threads in different brain regions used to stage and distinguish the different PSP phenotypes over time [37, 95, 160]. The basis for the anatomical restriction of PSP pathology and the focality of neuronal loss in the different clinical phenotypes at end-stage remains to be determined, with the concept of regional preservation of tissue in PSP an important distinguishing feature between this 4-repeat tauopathy and that of CBD.

For the remaining FTLD-tau subtypes, staging is somewhat similar but for different tau pathologies. For 4-repeat AGD, there are three well-established pathological stages based on the density and distribution of argyrophilic grains [128]. AGD stage I involves the ambient gyrus, entorhinal and transentorhinal cortices, and the hippocampal CA1 region; Stage II is characterised by further involvement of the medial temporal lobe and subiculum; and Stage III also involves the septum, insular and anterior cingulate cortices [128]. In 2008, the AGD pathological staging scheme was expanded to a four stage system to incorporate cases with moderate to severe neocortical and brainstem involvement [46]. For PART and NFTPD [34, 74] the 3-repeat and 4-repeat neurofibrillary pathologies follow the Braak staging scheme which suggests that the pathology may originate in the brainstem but that the subsequent involvement of the transentorhinal and entorhinal cortices accelerates the pathology into the hippocampus and then association neocortices [20]. Note that the type of tau in these diseases does not differ from that in AD (see introduction). While the earliest Braak stages a-c are characterised by tau-immunopositive deposits in the somatodendritic compartment of a few noradrenergic projection neurons in the locus coeruleus followed by pretangle and then tangle formation, there is not widespread tau pathology in this region until the entorhinal cortex becomes involved. These locus coeruleus neurons have long projections to the entorhinal cortex indicating that slow spreading of pathology (over decades) occurs via neuron-to-neuron transmission and largely anterograde transport of tau aggregates between functionally connected networks [21], consistent with recent data showing that the spreading of tau measured by tau PET is related to synaptic activity and release in connected regions [50]. Tau seeds are common in the cortical regions that will aggregate tau with regional tau seeding activity correlating with Braak staging [53, 79]. Importantly, the concept that tau seeding is important for PART progression has also been identified with seeding starting in the transentorhinal and entorhinal cortices before the locus coeruleus [79], suggesting a retrograde mode of transmission in this condition.

Recently, the novel 4-repeat ARTAG (Fig. 1y-bb) has been described predominantly, but not exclusively, in individuals over 60 years of age without evidence of cognitive impairment [86]. Based on the morphology and distribution of astrocytic inclusions, ARTAG can be differentiated from other tau-depositing disorders, but may also co-exist in FTLD-tau and other neurodegenerative diseases [89]. ARTAG is characterised by two types of astrocytic inclusions immunoreactive for phosphorylated tau: granular fuzzy astrocytes (Fig. 1y) and/or thorn-shaped astrocytes (Fig. 1z). Granular fuzzy astrocytes are characterised by dense peri-nuclear tau accumulation with fine, granular tau-immunopositive deposits in both proximal and distal astrocytic processes, and thorn-shaped astrocytes are characterised by dense, short and thick tau-immunopositive deposits in proximal astrocytic processes [86]. Based on observations of frequent tau-immunopositive dot-like structures in astrocytic processes in the ageing brain and in FTLD-tau, and the occurrence of granular fuzzy astrocytes in the same cortical regions that contain astrocytic inclusions in CBD, PSP and PiD, a recent study proposes that these dot-like structures can progress into granular fuzzy astrocytes, which might represent the earliest stages of pathological tau accumulation in astrocytes observed in FTLD-tau [89]. This is similar to the proposed pathological progression of NFT formation in AD (Braak Stage A) of neurofibrillary tangle development [20]. Hierarchical clustering of anatomical involvement has recently been proposed for the different types of ARTAG, which provides a framework for the initial steps and potential involvement in the pathogenesis of FTLD-tau [91].

Cellular and molecular basis for neuroanatomical selectivity

Why certain populations of neurons and/or non-neuronal cells in a particular brain region are selectively vulnerable to protein aggregation and subsequent degeneration while others are relatively spared or only affected at later disease stages remains a focus area of research. Since a number of different molecular and protein FTLD pathologies converge on the same neuronal populations and brain regions to produce similar clinical FTD syndromes, for example, FTLD-tau and FTLD-TDP underlying bvFTD, suggests common molecular mechanisms are likely to be involved in neuroanatomical vulnerability. In addition to the genetic variability discussed before, recent studies propose that regional and cellular differences in gene expression profiles and local environmental factors, including neuroinflammation, might contribute, at least in part, to selective cellular and regional vulnerability.

Neuroinflammation is a pathological feature of all neurodegenerative diseases characterised by microglial activation and up-regulated astrocytes in affected brain regions [31, 63, 113]. While acute inflammatory responses are usually beneficial, inflammation associated with

prolonged and uncontrolled glial cell activation and subsequent recruitment of inflammatory factors (including cytokines and chemokines) is detrimental and contributes to chronic neuroinflammation [135]. Emerging evidence suggests neuroinflammation plays a key role in the pathogenesis of FTLD. Indeed, recent GWAS have identified a number of genes associated with neuroinflammation [22, 44] and altered inflammatory markers in blood, serum and cerebrospinal fluid in FTD patients. However, few studies have investigated inflammatory markers in human post-mortem tissue.

