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REVIEW

Frontotemporal lobar degeneration: defining phenotypic diversity through personalized medicine

David J. Irwin · Nigel J. Cairns · Murray Grossman · Corey T. McMillan · Edward B. Lee · Vivianna M. Van Deerlin · Virginia M.-Y. Lee · John Q. Trojanowski

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Abstract Frontotemporal lobar degeneration (FTLD) comprises two main classes of neurodegenerative diseases characterized by neuronal/glial proteinaceous inclusions (i.e., proteinopathies) including tauopathies (i.e., FTLD-Tau) and TDP-43 proteinopathies (i.e., FTLD-TDP) while other very rare forms of FTLD are known such as FTLD with FUS pathology (FTLD-FUS). This review focuses mainly on FTLD-Tau and FLTD-TDP, which may present as several clinical syndromes: a behavioral/dysexecutive syndrome (behavioral variant frontotemporal dementia); language disorders (primary progressive aphasia variants); and motor disorders (amyotrophic lateral sclerosis, corticobasal syndrome, progressive supranuclear palsy syndrome). There is considerable heterogeneity in clinical presentations of underlying neuropathology and current clinical criteria do not reliably predict underlying proteinopathies *ante-mortem*. In contrast, molecular etiologies of hereditary FTLD are consistently associated with specific proteinopathies. These include *MAPT* mutations with FTLD-Tau and *GRN*, *C9orf72, VCP* and *TARDBP* with FTLD-TDP. The last decade has seen a rapid expansion in our knowledge of the molecular pathologies associated with this clinically and neuropathologically heterogeneous group of FTLD diseases. Moreover, in view of current limitations to reliably diagnose specific FTLD neuropathologies prior to autopsy, we summarize the current state of the science in FTLD biomarker research including neuroimaging, biofluid and genetic analyses. We propose that combining several of these biomarker modalities will improve diagnostic specificity in FTLD through a personalized medicine approach. The goals of these efforts are to enhance power for clinical trials focused on slowing or preventing progression of spread of tau, TDP-43 and other FTLD-associated pathologies and work toward the goal of defining clinical endophenotypes of FTD.

Keywords FTLD · TDP-43 · Tau · ALS · C9orf72 · GRN · MAPT

D. J. Irwin · V. M. Van Deerlin · V. M.-Y. Lee · J. Q. Trojanowski (✉)
Department of Pathology and Laboratory Medicine, Center for Neurodegenerative Disease Research, Institute on Ageing, University of Pennsylvania School of Medicine, HUP Maloney 3rd Floor, 36th and Spruce Streets, Philadelphia, PA 19104-4283, USA
e-mail: trojanow@mail.med.upenn.edu

D. J. Irwin · M. Grossman · C. T. McMillan
Department of Neurology, Penn Frontotemporal Degeneration Center, University of Pennsylvania, Philadelphia, PA 19104, USA

N. J. Cairns
Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, MO 63110, USA

E. B. Lee
Translational Neuropathology Research Laboratory, Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA

Introduction

Frontotemporal dementia (FTD) consists of a spectrum of clinical syndromes [6, 75, 135, 179, 201] associated with several underlying neurodegenerative diseases characterized by frontotemporal lobar degeneration (FTLD) [40, 140]. FTD often affects individuals younger than 65 years old and is nearly as common as Alzheimer's disease (AD) in this age range (i.e., prevalence of ~15–22/100,000 person-years) [122, 180]. Men and women are both roughly

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equally affected in most population-based studies, and the disorder has a worldwide distribution [122, 175]. Many cases of FTD have a family history of a similar dementing disorder with or without amyotrophic lateral sclerosis (ALS) [127, 218]. Non-genetic environmental risk factors have been studied in only small retrospective series, but these find a possible link between a history of head trauma and increased risk of FTD [114, 185].

FTLD neuropathology may present as one of three clinical FTD syndromes: a behavioral–dysexecutive disorder—behavioral variant FTD (bvFTD) [179]—the most frequent phenotype; three clinically distinct language disorders including primary progressive aphasia (PPA) variants [75] (non-fluent/agrammatic variant, naPPA; semantic variant, svPPA and, rarely, a logopenic variant, lvPPA); in addition to motor disorders such as ALS [201], corticobasal syndrome (CBS) [6], or progressive supranuclear palsy (PSP) syndrome [135]. There is considerable heterogeneity of clinical presentations and underlying pathology, as further described below. In particular, bvFTD and CBS clinical syndromes have a range of underlying neuropathologies, while naPPA is more commonly associated with tauopathies and svPPA with TDP-43 deposition, but these associations are not absolute. Motor presentations in FTD with ALS (FTD-ALS) and PSP are reliable indications of underlying TDP-43 and tauopathy, respectively [64]. There are few autopsy studies of the recently defined lvPPA variant and in vivo imaging studies suggest that this phenotype is largely due to an atypical presentation of AD neuropathology [178]; however, forms of FTLD neuropathology have also been described with this syndrome [154]. Thus, clinical syndrome alone cannot reliably predict underlying FTLD neuropathology ante-mortem. Indeed, clinical criteria for FTD syndromes are under continuous evaluation and revision to help refine the diagnostic entities to better reflect underlying neuropathology and although broadly accepted, there is some controversy over the specific diagnostic features of FTD/PPA. Further work using well-annotated autopsy-confirmed samples and emerging biomarkers will hopefully lead to the concept of an endophenotype (i.e., clinical syndrome that predicts underlying neuropathology).

