

Neuropathological background of phenotypical variability in frontotemporal dementia

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Received: 3 March 2011 / Revised: 10 May 2011 / Accepted: 15 May 2011 / Published online: 26 May 2011
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Abstract Frontotemporal lobar degeneration (FTLD) is the umbrella term encompassing a heterogeneous group of pathological disorders. With recent discoveries, the FTLDs have been shown to classify nicely into three main groups based on the major protein deposited in the brain: FTLD-tau, FTLD-TDP and FTLD-FUS. These pathological groups, and their specific pathologies, underlie a number of well-defined clinical syndromes, including three frontotemporal dementia (FTD) variants [behavioral variant frontotemporal dementia (bvFTD), progressive non-fluent aphasia, and semantic

dementia (SD)], progressive supranuclear palsy syndrome (PSPS) and corticobasal syndrome (CBS). Understanding the neuropathological background of the phenotypic variability in FTD, PSPS and CBS requires large clinicopathological studies. We review current knowledge on the relationship between the FTLD pathologies and clinical syndromes, and pool data from a number of large clinicopathological studies that collectively provide data on 544 cases. Strong relationships were identified as follows: FTD with motor neuron disease and FTLD-TDP; SD and FTLD-TDP; PSPS and FTLD-tau; and CBS and FTLD-tau. However, the relationship between some of these clinical diagnoses and specific pathologies is not so clear cut. In addition, the clinical diagnosis of bvFTD does not have a strong relationship to any FTLD subtype or specific pathology and therefore remains a diagnostic challenge. Some evidence suggests improved clinicopathological association of bvFTD by further refining clinical characteristics. Unlike FTLD-tau and FTLD-TDP, FTLD-FUS has been less well characterized, with only 69 cases reported. However, there appears to be some associations between clinical phenotypes and FTLD-FUS pathologies. Clinical diagnosis is therefore promising in predicting molecular pathology.

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Keywords Frontotemporal lobar degeneration ·
Progressive supranuclear palsy · Tau · TDP-43 ·
FUS

Abbreviations

Pathological terms

FTLD	Frontotemporal lobar degeneration
TDP-43	Transactive response DNA binding protein of 43 kD
FUS	Fused in sarcoma

AD	Alzheimer's disease
3R	Three repeat
4R	Four repeat
FTLD-tau	FTLD characterized by tau immunoreactive inclusions
FTLD-TDP	FTLD characterized by TDP-43 immunoreactive inclusions
FTLD-FUS	FTLD characterized by FUS immunoreactive inclusions
FTLD-other	Unclassified FTLD (not characterized by tau, TDP-43 or FUS immunoreactive inclusions)
FTLD-MND	FTLD with motor neuron degeneration
FTLD-U	FTLD with ubiquitin-only immunoreactive inclusions
PiD	Pick's disease
PSP	Progressive supranuclear palsy
CBD	Corticobasal degeneration
AGD	Argyrophilic grains disease
MST	Sporadic multisystem tauopathy with globular inclusions
DNTC	Diffuse neurofibrillary tangle dementia with calcifications
NIFID	Neuronal intermediate filament inclusion disease
BIBD	Basophilic inclusion body disease
aFTLD-U	Atypical FTLD with ubiquitin-only immunoreactive changes
FTLD-ni	FTLD without inclusions
FTLD-UPS	FTLD with immunohistochemistry against proteins of the ubiquitin proteasomal system
NCI	Neuronal cytoplasmic inclusions
H&E	Hematoxylin and eosin
NFT	Neurofibrillary tangle

Clinical terms

FTD	Frontotemporal dementia
bvFTD	Behavioral variant of FTD
MND	Motor neuron disease
FTD-MND	Frontotemporal dementia with motor neuron disease
SD	Semantic dementia
PNFA	Progressive non-fluent aphasia
AOS	Apraxia of speech
PSPS	Progressive supranuclear palsy syndrome
CBS	Corticobasal syndrome
PLS	Primary lateral sclerosis
VSGP	Vertical supranuclear gaze palsy

Genetic terms

<i>CHMP2B</i>	Charged multivesicular body protein 2B
<i>MAPT</i>	Microtubule associated protein tau

<i>GRN</i>	Progranulin
<i>VCP</i>	Valosin containing protein
<i>TARDBP</i>	Transactive response DNA binding protein

Introduction

The term frontotemporal dementia (FTD) is reserved for a cluster of syndromes that manifest as a result of pathological damage to the frontal and temporal lobes [14, 94]. It encompasses three main clinical syndromes: behavioral variant FTD (bvFTD); progressive non-fluent aphasia (PNFA) and semantic dementia (SD) [94]. The prevalence of FTD has been estimated to be approximately 15 per 100,000 [102] while the incidence ranges from 2.2 to 8.9 per 100,000 depending on the age of onset [70]. In addition, some patients present with features of FTD, as well as motor neuron disease (MND). When these two phenomena co-occur, the syndromic diagnosis rendered is FTD-MND [23, 46]. Two other syndromes, progressive supranuclear palsy syndrome (PSPS) [78] and corticobasal syndrome (CBS) [8] are closely related to the FTDs. These six clinical syndromes are linked to a number of molecular pathologies that target the frontal and temporal lobes, known as the frontotemporal lobar degenerations (FTLDs) [48].

Unlike FTD which is a clinical term, FTLD is a pathological term [87]. Like FTD, the term FTLD encompasses a cluster of diseases, in this instance, a cluster of molecular pathologies [48]. These molecular pathologies are classified according to the major biochemical abnormality identified at post-mortem, i.e. the major protein deposited.

Understanding the relationship between FTLD, FTD, PSPS and CBS has proven challenging. Over the last decade, many researchers have investigated the neuropathological background of the phenotypic variability of FTD, PSPS and CBS. Together these studies have identified variable associations between specific clinical syndromes and molecular pathologies. This review will address the relationship of the FTLD molecular pathologies to the associated clinical syndromes of FTD, PSP and CBS by dissecting each clinical syndrome and molecular pathology. In addition, we pool data from several large clinicopathological studies assessing 544 cases (Table 1) in order to determine associations between clinical syndromes and molecular pathologies. Chi-square tests were performed to assess the strengths of the associations between clinical syndromes and molecular pathologies. These studies were all from different institutions and all studies were reviewed in detail to remove any overlapping cases.