Chitinase 3-like I (YKL-40) is frequently used as a surrogate marker of neuroinflammation in bodily fluids in AD and a range of other neurodegenerative diseases [42]. Elevated YKL-40 has also been found in the CSF of patients with AD, FTD, CBD and PSP [4, 145]. Recently, in a neuropathological cohort of AD, PiD, CBD and PSP cases, Querol-Vilaseca et al. [118] demonstrated that YKL-40 is expressed in a subset of astrocytes. Although YKL-40 immunostaining was found in astrocytes that did not contain tau-immunopositive inclusions, the density of astrocytes containing YKL-40 immunostaining was increased in CBD and PSP, and correlated to tau pathological burden.

As one of the major cellular and metabolic supporting cells in the central nervous system, astrocytes are also known to release cytokines, contributing to the neuroinflammatory response [63]. The density of up-regulated astrocytes as visualised using glial fibrillary acidic protein (GFAP) immunohistochemistry, are increased in cortical predilection regions known to contain FTLD-tau pathology [12]. GFAP-immunostaining identifies the astrocytic cytoskeleton and processes but GFAP filaments are redistributed in astrocytes with tau-immunopositive inclusions in FTLD-tau subtypes, suggesting disruption to the astrocytic cytoskeleton in FTLD-tau [45]. These changes occur in association with astrocytic apoptosis and loss, which are both associated with neuronal loss rather than the severity of tau pathologies [23, 80]. Of interest is the concept that astrocytes could be the primary target of offending agents causing primary neurodegenerative diseases [134] and a recent study has found a transmissible cytotoxic agent from patients with different acute neurological diseases that causes an inflammatory response followed by apoptosis in cultured astrocytes [15]. In addition, a recent finding that astrocytes and microglia that become senescent in a model of tauopathy can be removed to prevent gliosis, tau deposition, neuronal degeneration and cognitive decline [29]. Of interest is the finding that a similar cell senescence occurs in PSP parietal cortex [109], although the cell type involved has not been identified. How this relates to the type and/or progression of PSP and other FTLD-tau subtypes needs to be determined.

Future directions

In concentrating on the pathological subtypes of frontotemporal tauopathies, this review has highlighted novel concepts on pathogenesis and potential biomarkers for FTLD-tau subtypes that require further analyses (Fig. 4), including:

- Correlations between different parts of the *MAPT* gene and pathology. The data presented indicate that correlations between different regions of the *MAPT* gene give rise to particular FTLD-tau subtypes or predispose to particular FTLD-tau subtypes. More research on the diversity of tau pathologies when different regions of the *MAPT* gene are perturbed is required to model the different FTLD-tau subtypes.
- Differentiating genetic risk. The data presented indicate that there are shared genetic risk factors but also distinct genetic risk factors that may be important for the cell type and region-specific pathologies observed in the FTLD-tau subtypes. Further analyses, including cell- and region-specific associations, are required to understand the impact of these different molecular pathways.
- Neuroanatomical selectivity and progression of the different tau pathologies. The data presented indicate that the neuroanatomical selectivity may relate more to clinical subtype than FTLD-tau subtype, and that the FTLD-tau subtypes differ significantly in the way they may initiate disease within the same brain regions, and particularly differ in their potential for spreading. More comparative research within the FTLD-tau subtypes that have different regional patterns (including brain regions that are spared at end-stage), as well as in those with widespread tau pathology but focal neuronal loss, is warranted.
- The role of astrocytes. The data presented highlights the limited research on how astrocytes are involved in the FTLD-tau subtypes, even though the diversity of astrocytic pathologies is a major determinant of these subtypes. New research has focussed attention on these glia [29], and further work is needed to determine whether different or similar types of astrocytes are targeted and how the different types of tau pathologies impact on these cells.
- The development of strain specific biomarkers. This is perhaps the most needed type of research, but it is difficult to identify the best route forward to make headway on this aspect until some of the research suggested above is performed. At present biomarkers are being developed to differentiate the main types of protein abnormalities in FTD syndromes (TDP-43 versus tau versus FUS) [139, 171] rather than the FTLD-tau subtypes, even though these tau subtypes appear to differ significantly biologi-