There has been a rapid increase in the past decade of knowledge about genetic etiologies of FTLD and the molecular pathologies associated with this clinically and neuropathologically heterogeneous group of diseases. FTLD neuropathology is characterized by the pathological aggregation of misfolded proteins, either in neurons or glial cells, or both. Further, increasing evidence from animal [48, 98] and cell models [84] of FTLD-Tau and to a lesser extent FTLD-TDP [174] and other neurodegenerative conditions implicate neuron-to-neuron transmission of misfolded proteins as a central process for disease progress or spread and subsequent neurodegeneration (for review please see [83]). These findings mirror hierarchical staging models of human neurodegenerative disease [29, 33, 35] and morphological studies of the spatial organization of inclusions [8]. However, AD, FTLD and other non-prion neurodegenerative diseases do not appear to be transmitted between humans and cattle like prions [100]. The central aspect of protein aggregation and spread throughout the CNS provides a promising target for therapeutic development for these currently incurable disorders and accurate as well as rapid *ante-mortem* diagnosis is crucial for this effort.

To follow, we describe the pathological substrates of the FTLD pathologies underlying the different FTD variants and key clinical and genetic associations with a special focus on current and future efforts to improve diagnostic accuracy for the development of disease-modifying therapies.

TDP-43 proteinopathies (FTLD-TDP and ALS)

Neuropathology

About 50 % of all FTLD is characterized by inclusion bodies containing the transactive response (TAR) DNA-binding protein of 43 kDa (FTLD-TDP). TDP-43 was first identified in 2006 as the main constituent of ubiquitin-positive, tau-negative and α-synuclein-negative inclusions [5, 173], which was previously called FTLD with ubiquitin-positive inclusions or FTLD-U [40, 140]. TDP-43 is also the characteristic inclusion found in >95 % of ALS patients including nearly all sporadic cases of ALS [169, 173]. Further, there is considerable clinical overlap between ALS and FTD corresponding to the regional distribution of TDP-43 neuropathology [71] and both share common genetic etiologies [55, 169, 181]. Thus ALS and FTLD-TDP are best viewed as a clinicopathological continuum of TDP-43 proteinopathies [71, 130].

TDP-43 is a nuclear protein implicated in exon skipping and transcription regulation [18, 38, 176]. As such, TDP-43 is typically seen in most nuclei of normal cells. In disease, this protein becomes aberrantly localized to the cytoplasm where it forms cytoplasmic inclusions [173]. There are several potential mechanisms for neurodegeneration associated with TDP-43 proteinopathies (reviewed in [130]) (Fig. 1) including RNA sequestration and dysfunction, loss of normal TDP-43 function through mislocalization and nuclear clearance and potential toxicity of pathological TDP-43 aggregates.

The neuropathology of FTLD-TDP and ALS is generally characterized by TDP-43-positive neuronal cytoplasmic inclusions (NCIs), neuronal intranuclear inclusions (NIIs),

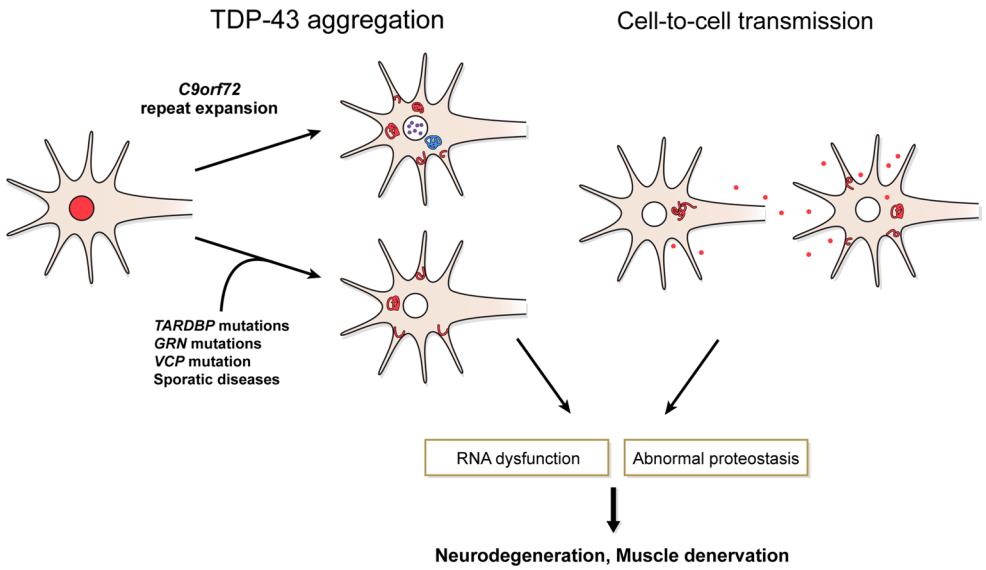

Fig. 1 TDP-43-mediated neurodegeneration in FTLD-TDP/ALS. Pathological TDP-43 translocation from the nucleus (*red*) to the cytoplasmic compartment occurs in sporadic disease and hereditary cases with *C9orf72, TARDBP, GRN,* and *VCP* mutations. *VCP* mutation cases also have intranuclear TDP-43 inclusions (not shown). *C9orf72* mutation is associated with additional RNA foci in the nucleus (*green*) and cytoplasmic dipeptide repeat inclusions (*blue*), but the specific association with neurodegeneration is currently unclear. Neuron-to-neuron transmission is the likely mechanism for the non-random pattern of spread of neurodegeneration. These processes are linked to RNA dysfunction and abnormal proteostasis, ultimately leading to neuronal cell loss and/or muscle denervation from lower motor neuron loss. Drug development efforts to slow or halt this process may provide novel disease-modifying therapies in the future