Table 1 Studies used to gather data for clinicopathological associations of FTLD-tau and FTLD-TDP

Study	Hodges et al. [38]	Kertesz et al. [67]	MacKenzie et al. [80]/Davidson et al. [25]	Josephs et al. [56]	Forman et al. [31]	Snowden et al. [111]	Grossman et al. [35]	Josephs et al. [57]
Institution	Sydney, Australia and Cambridge, UK	London, Ontario, Canada	Manchester, UK	Rochester, MN, USA	Philadelphia, PA, USA	Manchester, UK	Philadelphia, PA, USA	Jacksonville, FL, USA
Study criteria	Path proven FTLD or CBD from dementia clinics. Excluded PSP	Clinical diagnosis of FTD, CBS or PSP that went to autopsy	Path diagnosis of FTLD-U or FTLD-MND.	Path diagnosis of FTLD, CBD or PSP from movement disorders and dementia clinics	Clinical diagnosis of dementia as well as FTLD, CBD or PSP path diagnosis	Path diagnosis of FTLD or CBD from a cerebral function unit	Path diagnosis of FTLD-U or FTLD-MND	Path diagnosis of FTLD-U or FTLD-MND
No. of cases reported								
Total	61	60	37	127	90	65	23	39
Tau	31	21	0	87	53	25	0	0
TDP	30	24	37	39	37	40	23	39
FUS	0	0	0	0	0	0	0	0
Other	0	15	0	1	0	0	0	0
No. of FTLD pathological cases reported that had syndromic diagnoses of bvFTD, PNFA, SD, FTD-MND, CBS or PSPs								
Total	61	33 ^a	37	119	0 ^b	62	18 ^d	39
Tau	31	13	0	80	0	22 ^c	0	0
TDP	30	20	37	39	0	40	18	39
FUS	0	0	0	0	0	0	0	0
Fig. 2a	X	X	–	X	X	X	–	–
Fig. 2b	–	–	X	–	–	–	X	X
Fig. 8	X	X	–	X	–	X	–	–
Fig. 9a	X	X	–	X	–	X	–	–
Fig. 9b	–	–	X	–	–	–	X	X

^a 22 cases were diagnosed as PPA, and could not be classified as PNFA or SD, and 5 cases were not included in the review since they did not have an FTLD, CBD or PSP pathological diagnosis

^b Specific clinical diagnoses (bvFTD, PNFA, SD, FTD-MND, CBS or PSPs) were not provided separately for the FTLD-tau and FTLD-TDP cases

^c Three patients were diagnosed with apraxia (PAX), but not CBS

^d Three cases had a clinical diagnosis of AD and two had a clinical diagnosis of dementia with Lewy bodies

The frontotemporal lobar degenerations

The frontotemporal lobar degenerations (FTLDs) are a heterogeneous group of diseases that overlap in gross and histological features. All are associated with varying degrees of atrophy, neuronal loss and gliosis of the frontal and temporal lobes. However, each disease differs from one another by differences in protein deposition or biochemical signature, and inclusion morphology and distribution [15]. Three major proteins have been identified as leading players in the mechanism of neurodegeneration of the FTLDs. These three proteins are the microtubule-

associated protein, tau [43], the transactive response DNA binding protein of 43 kD (TDP-43) [1, 98], and the tumor associated protein fused in sarcoma (FUS) [75]. Therefore, at the highest stratum, the majority of FTLDs can be sub-classified into FTLD-tau, FTLD-TDP and FTLD-FUS [84], based on the biochemical signature of the abnormally deposited protein (Fig. 1). Further sub-classification within each of these three groups is predominantly based on inclusion morphology and lesion distribution [15, 84, 85], although other characteristics may also be utilized, such as, tau isoform dominance, phosphorylation and ubiquitination status, and cleavage sites. Using this classification scheme

almost 100% of the FTLDs can be sub-classified, with only a handful of extremely rare cases remaining unclassified (FTLD-other).

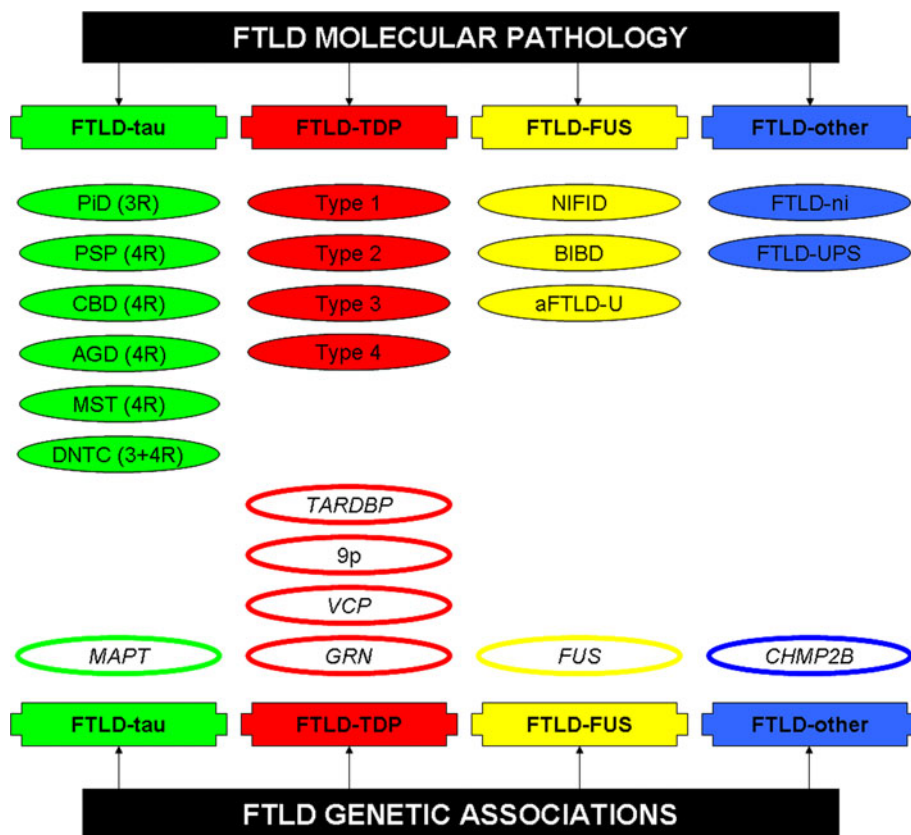
FTLD-tau

The FTLD-tau group consists of diseases in which the major abnormal protein, identified by immunohistochemistry, is the microtubule-associated protein, tau. This group consists of the following diseases: Pick’s disease (PiD) [28, 29], progressive supranuclear palsy (PSP) [37], corticobasal degeneration (CBD) [30], argyrophilic grains disease (AGD) [11, 12], sporadic multisystem tauopathy with globular inclusions (MST) [7, 53, 73], and diffuse neurofibrillary tangle dementia with calcifications (DNTC) [71, 72] (Fig. 1). Combining data from five large clinicopathological studies [31, 38, 56, 67, 111] of 544 pathologically confirmed FTLD patients, it appears that some FTLD-tau pathologies are much more common than others. The most common pathology was CBD accounting for 35% of cases, followed by PSP with 31%, PiD with 30% and AGD accounting for the remaining 4% of all FTLD-tau (Fig. 2a). No cases of MST or DNTC were reported in any of these large clinicopathological studies. It should be noted that PSP in general is a more common pathology than CBD suggesting a recruitment bias likely driven by the fact that

these autopsy cases were mainly from dementia clinics. These studies only recruited patients with FTD-like diagnoses, some even excluded PSPS, and therefore patients with relatively pure motor syndromes without prominent behavioral changes would not have been included in these series; hence it is no surprise that PSP was less common than CBD since cognitive impairment is more likely a feature of CBD than PSP (manuscript in press).