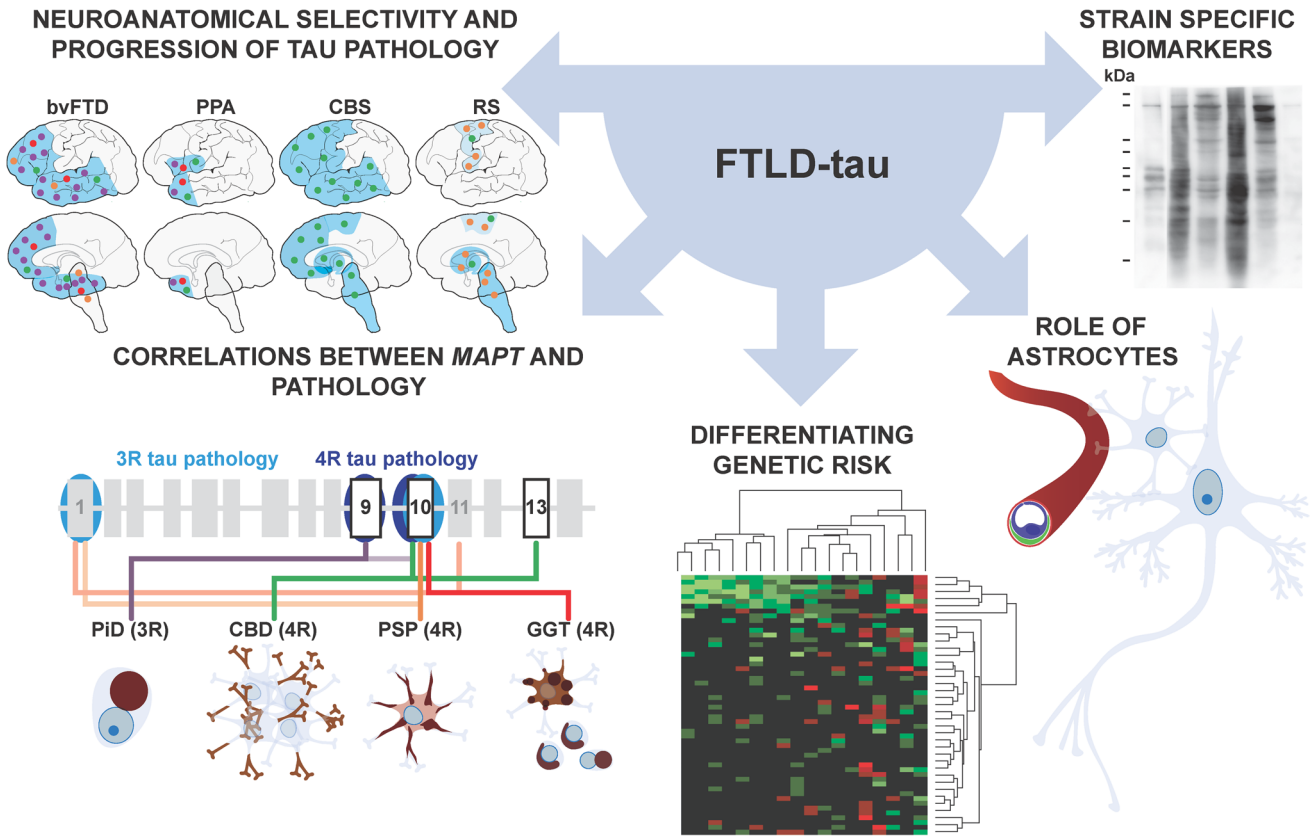


Fig. 4 Future directions to address the regional and cellular vulnerabilities of FTLD-tau. Summary diagram of the proposed areas of future research requiring further analysis to determine the regional and cellular vulnerabilities of FTLD-tau. Importantly, each FTLD-tau subtype with their distinct pathological features differ substantially in the cell type affected, morphology, biochemical and anatomical distribution of inclusions. This fundamental concept is central to future success in understanding the disease pathogenesis required for developing potential biomarkers for FTLD-tau subtypes and disease modifying therapies

cally. Eventually biomarkers for the different FTLD-tau subtypes will be required.

While there has been enormous progress on our understanding of frontotemporal tauopathies, further advances will be enhanced by current developments in neuroimaging ligands for tau and also by computer systems that enable real-time evaluations of large datasets on individuals. These advances are needed to build longitudinal information that can test the concepts identified from cross-sectional pathological studies on the hierarchical anatomical involvement and spread of pathology in the different FTLD-tau subtypes, and implement new predictive models in a clinical setting. There are already a number of tau directed therapies being trialled in clinical phenotypes most predictive as having tau pathologies [71, 133]. These therapies are targeting genetic mechanisms, abnormal post-translational modifications of tau protein, and transcellular tau spread, all of which require more information for the different FTLD-tau subtypes as described above. Another therapeutic avenue includes directly targeting *MAPT* gene expression with antisense oligonucleotide (ASO) therapies [36, 41, 142]. Future studies are also required to focus on the initial regional changes in neuronal and glial functions that at present are still unknown. Investigating molecular and biochemical properties of the initial cells and brain regions involved versus those not affected both in the same brain region as well as in remote brain regions is required to determine pathways for further therapeutic targeting. The fundamental concept that the FTLD-tau subtypes differ significantly in their biology is central to future success in understanding and combating these diseases.

Search strategies. We examined all literature on frontotemporal lobar degeneration, Pick's disease, corticobasal degeneration, corticobasal syndrome, progressive supranuclear palsy, globular glial tauopathy, argyrophilic grain disease, primary age-related tauopathy, neurofibrillary tangle predominant dementia, and tauopathy targeting full text English language studies. We selected articles on the basis of our personal knowledge and the Pubmed database searches for their relevance and completeness of information related

to the clinical, genetic, pathological, and mechanistic data presented for the different frontotemporal tauopathies.

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