dystrophic neurites (DNs), and glial cytoplasmic inclusions (GCIs) often in association with accumulations of ubiquitin and p62 [41]. Biochemistry of postmortem brain samples of these disorders shows TDP-43 to be abnormally phosphorylated, ubiquitinated and cleaved to generate C-terminal fragments [5, 173]. Interestingly, C-terminal fragments appear to be more prominent in cortical TDP-43 deposits in comparison with lower motor neuron inclusions in the spinal cord that contain TDP-43 inclusions that are reactive to both C-terminal and N-terminal domain-specific monoclonal antibodies (MAbs) [99, 125]. The abnormal phosphorylation of the C-terminal region of the protein (pTDP-43) has led to the development of disease-specific antibodies that readily detect pathological aggregates, but leave normal TDP-43 unstained [171]. Thus, pTDP-43 immunohistochemistry (IHC) is the method of choice for detecting FTLD-TDP for routine diagnostic neuropathological evaluation [159]. Interestingly, one MAb generated against amino acid sequence in the RNA-recognition motif (RRM) has a similar immunohistochemical staining pattern to phospho-TDP epitopes, with predominance of reactivity for pathological inclusions and minimal normal nuclear TDP-43 reactivity, suggesting the possibility of phospho-independent pathological conformers of TDP-43 [125]. Rare NCIs may be thioflavin-S positive in spinal cord indicating that they contain amyloid (i.e., beta-pleated sheets), but most TDP-43-immunoreactive inclusions are thioflavin-S negative and those in the hippocampus are never thioflavin-S positive [182]. In contrast, Bigio and coworkers [21] found more widespread thioflavin-S-positive TDP-43 inclusions in neocortical regions and dentate gyrus of the hippocampus in FTLD-TDP. The reasons for these discrepancies are not clear, but they may depend on methodological differences in fixation, tissue preparation and staining techniques. Indeed, Bigio et al. [21] used a modified thioflavin-S staining protocol in their study and also reported exuberant thioflavin-S-positive astrocytosis which does not result in amyloidosis.

The variability in the morphologic types of neuronal inclusions, their distribution, density, and immunohistochemical profile has led to several proposed classifications based broadly on four pathologic subtypes which map more closely with genetic forms of FTLD-TDP but not as closely with clinical phenotypes [41, 139]. The harmonized "Type A" [139] is equivalent to type 3 of Sampathu et al. [188], and Cairns et al. [41] and is characterized by numerous short DNs and crescentic or oval NCIs, concentrated primarily in neocortical layer two (Fig. 2g). Moderate numbers of lentiform or globose NIIs are an inconsistent feature of this subtype. Harmonized "Type B" matches Sampathu et al./Cairns et al. type 2, with moderate numbers of NCIs, throughout all cortical layers, but very few DNs (Fig. 2h). Harmonized "Type C" is the same as Sampathu et al./Cairns et al. type 1,