The characteristic histological features of the FTLD-tau molecular pathologies are shown in Figs. 3, 4. Unlike the other diseases in this category, PiD is a 3 repeat (3R) tauopathy [13], i.e. deposited tau is characterized by 3 binding domains in the carboxyl terminus of the protein, as opposed to 4 binding domains (4R) in PSP [20], CBD [115], AGD [119] and MST [7]. A mixture of 3R and 4R binding domains is observed in intracellular neurofibrillary tangles in DNTC [45], although extracellular tangles (ghost tangles) are predominantly 3R tau (Fig. 4). Additional features differentiating PiD from the other pathologies are the rounded appearance of the inclusions, the fact that inclusions are strongly argyrophilic but do not stain with Gallyas [120, 121], and are localized to the cytoplasm of the neuron, and the absence of features typical for the other diseases [28, 29]. Unlike PiD, neuronal inclusions in PSP are much larger and globose in morphology. In addition, PSP is characterized by the presence of astrocytic lesions,

Fig. 1 Diagram illustrating the current classification scheme for the FTLDs. FTLD-tau pathologies are shown in green, FTLD-TDP in red, FTLD-FUS in yellow and FTLD-other in blue. The genes associated with each pathological group are also shown. FTLD-TDP typing (1–3) is based on the classification by Mackenzie et al.; type 4 is based on the classification of Cairns et al. 9p Linkage identified on chromosome 9p



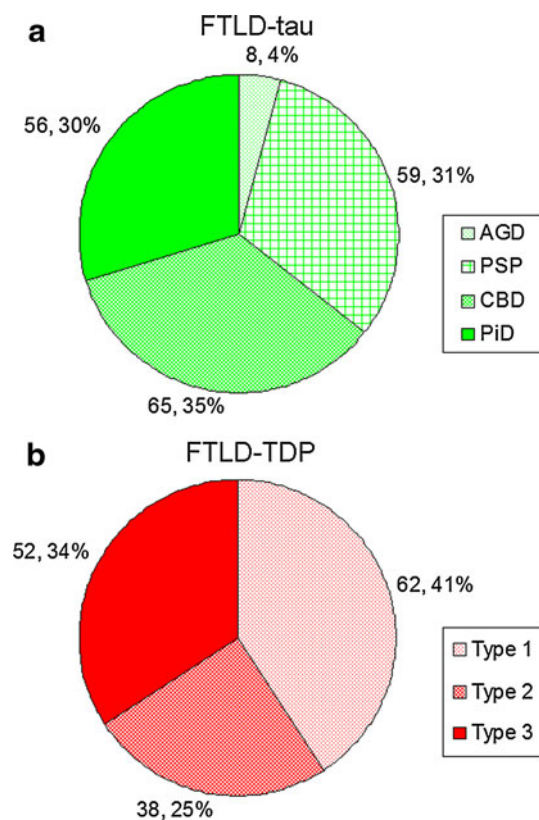


Fig. 2 Pie charts showing the proportion of specific pathologies observed in FTLD-tau (**a**) and FTLD-TDP (**b**), based on pooled data from eight large clinicopathological studies. The number and percentage associated with each pathology is also shown. FTLD-TDP typing is based on the classification by Mackenzie et al.

better known as tufted astrocytes. Corticobasal degeneration, like PSP, can show large neuronal inclusions, but they tend to be more rounded (so called cortico-basal bodies) [33]. In addition, CBD is characterized by the presence of a different type of astrocytic lesion, known as the astrocytic plaque [30]. In CBD, unlike in PSP, there is also widespread white matter pathology where numerous thread-like lesions are easily identified. There is also a biochemical difference between PSP and CBD, with PSP showing a 33-kD tau band on immunoblots of sarkosyl-insoluble brain extracts while CBD shows a 37-kD band [2]. Given these differences, many researchers have continued to support splitting PSP and CBD [27]. The other two FTLD-tau entities are characterized by: the presence of globular oligodendroglial inclusions in MST [7, 53, 73]; and a prominence of widespread intracellular neurofibrillary tangles and ghost tangles with intraparenchymal calcification in DNTC [71].

There are very good clinicopathological associations between FTLD-tau as a group, FTD, PSPS and CBS which are discussed below. However, it is still difficult to differentiate the individual pathologies, such as PSP from CBD, based solely on clinical presentation. The other

entities in this group, MST, AGD and DNTC are rare when compared to PiD, PSP and CBD with only a handful of case reports or small case series of each of these pathologies being associated with FTD, PSPS or CBS [7, 26, 44, 45, 53, 71, 73, 93]. Therefore, no strong clinicopathological associations exist for MST, AGD and DNTC.

FTLD-TDP

Similar to FTLD-tau, classification of the subtypes of FTLD-TDP is based on the morphological appearance of the inclusions and the distribution of the lesions. Four subtypes of FTLD-TDP are currently recognized (Fig. 1) [15, 80, 105], although overlap across subtypes have been reported [3]. FTLD-TDP types 1–3 have been described in two different classification schemes by MacKenzie et al. and Sampathu et al. [80, 105], although each classification scheme maps well onto the other. Therefore, FTLD-TDP type 1 in Mackenzie's scheme maps to FTLD-TDP type 3 in Sampathu's scheme; Mackenzie's type 2 maps to Sampathu's type 1 and Mackenzie's type 3 maps to Sampathu's type 2. In this review we use the Mackenzie's classification scheme since that scheme was initially shown to have good association with clinical phenotype. Based on data from four clinicopathological studies [35, 57, 80, 111], the most common subtype was FTLD-TDP type 1 accounting for 41% of cases followed by FTLD-TDP type 3 with 34% and then FTLD-TDP-type 2 with 25% (Fig. 2b). There were no cases of FTLD-TDP type 4 in any of these large clinicopathological studies.

In Mackenzie's scheme, FTLD-TDP type 1 is characterized by a combination of neuronal cytoplasmic inclusions (NCI) and short, comma shaped, dystrophic neurites in frontotemporal cortex, as well as the common occurrence of neuronal intranuclear inclusions; FTLD-TDP type 2 by a predominance of long thicker dystrophic neurites and minimal to absent NCI in frontotemporal cortex, and FTLD-TDP type 3 by a predominance of NCI in frontotemporal cortex or the dentate granule cell layer of the hippocampus and absent to minimal dystrophic neurites in cortex (Fig. 5). FTLD-TDP type 4 is characterized by a predominance of intranuclear inclusions, dystrophic neurites and absent to little NCI [95], and is associated with mutations in the valosin containing protein gene [128]. There is good association between FTLD-TDP types and clinical syndromes as discussed below.

FTLD-FUS

This newest FTLD category consists of three relatively rare diseases: neuronal intermediate filament inclusion disease (NIFID) [16, 52], basophilic inclusion body disease (BIBD) [74] and atypical FTLD with ubiquitin-only