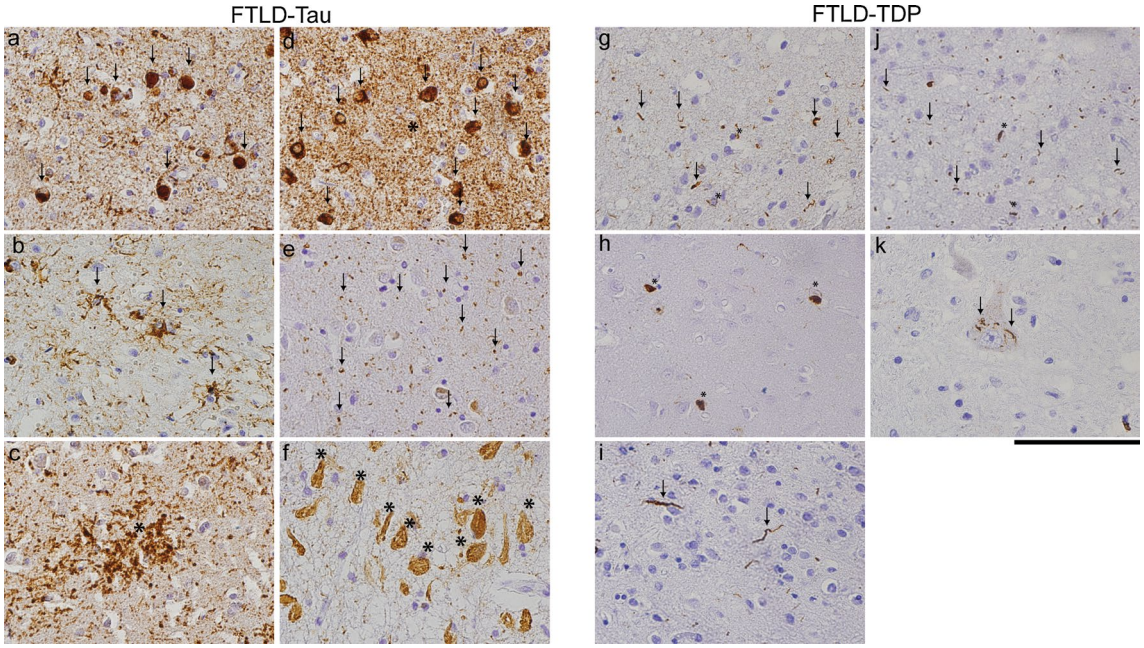

Fig. 2 Neuropathological subtypes of FTLD. Photomicrographs of FTLD-Tau (**a–f**) and FTLD-TDP (**g–k**). Images illustrate characteristic inclusion bodies including neocortical (**a**) round tau-positive Pick bodies (*arrows*) in PiD (**b**) tufted astrocytes (*arrows*) in PSP, **c** astrocytic plaques (*asterisk*) in CBD, **d** tau-positive neuronal inclusions (*arrows*) and threads (*asterisk*) in FTLD-Tau with a *MAPT* mutation (p.P301L), **e** tau-positive grains (*arrows*) in limbic cortex in AGD, **f** extracellular ghost tangles (*asterisks*) in the cornu ammonis in tangle predominant dementia or primary age-related tauopathy (PART). Neocortical sections illustrate in **g–j** FTLD-TDP morphological subtype A (**g**) with superficial layer short dystrophic neurites (*arrows*) and neuronal cytoplasmic inclusions (*asterisks*) containing pathological TDP-43, **h** subtype B with mainly cytoplasmic inclusions (*asterisks*), **i** subtype C with long dystrophic neurites (*arrows*), **j** and subtype D with superficial layer lentiform intranuclear inclusions (*asterisks*) and short dystrophic neurites (*arrows*) while **k** shows skin-like inclusions (*arrows*) in anterior horn cell in ALS. *Scale bar* 100 µm

having a predominance of elongated DNs in upper cortical layers, with very few NCIs (Fig. 2i). Finally, harmonized Type D, Cairns et al. type 4, refers to the pathology associated with FTLD-TDP with VCP mutation (see below) and is characterized by numerous short DNs and frequent lentiform NIIs (Fig. 2j). TDP-43 positive skin (Fig. 2k) or "Lewy-like inclusions" in remaining lower motor neurons along with motor cortex TDP-43 inclusions and corticospinal tract degeneration characterize ALS pathologically. Notably, efforts to stage the spread or progression of TDP-43 pathology in FTLD-TDP and ALS-TDP have been reported using 70-µm-thick tissue sections which reveals far more TDP-43 pathology than traditional thin (6–10 µm) sections, but this renders subtyping more difficult due to the greater abundance of pathology that is visualized [33, 34]. These efforts have identified a non-random hierarchical pattern of TDP-43 neuropathology in ALS and FTLD-TDP and suggest that neuron-to-neuron spread of pathological TDP-43 aggregation may be central to disease pathogenesis (reviewed by [30]). Due to current technical limitations of TDP-43 biochemistry and lack of a murine model that recapitulates all features of ALS/FTLD-TDP, cell and animal model data for transmission are currently limited but this is an area of intense research [174].

TDP-43 pathology is not specific to FTLD-ALS as it is also found commonly in over 50 % of AD cases and related tauopathies, hippocampal sclerosis, pathological aging and other neurodegenerative diseases [4, 67, 68, 72, 167, 205, 217]. Indeed, hippocampal sclerosis of aging and TDP-43 proteinopathy appear to be closely linked [168]. Careful clinicopathological correlation studies find that comorbid TDP-43 pathology in aging and AD may have an independent impact on cognition and neurodegeneration [111, 217]. Further, staging efforts have been made for TDP-43 in AD and they suggest a spatiotemporal progression starting in the amygdala [110] that differs from staging schemes proposed for bvFTD due to FTLD-TDP [33]. These findings suggest that TDP-43 aggregation may result from several potential mechanisms with an independent impact on cognitive function; indeed, the genetic heterogeneity of familial FTLD-TDP also implies multiple potential upstream paths (i.e., *GRN, TARDBP, C9orf72, VCP,* etc.) for TDP-43-mediated neurodegeneration that is central to FTLD-TDP/ALS. Future studies will help clarify the overlap of TDP-43 with other neuropathologies that characterize

different neurodegenerative disorders, and perhaps future TDP-43-directed therapies may be of utility in AD cases with dual pathology. Thus, TDP-43-specific biomarkers are of critical importance.