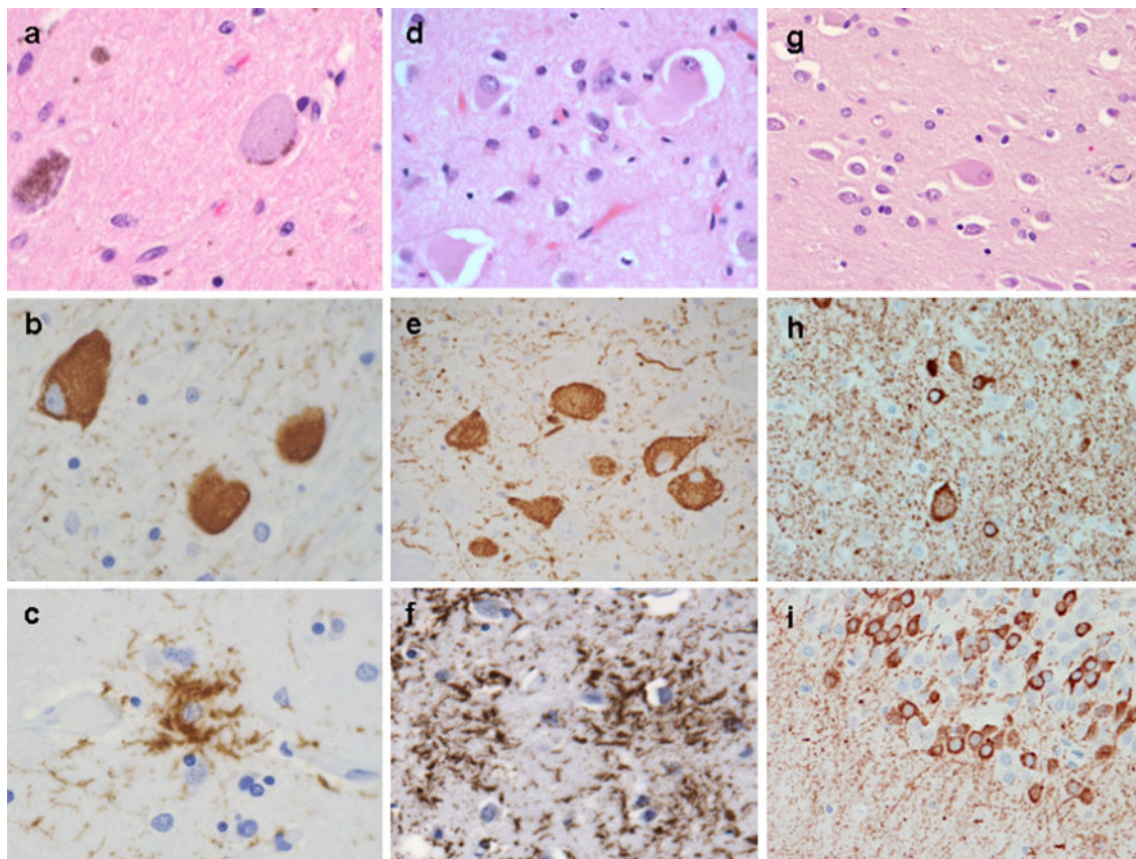


Fig. 3 Histological features of the more common 4R FTLD-tau molecular pathologies. PSP features, including globose NFT with H&E (a) and tau (b), and a tufted astrocyte (c) with tau immunohistochemistry. CBD features, including ballooned neurons with H&E (d), and pretangles in basal nucleus (e) and astrocytic plaques in the

cortex (f) both with tau immunohistochemistry. Features of a *MAPT* mutation (P301L) with tau deposition, including ballooned neurons with H&E (g) and threads, ballooned neurons and pretangles in cortex (h), and pretangles in dentate fascia (i) with tau immunohistochemistry

immunoreactive changes (aFTLD-U) [54, 82, 103] (Fig. 1). These three entities share the fact that they all show striking FUS immunoreactivity [92, 96, 97], but there are differences between each of them that allow each to be considered a separate pathological entity (Fig. 6). The first, NIFID, originally known as neurofilament inclusion body disease [52], is characterized by the presence of variable shaped inclusions that appear more eosinophilic on hematoxylin and eosin (H&E), variable immunoreactivity to ubiquitin, but strikingly immunoreactivity to intermediate filaments, including neurofilament and alpha-internexin [18, 58, 122]. Similar to NIFID, in BIBD, the inclusions are visible on H&E, although in BIBD the inclusions appear basophilic. Unlike in NIFID, antibodies to epitopes of neuronal intermediate filaments do not immunostain the neuronal inclusions, however, like NIFID, ubiquitin staining is variable in BIBD. The third FTLD-FUS entity, aFTLD-U, differs from both NIFID and BIBD as inclusions are not observed on H&E. In addition, aFTLD-U can be further differentiated from NIFID since the inclusions are not immunoreactive to intermediate filaments, and can be

further differentiated from BIBD since vermiform intranuclear inclusions present in aFTLD-U are absent or rare in BIBD [83]. Motor neuron degeneration is found in around 50% of NIFID and BIBD cases but has not been reported in aFTLD-U. One feature that appears to be characteristic of the FTLD-FUS group is striking early caudate atrophy [63, 106]; by the time of autopsy, the caudate nucleus usually has a concave appearance.

FTLD-other

The FTLD-other category is reserved for diseases in which the major protein associated with the disease entity remains unknown. Currently, there are two rare pathological entities in this category [123]. The first, FTLD without inclusions (FTLD-ni), is diagnosed when there is histological evidence of frontotemporal neuronal loss and gliosis but all routine and immunohistochemical stains fail to reveal the presence of any inclusions. The term FTLD-ni is the preferred terminology, replacing the older terminology of dementia lacking distinctive histology. The second,

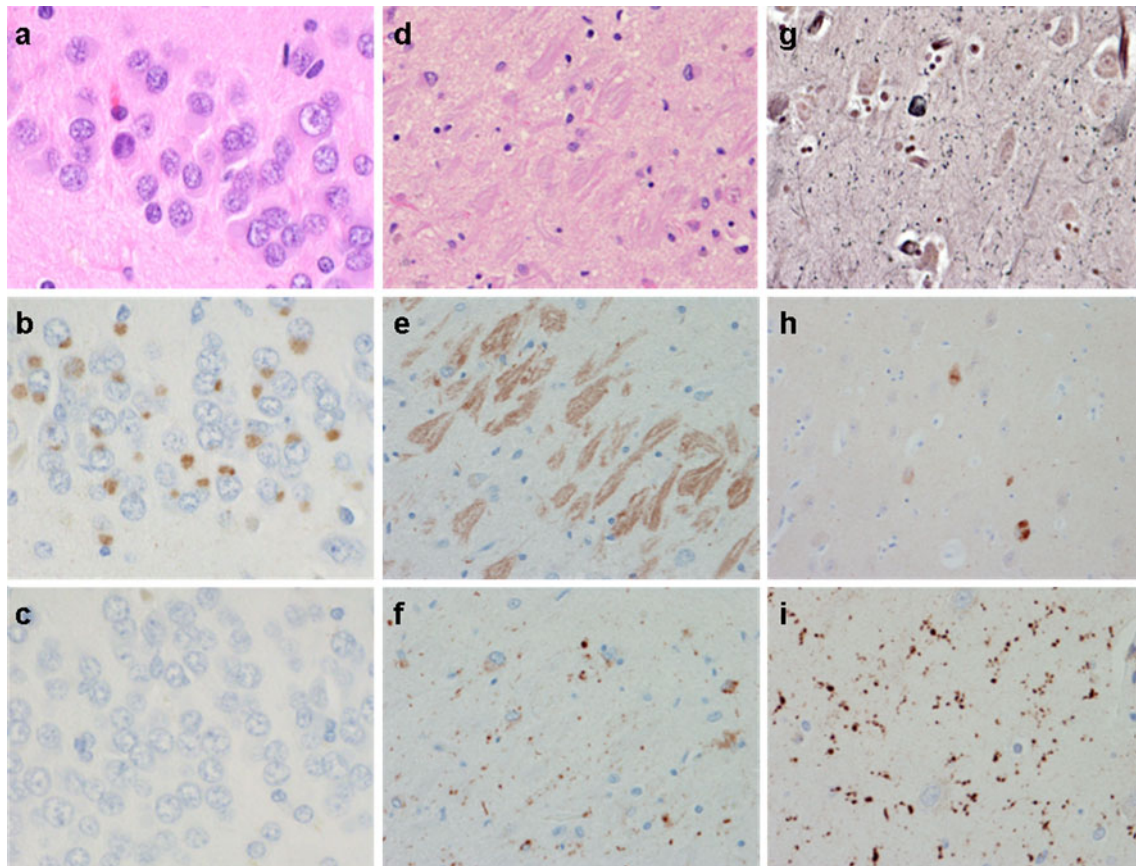


Fig. 4 Histological features of the 3R, 3R + 4R and remaining 4R FTLD-tau molecular pathologies. Features of Pick disease, including globose Pick bodies in dentate fascia with H&E (a) and with 3R tau (b), but negative for 4R tau (c). Features of DNTC, including extracellular NFT with H&E (d) and with 3R tau (e), but mostly

negative for 4R tau (note some neurites and glial 4R tau immunoreactivity) (f). Features of AGD, including argyrophilic grains with Bielschowsky (g) and sparse pretangles but negative grains with 3R tau (h), and many grains with 4R tau (i)

FTLD with immunohistochemistry against proteins of the ubiquitin proteasomal system (FTLD-UPS), is diagnosed when there are ubiquitin or p62 immunoreactive inclusions, that are negative to tau, alpha-synuclein, alpha-internexin, TDP-43 and FUS. The majority of FTLD-UPS cases are associated with mutations in the charged multivesicular body protein 2B (CHMP2B) gene [40], although a few sporadic cases exist [123]. The FTLD-other category may also be used for extremely rare FTLD cases that do not conform to the pathological criteria discussed above.

The frontotemporal dementias

Three classic syndromes are subsumed under the rubric of frontotemporal dementia (FTD): bvFTD, PNFA and SD [94]. The behavioral variant of FTD is characterized by changes in behavior and personality, resulting in disruption of social interactions. Executive dysfunction is common. Symptoms suggestive of the diagnosis of bvFTD include apathy, disinhibition, poor planning, poor organization,

hyperactive behaviors such as wandering and pacing, as well as changes in eating, sleeping and sexual behaviors. The age of onset of patients with bvFTD is typically less than 65 years with an average age of onset around 58 [47]. The syndrome of bvFTD can be associated with many different FTLD pathologies. However, given recent molecular pathological discoveries, some investigators have argued that there may be subtypes of bvFTD that more tightly link to specific molecular pathologies (Fig. 7). Recent clinicopathological studies have identified, for example, a clinical syndrome of behavioral and personality change dominated by hypersexual and hyperphagic behaviors, prominent stereotypy and obsessionality that tightly links to the molecular pathology of aFTLD-U [113, 123]. This finding links two previous reports of (1) striking striatal atrophy in patients with bvFTD and stereotypy [61], and (2) striking striatal atrophy in aFTLD-U [63]. An additional feature common to these patients is a very young age at onset, as patients tend to present with a mean age of onset of around 40 years. Another less well-established association is that of bvFTD with psychosis and FTLD-

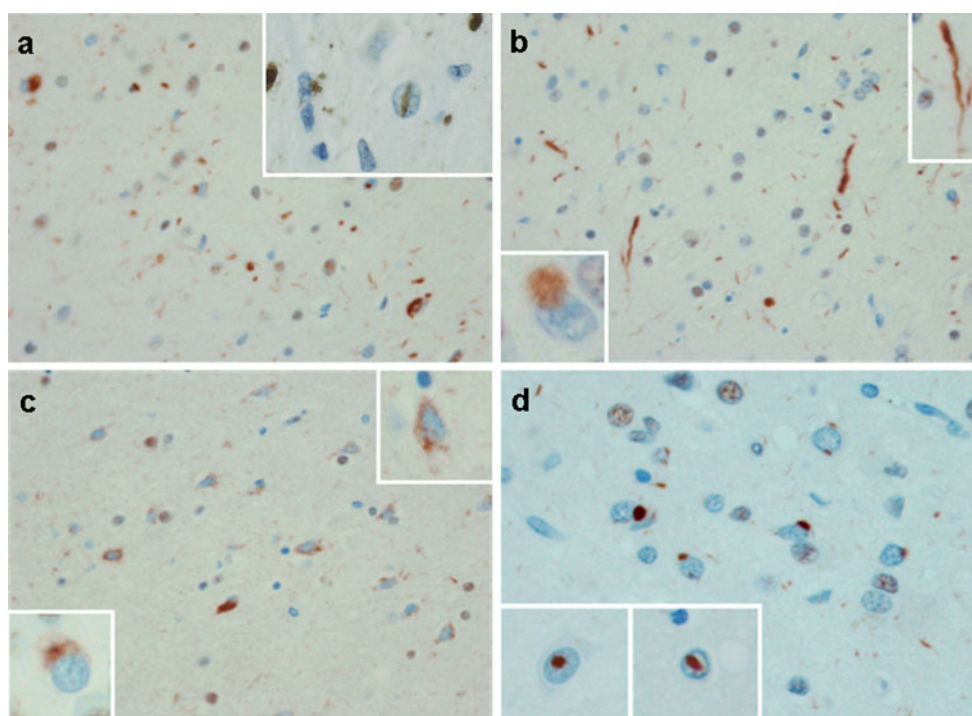


Fig. 5 Histological features of FTLD-TDP types based on the classification of Mackenzie et al. **a** Features of FTLD-TDP type 1 (Sampathu, type 3) including short, thin neurites and pleomorphic neuronal cytoplasmic inclusions (NCI) with neuronal intranuclear inclusions (*upper inset*). **b** shows features of FTLD-TDP type 2 (Sampathu, type 1) including long, thick neurites in cortex (*upper inset*) as well as a Pick-body-like NCI in dentate fascia (*lower inset*).

c Features of FTLD-TDP type 3 (Sampathu, type 2) including NCI and granular cytoplasmic staining (pre-inclusions—*upper inset*) with irregular granular NCI in dentate fascia (*lower inset*). **c, d** Features of FTLD-TDP type 4 including NCI, neurites and many neuronal intranuclear inclusions (*lower insets*). All with TDP-43 immunohistochemistry

TDP type 3 with MND [76]. Unlike bvFTD associated with aFTLD-U, bvFTD associated with FTLD-TDP type 3 tends to have a more typical age of onset; patients are also not hypersexual, stereotypic or hyperphagic. This latter bvFTD with psychosis sub-syndrome is reminiscent of the syndrome of dementia with Lewy bodies [22]. One could argue that these ‘sub-syndromes’ are all bvFTD, although there appears to be benefit in separating these sub-syndromes in order to better predict the underlying molecular pathology (Fig. 7).

The syndrome of PNFA is characterized by ‘non-fluent’ speech output with agrammatic and telegraphic speech [94]. Frequently accompanying the aphasia is a motor speech disorder known as apraxia of speech (AOS) [51, 99]. Many researchers do not separate AOS from PNFA and hence the term PNFA typically implies the presence of aphasia and AOS [34]. Detailed studies of PNFA, however, have demonstrated that the presence of AOS is tightly associated with FTLD-tau, especially PSP and CBD [26, 51]. Neuroanatomic studies have also demonstrated that the presence of AOS correlates with atrophy of the premotor and supplemental motor cortices [51], regions that are prominently and focally affected in PSP and CBD. It is therefore not surprising that the most common pathologies

underlying AOS, and hence PNFA, are PSP and CBD, as discussed below. Predicting PSP over CBD, and vice versa, is difficult in PNFA, although there is some evidence to suggest that pure or dominant AOS is more suggestive of PSP, while AOS plus prominent aphasia is more suggestive of CBD [50]. This hypothesis would be supported by the fact that CBD pathology is associated with slightly less focal atrophy than PSP [59], and tends to also involve the inferior posterior lateral frontal lobe or Broca’s area [129]. It remains to be determined whether aphasia without AOS is linked to a specific molecular pathology but evidence exists to suggest that it is linked to FTLD-TDP [26], particularly FTLD-TDP type 1 pathology [111], as discussed below.