Genetics

FTLD-TDP is extraordinarily diverse from a genetic standpoint (Fig. 3). Four main molecular etiologies of autosomal dominantly inherited pathogenic mutations have been identified for TDP-43 proteinopathies: variably but abnormally long expansions of a hexanucleotide (GGGGCC) repeat in the chromosome 9 open reading frame 72 gene (*C9orf72*) [55, 143, 181] are the most frequent genetic cause of familial FTD, FTD-ALS and ALS; mutations in the progranulin gene (*GRN*) [13, 53, 163] are the second most frequent genetic cause of familial FTLD-TDP while mutations in valosin-containing protein gene (*VCP*) [214, 215] and TAR DNA-binding protein gene (*TARDBP*) [73, 113, 207] are less common causes of familial FTLD-TDP and/or ALS. Although each genetic cause is characterized neuropathologically by the presence of TDP-43-immunoreactive inclusions, the morphology, IHC, distribution of the inclusion bodies, and clinical phenotype vary between the different genotypes.

Sporadic disease and genetic risk factors

One genome-wide association study (GWAS) was performed using only FTLD-TDP patients with either a pathologically confirmed TDP-43 pathology or a *GRN* mutation and genome-wide significance was detected for a single gene, transmembrane protein 106B (*TMEM106B*) on chromosome 7 [208]. Although this risk factor has not been replicated in all follow-up studies using clinically derived cohorts, perhaps due to the underlying pathologic heterogeneity among clinically defined cohorts, the most significant *TMEM106b* association was in FTLD-TDP patients carrying *GRN* mutations [52, 62, 184, 208, 209]. An international GWAS including all subtypes of clinical FTLD was recently completed and found two novel single-nucleotide polymorphisms (SNPs) associated with disease possibly related to immune function and lysosomal pathways and autophagy [59]. Finally, *C9orf72* expansion is seen in

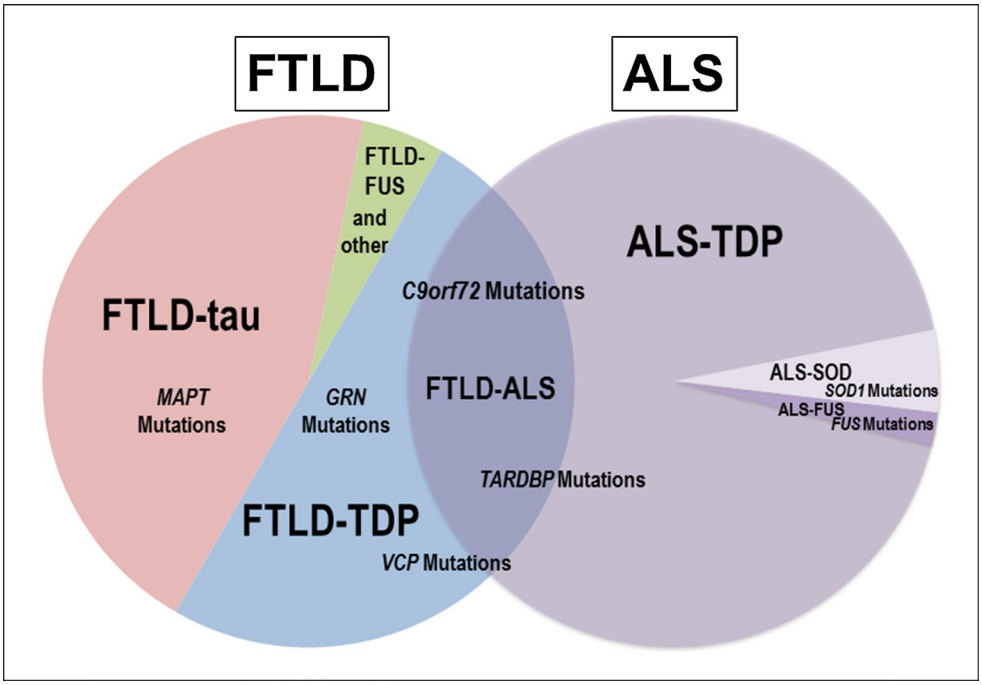

Fig. 3 Genetic associations in FTLD/ALS. Relative frequencies of neuropathological subtypes and associated molecular etiologies of FTLD and ALS are depicted. FTLD-Tau represents roughly 45 % of all FTLD and mutations in *MAPT* are the sole known cause of hereditary forms of this disorder. FTLD-TDP accounts for roughly 50 % of all FTLD and hereditary forms are associated with pathogenic mutations in *GRN, C9orf72, TARDBP and VCP* and other rare genes. ALS is associated with TDP-43 neuropathology in >95 % of cases and there is considerable clinicopathological and genetic overlap of FTLD-TDP and ALS as demonstrated by the overlapping Venn diagrams. Placement of gene names reflects these associations, with FTLD-ALS/ALS cases more associated with *C9orf72 and TARDBP* while less commonly linked to *VCP* and rarely *GRN*. *TARDBP* is rarely associated with FTLD without comorbid ALS. A minority of ALS is associated with pathogenic mutations in *SOD1* and *FUS*, while FTLD-FUS also may occur in a sporadic condition. Extremely rare cases of FTLD (other) are associated with pathogenic mutations in *CHMP2B* and FTLD-U neuropathology

a small subset of sporadic ALS (~5–10 %) and less commonly FTD (~5 %) [143]. Thus, the contribution of genetic modifiers to phenotypic variation in genetic and sporadic FTLD-TDP is evolving and these discrepancies highlight the importance of autopsy confirmation for genetic and biomarker discovery studies in FTLD.

Progranulin (GRN)

Mutations in GRN located on chromosome 17q21 are the molecular genetic basis of about one quarter of all familial cases of FTLD-TDP [13, 15, 53, 163]. Pathogenic mutations in GRN are mainly nonsense and splice site mutations resulting in the loss of one *GRN* allele (i.e., null mutations); some mutations, however, are missense mutations causing mis-trafficking within the cell and a functional haploinsufficiency; both mechanisms result in progranulin protein haploinsufficiency. More than 70 different pathogenic mutations in *GRN* have been reported. Further, recent studies show that microRNA-132 and microRNA-212 repress *TMEM106B* expression through shared microRNA-132/212 binding sites in the *TMEM106B* 3′UTR and that endogenous neuronal TMEM106B proteins colocalize with progranulin proteins in late endolysosomes, while TMEM106B overexpression increases intracellular levels of progranulin. Thus, *TMEM106B* is an FTLD-TDP risk gene that alters progranulin pathways [44]. *GRN* mutation cases are exclusively associated with TDP-43 "subtype A" [139]. Interestingly, progranulin protein is not found in TDP-43 inclusions [140], but *GRN* mRNA expression from the normal allele is increased in cortical areas of neurodegeneration in *GRN* mutation carriers and this may be mediated by reactive proliferation of microglia in affected brain regions [45]. Low serum progranulin levels are found in the serum/plasma of *GRN* mutation carriers [61, 196] and thus provide a promising biomarker for potential emerging progranulin-restorative therapies [26].

C9orf72 hexanucleotide expansion

The expansion of a hexanucleotide (GGGGCC) repeat in a non-coding region of the *C9orf72* gene was recently discovered [55, 181] and is the most common molecular etiology of hereditary and sporadic ALS and/or FTLD-TDP. *C9orf72* encodes a protein of unknown function. Pathologic expansion repeats extend from approximately 30 to more than 1,000, and there appears to be no direct association between the severity of disease and expansion size above the normal range. These analyses may be confounded by differences in *C9orf72* expansion in peripheral blood and various regions of CNS, as some correlations of repeat length with demographic features in FTD have been described for some specific brain regions [206]. The *C9orf72* expansion is more common in patients with familial ALS and FTD-ALS than familial FTLD. Notably, however, *TMEM106B*, the risk gene for FTLD-TDP, has also been identified as a genetic modifier of FTD with *C9orf72* expansions with the minor allele protective of developing FTD, but not MND [206]. Interestingly, the genotype that confers increased risk for developing FTLD-TDP has been associated with later age at onset and death in *C9orf72* expansion carriers with FTD [69].

Neuropathologically, the majority of *C9orf72* mutation cases have TDP subtype B [22, 141, 199] but unlike other TDP-43 proteinopathies, cases with the hexanucleotide expansion also have additional proteinaceous inclusions of unclear clinical significance that are not reactive for TDP-43 (Fig. 1). *C9orf72* cases have small p62-positive NCIs and rare NIIs in cerebellar granular neurons and p62-immunoreactive star-shaped NCIs and occasional punctate NIIs in the hippocampus [2]. *C9orf72* cases also have additional ubiquillin-positive pathology in cerebellum and hippocampus, and the presence of these at autopsy predicts the occurrence of pathological hexanucleotide *C9orf72* expansions [36, 103]. There are also foci of RNA aggregations in neuronal nuclei in these regions [55, 158]. Finally, the hexanucleotide repeat region is bi-directionally translated by an unconventional repeat-associated non-ATG translation of the expanded C9orf72 transcript to form aggregating dipeptide repeat (DPR) proteins (poly-(Gly-Ala), poly-(Gly-Pro) and poly-(Gly-Arg), poly-(Pro-Ala) and poly-(Pro-Arg)) which also are predictive of *C9orf72* expansion [10, 70, 161]. Indeed, DPR proteins are highly co-localized in p62-positive, TDP-43-negative, inclusions in FTLD-ALS spectrum cases with *C9orf72* repeat expansion [144, 161] and share a similar morphology and regional distribution; although DPR proteins are more widespread [10]. Double-labeling immunofluorescence studies of ubiquillin and DPR are lacking but the regional distribution and minimal co-localization with TDP-43 suggest a similar relationship to DPR as p62. Interestingly, there does not appear to be a correlation between DPR pathology and neurodegeneration [138]; however, recent cell and *Drosophila* model experiments suggest a potential toxicity of DPR protein accumulation distinct from RNA foci-associated gene dysregulation [124, 157, 220]. Indeed, substantial DPR pathology has been reported in early/pre-symptomatic *C9orf72* autopsy cases with an absence or minimal TDP-43 neuropathology [11, 177]. Further, DPR proteins are detectable in the cerebrospinal fluid of *C9orf72* mutation carriers and could serve as a useful biomarker for *C9orf72* associated TDP-43 proteinopathies [202]. Finally, transcriptional silencing of mutant *C9orf72* due to promoter hypermethylation is associated with lower RNA foci and DPR aggregate burden in human brains, and later age of death in FTD suggesting that expression of the mutant gene is indeed

deleterious [136, 186]. Further work is needed to clarify the link between *C9Orf72* expansion, p62, ubiquillin, DPR aggregation, RNA foci and TDP-43 aggregation with neurodegeneration; however, presently it is TDP-43 accumulation that is most closely linked with neurodegeneration in ALS/FTLD-TDP [36, 138].