The term SD is reserved for a clinical syndrome characterized by fluent speech with prominent anomia, loss of word and object meaning, and poor single word comprehension [110, 127]. The clinical syndrome of SD has been found to highly associate with FTLD-TDP type 2 pathology [39, 57, 80, 111]. Patients with SD commonly present with aphasia that is associated with left anterior medial temporal lobe atrophy [21, 91]. The right temporal lobe is typically also affected in SD, and in some instances is even more atrophic than the left [118]. In such cases of right

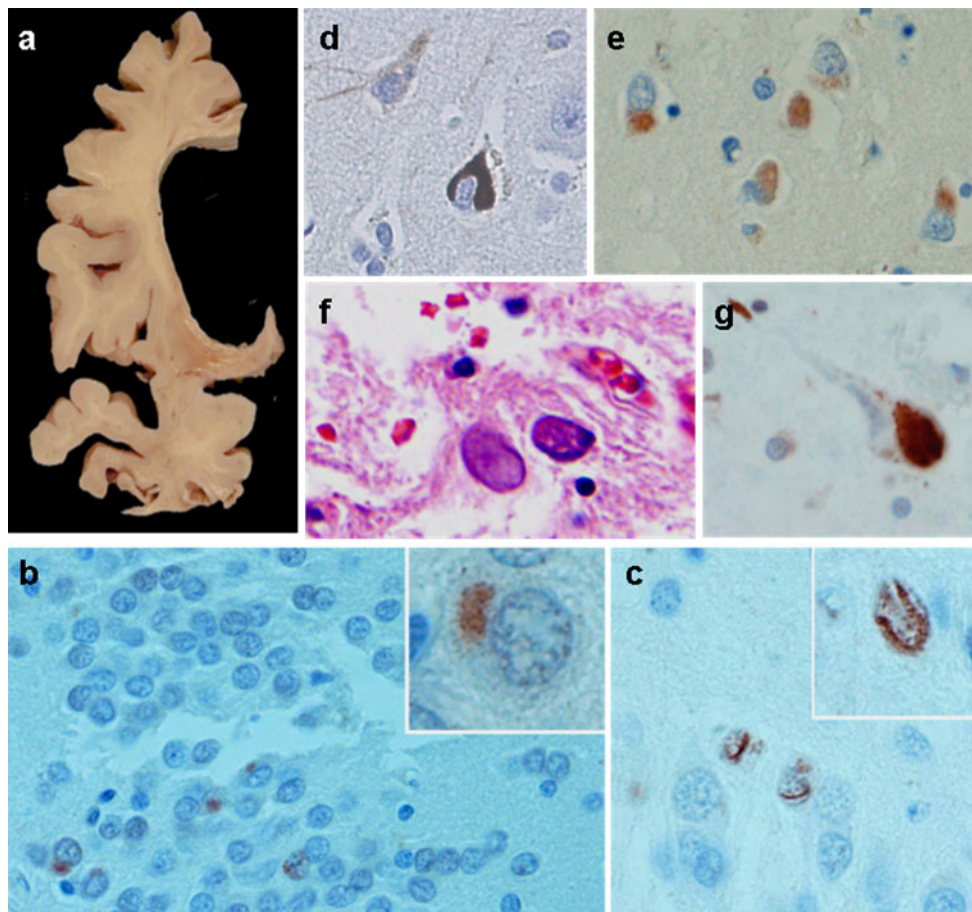


Fig. 6 Histological features of FTLD-FUS molecular pathologies. Features of aFTLD-U, including striking striatal atrophy (a), neuronal cytoplasmic inclusions (NCI) (b) and vermiform neuronal intranuclear inclusions (c) with FUS immunohistochemistry. Features of NIFID, including internexin positive NCI (note weak cytoplasmic

staining in pyramidal neurons) (d) and FUS positive NCI in cortex with FUS immunohistochemistry (e). Features of BIBD with juvenile motor neuron disease, including large basophilic cytoplasmic inclusions (f) that are positive with FUS immunohistochemistry (g)

greater than left temporal lobe atrophy, the clinical presentation of SD is dominated, not by aphasia, but by prosopagnosia and behavioral dyscontrol [64, 107, 118]. Not surprisingly, therefore, behavioral changes have been shown to be prominent in SD [112]. Unlike the amonic presentation of SD that has been strongly associated with FTLD-TDP type 2 pathology, the behavioral/prosopagnostic presentation of SD is more easily confused with bvFTD. Detailed studies on SD, however, have shown that the behavioral/prosopagnostic presentation of SD also links to FTLD-TDP type 2 pathology. One study suggested that the presence or absence of prosopagnosia is helpful in differentiating SD with greater right temporal lobe atrophy and behavioral features from bvFTD with prominent right temporal lobe atrophy [62]. This is important since it appears that bvFTD with prominent right temporal lobe atrophy is associated with FTLD-tau pathology [62].

Some patients present with symptoms suggestive of a diagnosis of FTD, however, clinical and electrophysiological examination confirms coexisting MND (FTD-

MND) [23, 79]. In FTD-MND, the FTD syndrome is typically characterized by behavioral change, although cases with prominent aphasia have been described [19]. The MND domain can be characterized by bulbar problems such as swallowing or speech difficulties [42, 76], although limb weakness associated with fasciculations in the weak limb is also common. Signs of upper motor neuron disease or pyramidal tract signs, such as spasticity, hyper-reflexia, Babinski and clonus, are less common, but have been described [55]. A clinical diagnosis of FTD-MND has almost perfect association with molecular pathology as revealed below.

Progressive supranuclear palsy and corticobasal syndromes

The terms PSPS and CBS are reserved for clinical diagnosis, while the terms PSP and CBD are now reserved for pathological diagnosis. Progressive supranuclear palsy

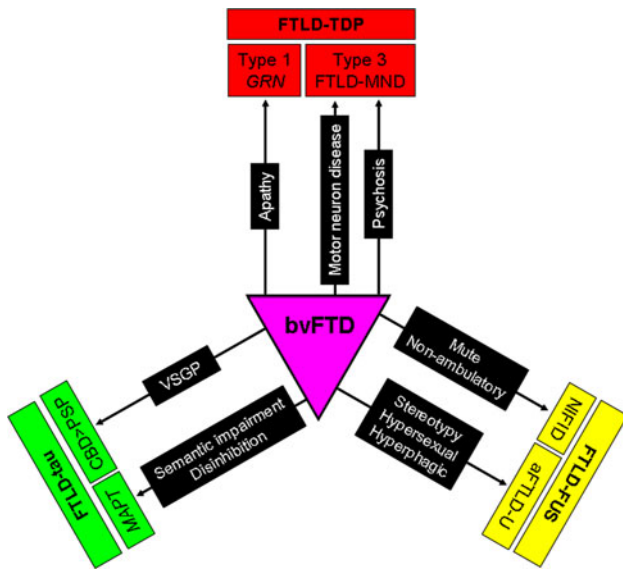


Fig. 7 Diagram showing clinical features that help to predict the underlying FTLT-tau, FTLT-TDP or FTLT-FUS molecular pathology in patients presenting with bvFTD. VSGP vertical supranuclear gaze palsy. FTLT-TDP types based on the classification of Mackenzie et al.