Tardbp

The discovery of mutations in *TARDBP* on chromosome 1 indicated that abnormal TDP-43 is sufficient to cause neurodegeneration [207], thereby confirming the initial discovery of the linkage of TDP-43 pathology to FTLD and ALS [173]. However, mutations in *TARDBP* account for only a small number, <4 %, of FALS cases, and are rare causes of FTD. In limited autopsy studies, TDP-43 proteinopathy seen in *TARDBP* mutation cases is similar to that seen in sporadic ALS/FTLD-TDP; however, there may be more extensive proteinopathy outside motor areas than in sporadic cases [42].

VCP

VCP is located on chromosome 9p13.3-p12 and several pathogenic missense mutations have been linked to a rare phenotype of hereditary inclusion body myopathy (IBM) associated with Paget disease of bone (PDB) and early onset frontotemporal dementia (IBMPFD) [214, 215]. More recently, mutations in *VCP* have also been reported in patients with an ALS without dementia phenotype [108]. Human *VCP* (also called p97, ter94, or CDC48) is a 644 amino acid protein encoded by a gene with 17 exons. It is a member of the AAA-ATPase superfamily involved in multiple functions including: vesicle transport and fusion, 26S proteasome function, and assembly of peroxisomes [54, 155]. The neuropathology in FTLD-TDP with a *VCP* mutation is a unique subtype of FTLD-TDP, subtype D [139], characterized by numerous NIIs (Fig. 2j). Identification of pTDP-43, but not *VCP*, within ubiquitin-positive inclusions supports the hypothesis that *VCP* mutations lead to a dominant-negative loss or alteration of *VCP* function culminating in impaired degradation of TDP-43.

Finally, it is noteworthy that in addition to the mutations noted above that cause ALS/FTLD-TDP, multiple pathogenic mutations in four other genes (including those encoding ataxin-2, optineurin, NIPA1 and angiogenin) for ALS and/or FTLD-TDP have been discovered that also are linked to TDP-43 pathology thereby suggesting that ALS and FTLD share similar disease mechanisms all of which involve TDP-43 pathology [86, 115, 119, 145].

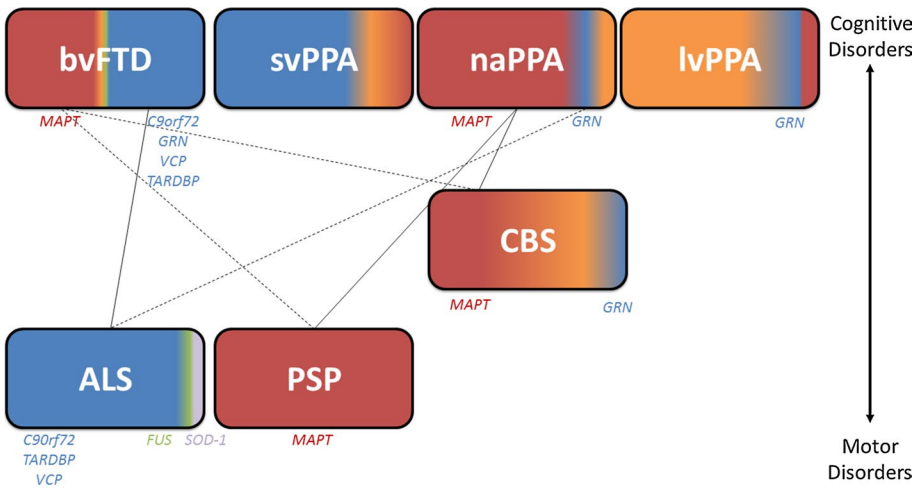

Fig. 4 Clinicopathological and genetic associations in FTLD/ALS. The scheme portrays relative frequencies of neuropathological subtypes of FTLD and pathogenic mutations associated with FTD clinical phenotypes arranged with predominant cognitive syndromes above and predominant motor disorders below (CBS is intermediate with largely mixed cognitive/motor features). Common associations between syndromes (i.e., ALS-bvFTD, PSP-naPPA) are identified with *solid lines* and *dashed line* represents less common comorbid syndromes (i.e., ALS-naPPA, PSP-bvFTD, CBS-bvFTD). FTLD-Tau pathology (*red*) is found in virtually all PSP cases and the majority of naPPA. FTLD-Tau is also found in a significant proportion of CBS and bvFTD and rare in svPPA. TDP-43 pathology (*blue*) is found in almost all ALSs and the majority of svPPA, while roughly half of bvFTD cases harbor FTLD-TDP at autopsy while FTLD-TDP pathology is less commonly found in naPPA and CBS. Atypical presentations of AD are seen in a significant proportion of CBS and less commonly in svPPA and naPPA, but very rarely in bvFTD. Finally, a small percentage of ALS has FUS or SOD-1 (*green*) pathology at autopsy and FUS is a rare substrate for bvFTD. Genetic etiologies linked to clinical phenotypes are written below in order of frequency; svPPA is largely a sporadic condition

Clinicopathological correlations

FTLD-TDP can present clinically as bvFTD, FTD-ALS, CBS or PPA [64] (Fig. 4). Of note, the majority of svPPA cases are associated with FTLD-TDP [78], in particular "subtype C" [139, 183]; while roughly half of bvFTD [64, 88, 183] and ~15 % of CBS have TDP-43 neuropathology [133]. FTLD-TDP can also less commonly present with slow hesitant speech, consistent with lvPPA [154] and motor speech difficulties consistent with naPPA [78, 120, 197]. A small percentage of patients with FTLD-TDP neuropathology may present clinically with an amnestic disorder similar to AD, especially those with an older onset and comorbid hippocampal sclerosis at autopsy [168]. The development of clinical motor neuron disease in FTD patients is highly associated with underlying TDP-43 neuropathology and is a poor prognostic marker [96].