syndrome is characterized by a symmetric akinetic syndrome with prominent axial rigidity, vertical supranuclear gaze palsy (VSGP) and early falls [131]. Apathy is common in PSPS, while other behavioral and personality changes are less common [4, 10, 60]. A diagnosis of classic PSPS, i.e. without prominent behavioral dyscontrol, is highly predictive of PSP pathology [56]. Recent evidence suggests, however, that patients with VSGP, as in PSPS, but prominent behavioral dyscontrol and dementia as in bvFTD, may actually more likely be CBD, instead of PSP (manuscript in press) (Fig. 7). Corticobasal syndrome is characterized by asymmetric cortical and extrapyramidal signs occurring together [8]. Cortical signs include limb apraxia, action-induced myoclonus and alien limb phenomenon, while limb rigidity and dystonia are relatively common extrapyramidal features. Unfortunately, CBS shows poor association to any single molecular pathology [9], although CBD and PSP, both FTLT-tau, account for the majority of cases of CBS.

Clinicopathological associations

Four large studies representing work from six different centers in the United States, Canada, United Kingdom and Australia have been published on clinicopathological associations between FTLT, and specific FTD, PSPS and CBS clinical diagnoses [38, 56, 67, 111]. When data from all four studies were pooled, variable clinicopathological associations were observed. The observed proportions of

FTLD-tau to FTLT-TDP differed significantly across the different clinical syndromes ($p < 0.0001$) (Fig. 8). In addition, the observed proportions of FTLT-tau to FTLT-TDP differed from that expected by chance in all clinical groups ($p < 0.05$), except for bvFTD ($p = 0.22$). Almost all cases of PSPS and CBS had FTLT-tau pathology, while 100% of FTD-MND cases had FTLT-TDP pathology. Semantic dementia was associated with FTLT-TDP, with 83% of cases showing FTLT-TDP pathology, and PNFA was associated predominantly with FTLT-tau (70%). The bvFTD syndrome showed almost equal proportions of FTLT-tau and FTLT-TDP.

Associations between clinical syndromes and specific FTLT-tau pathologies are shown in Fig. 9a. The observed proportions of FTLT-tau pathologies (PiD, CBD, PSP, AGD) differed significantly across the different clinical syndromes ($p < 0.0001$). In addition, the observed proportions of FTLT-tau pathologies differed from that expected by chance in all clinical groups ($p < 0.05$), except for PNFA ($p = 0.10$). Of the patients diagnosed with SD and having FTLT-tau pathology ($n = 3$), all showed PiD, suggesting that PSP and CBD are extremely unlikely to be associated with the SD syndrome. Another excellent association was noted between PSPS and PSP pathology, where over 90% of patients with PSPS had PSP, and the remainder had CBD. Weaker associations were found between the clinical diagnosis of bvFTD and pathology, although the data showed that if bvFTD was associated with FTLT-tau there was almost a 70% chance that the pathology would be PiD. The diagnosis of PNFA was not associated with any specific FTLT-tau pathology, and was split almost equally between PiD, CBD and PSP. The most common tau pathology associated with CBS was CBD, followed by PSP and PiD.

For the FTLT-TDP group, when we pooled data we also found variable clinicopathological associations [25, 35, 57,

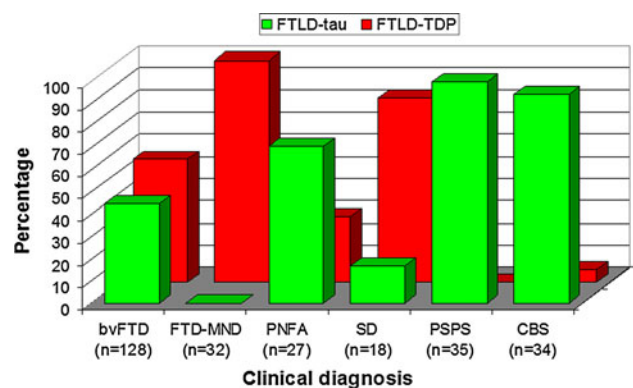


Fig. 8 Bar chart showing the proportion of patients with FTLT-tau or FTLT-TDP within each clinical diagnosis based on pooled data from large clinicopathological studies. Actual number of subjects with each clinical diagnosis is also shown

80] (Fig. 9b). The observed proportions of FTLT-DTP types differed significantly across the different clinical syndromes ($p < 0.0001$) and differed from that expected by chance in all clinical groups ($p < 0.05$). The strongest associations were identified between FTD-MND and FTLT-DTP type 3 pathology, between SD and FTLT-DTP type 2 pathology, and between PNFA and FTLT-DTP type 1 pathology. These clinicopathological associations support the sub-typing of FTLT-DTP. Once again, bvFTD was not as strongly associated with any one type, although the most common was FTLT-DTP type 1. As mentioned earlier, one has to wonder whether the syndrome of bvFTD is too loose and hence needs to be revised. One has to also wonder whether bvFTD associated with FTLT-DTP type 2 represents misdiagnosed cases of SD.

There are no large clinicopathological studies that take into account FTLT-tau, FTLT-DTP and FTLT-FUS. Therefore, less is known about associations between FTLT-FUS, FTD, PSPS and CBS. With that said, there are many small case series and a few large ones that allow us

to pool data on 69 FTLT-FUS cases and get a glimpse of possible associations between clinical syndromes and FTLT-FUS [16, 54, 58, 90, 92, 96, 97, 123] (Fig. 10). It appears that NIFID is associated with three syndromes; the most common of which is bvFTD (Fig. 10a). It can also be associated with FTD-MND. A third syndrome associated with NIFID is a CBS/primary lateral sclerosis (PLS) hybrid which not only shows features of CBS but also prominent upper motor neuron signs such as spasticity, Babinski and clonus. On the flip side, one could say that this CBS/PLS syndrome is characterized by asymmetric upper motor neuron disease plus parkinsonism. Many syndromes can underlie the pathology of BIBD including bvFTD, FTD-MND, PSPS, CBS/PLS and others, such as, pure MND (Fig. 10b) or juvenile amyotrophic lateral sclerosis. An excellent association was, however, identified between aFTLT-U and bvFTD (Fig. 10c), as discussed earlier.

There are no clinicopathological studies on FTLT-UPS or FTLT-ni. Furthermore, less than a handful of such cases exists [123] with the exception of the CHMP2B subtype of FTLT-UPS which is discussed below.

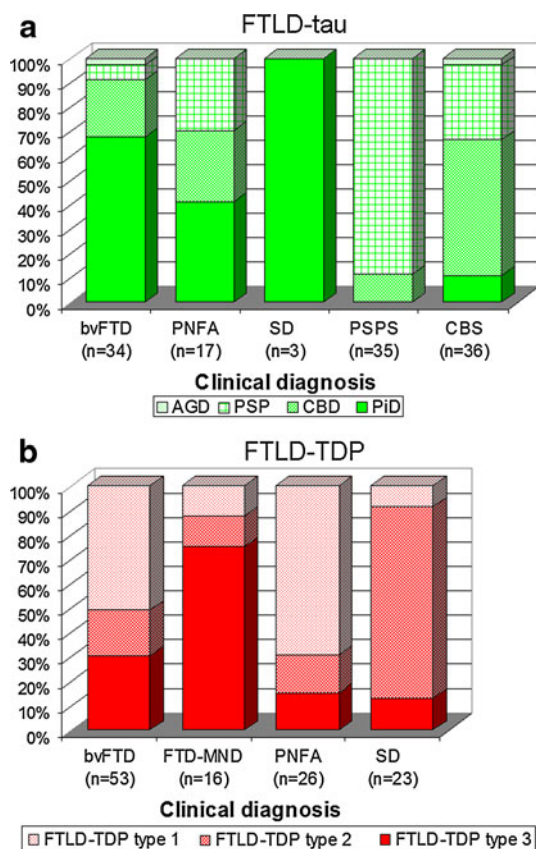


Fig. 9 Bar charts showing the proportion of patients with specific FTLT-tau (a) or FTLT-DTP (b) pathologies within each clinical diagnosis, based on pooled data from large clinicopathological studies. Actual number of subjects with each clinical diagnosis is also shown. FTLT-DTP types based on the classification of Mackenzie et al.

Clinicopathological associations of genetic variants of FTLT

Although the majority of FTLT cases are sporadic, a small familial subset is associated with gene mutations. In many instances, these gene mutations result in a syndrome presenting similar to one of the syndromes described above. Six genes are currently associated with FTLT. Mutations in the microtubule-associated tau gene, *MAPT* [43], are typically associated with neuronal and glial tau deposition (Fig. 3), and although there is no consistent pattern to the tau deposition [125] it can sometimes resemble other sporadic tauopathies such as PiD, PSP and CBD [32]. Most commonly, patients with *MAPT* mutations present with a bvFTD-like phenotype [100] in which extrapyramidal features may also be present. Not surprisingly, however, given the prominent anterior medial temporal lobe atrophy identified in patients with a *MAPT* mutation [104, 130], an SD-like presentation associated with features of bvFTD (or bvFTD with semantic impairment), in particular disinhibition, has also been associated with *MAPT* mutations [62, 100, 111] (Fig. 7). Another gene associated with familial FTLT is progranulin (GRN) [5, 24]. Unlike *MAPT* that is associated with tau, GRN mutations are associated with TDP-43 deposition; specifically FTLT-DTP type 1 pathology with neuronal intranuclear inclusions [17, 49, 81]. It is now well recognized that familial GRN is strongly associated with a CBS-like presentation [66, 86, 116], as well as a PNFA-like presentation [88, 111, 114] and a bvFTD-like presentation [66], especially with apathy [101] (Fig. 7). Mutations in

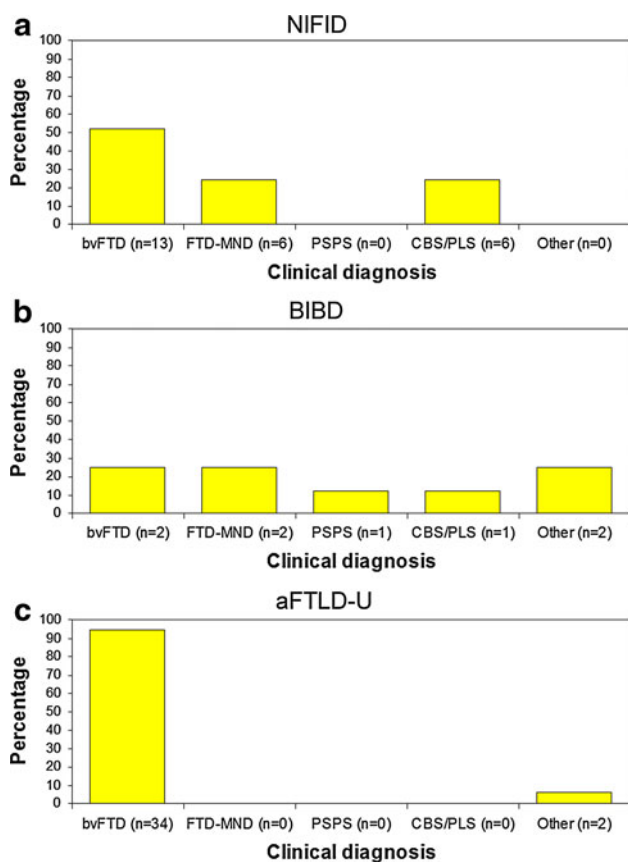


Fig. 10 Bar charts showing the proportion of patients with each clinical diagnosis in the FTLD-FUS variants, NIFID (a), BIBD (b), and aFTLD-U (c). Data is pooled from small case series on FTLD-FUS variants. Actual number of subjects with each clinical diagnosis is also shown

other genes associated with FTLD pathology are extremely rare and include mutations in the VCP gene [128], the CHMP2B gene [109], the TDP-43 (TARDBP) gene [6] and the FUS gene [132]. While mutations in the VCP gene are associated with a syndrome combining FTD, Paget's disease of the bone and myopathy [128], mutations in CHMP2B are typically associated with a bvFTD-like syndrome [36] and has only been identified in two families to date [36, 124]. Mutations in the TARDBP and FUS genes are predominantly associated with familial MND [65, 75, 117, 126], but rarely with an FTD-like syndrome.

These genetic clinicopathological associations differ somewhat from the clinicopathological associations identified in sporadic FTD and related disorders. For example, clinical diagnoses of PNFA and CBS are more likely to be associated with FTLD-tau in sporadic cases while in familial cases they are more likely to be associated with FTLD-TDP, particularly type 1, pathology. However, a diagnosis of sporadic or familial bvFTD could be associated with either FTLD-tau or FTLD-TDP. Semantic dementia and PSP are almost always sporadic.

Overlap with Alzheimer's disease

Distinguishing FTLD from Alzheimer's disease (AD) is also of paramount importance. AD, like DNTC, is characterized by 3R + 4R tau deposition. Alzheimer's disease is usually associated with loss of episodic memory. However, there have been reports of AD being associated with some variants of FTD, commonly PNFA, and CBS which would not be captured in clinicopathological studies of FTLD pathology [41, 67, 68, 77, 108]. Recent work has revealed that AD is more likely present when the aphasia syndrome is dominated by phonological errors, i.e. logopenic progressive aphasia [89], a syndrome that can be mistaken for PNFA. A diagnosis of frontal variant AD is given when the ante-mortem clinical diagnosis is bvFTD and the pathological diagnosis is AD. Such cases occur but are rare, with AD pathology being reported in only 5–6% of bvFTD cases [67, 69].

Summary

In this review, we have discussed the neuropathological background of phenotypic variability of FTD. Some clinical syndromes have good–excellent associations with the FTLD pathological group, and even with specific molecular pathologies. These syndromes allow for better prediction of pathology than those syndromes with average–poor clinicopathological associations. One such syndrome with excellent prediction of underlying pathology is FTD-MND. Other syndromes, however, show little association with a single FTLD pathological group and even less association with any single FTLD pathology. This latter finding, implores us, as researchers, to continue to dissect the complex labyrinth of FTLD.

Conflict of interest The authors declare that they have no conflict of interest.

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