Hereditary forms of FTLD-TDP have specific associations with clinical phenotypes of FTD. The most frequent clinical presentation of FTLD-TDP with *GRN* mutation is bvFTD [128]; although there is considerable heterogeneity between patients within and between families, including language dysfunction, consistent with PPA variants while extrapyramidal symptoms (parkinsonism and CBS) are less frequent and ALS is extremely rare [43]. Mutant *GRN* has been associated with lvPPA as well [154]. *C9orf72* expansion may present with ALS and/or several clinical FTD syndromes, most commonly bvFTD but also PPA [22, 103, 141]; interestingly, neuropsychiatric features uncommon to bvFTD have been described [199]. In addition, clinical cases of AD with FTLD-TDP with varying degrees of AD neuropathologic change or unknown neuropathology have been associated with *C9orf72* expansions [14, 85, 142]. Other reported *C9orf72* clinical phenotypes include neuropsychiatric disease [20], Huntington's disease-like presentation [87] and multiple system atrophy [74]. *C9orf72* expansion carriers with clinical ALS have a shorter disease duration than sporadic cases [39, 103] and *C9orf72* expansion carriers with FTD may have a more rapid cognitive decline associated with more severe cortical atrophy compared with other forms of FTLD-TDP [103]; however, cases of slowly progressive *C9orf72* mutation-positive FTD with minimal cortical atrophy have also been reported [117]. Indeed, several studies find additional areas of cortical atrophy in *C9orf72* FTD in the thalamus, parietal lobes and cerebellum on neuroimaging [103, 141, 191], while some cases may have minimal atrophy and non-progressive clinical symptoms [22, 117]. Further, *C9orf72* ALS-FTD may have a longer disease duration than ALS-FTD without a mutation [191], although a wide range of age at onset, death and disease duration has been reported [22, 93, 141, 194]. Thus, significant heterogeneity exists for *C9orf72*-associated cases with potential multiple genetic or other modifying factors. Although the *TARDBP* mutations are most frequently associated with ALS and ALS-FTD clinical phenotypes, additional features of chorea and PSP-like presentations may be seen in patients with *TARDBP* mutations. Indeed, patients with "ALS-plus" symptoms (i.e., extrapyramidal, autonomic, oculomotor or cerebellar dysfunction) are more likely to harbor a pathogenic mutation in *TARDBP*, *C9orf72* or *VCP* compared with sporadic cases [148].

Tauopathies (FTLD-Tau)

Neuropathology

Roughly 45 % of FTLD is caused by a diverse class of neurodegenerative diseases characterized by neuronal and glial inclusions composed of the microtubule-binding protein, tau (FTLD-Tau) (Fig. 3). The discovery of multiple pathogenic mutations in *MAPT* associated with diverse FTD syndromes, formerly known as FTDP-17 and now called FTLD-Tau with *MAPT* mutation (see below), has led to the unequivocal evidence that tau abnormalities alone are sufficient to cause neurodegenerative disease (similar to previously described *TARDBP* mutations in ALS/FTLD-TDP) (Fig. 5).

As reviewed recently [134, 219], tau proteins are low-molecular-weight MAPs that are abundant in the central nervous system (CNS), where they are expressed predominantly in axons, and at very low or negligible levels in astrocytes and oligodendrocytes. Human tau proteins are encoded on a single gene located on chromosome 17q21 with 16 exons leading to the generation of 6 different CNS tau isoforms generated by alternative splicing of 11 of these exons in the messenger RNA (mRNA) transcript. In the adult human brain, alternative splicing of exons 2, 3, and 10 generates 6 tau isoforms ranging from 352 to 441 amino acids in length, which differ by the presence of either 3 or 4 microtubule (MT)-binding repeats (3R tau or 4R tau, respectively) consisting of repeat sequences of 31 or 32 amino acids each that are encoded by exons 9–12. In addition, alternative splicing of exons 2 and 3 leads to the absence (0N) or presence of inserted sequences of 29 (1N) or 58 (2N) amino acids in the amino-terminal third of the molecule thereby resulting in 4R0N, 4R1N, 4R2N, 3R0N, 3R1N and 3R2N tau proteins at a 1:1 ratio of 3R to 4R tau in the adult CNS.

Tau functions by binding to and stabilizing MT and this process is regulated by phosphorylation. Several protein kinases and protein phosphatases have been implicated in regulating the phosphorylation state and thus the function of tau. The phosphorylation sites are clustered in regions flanking the MT-binding repeats,

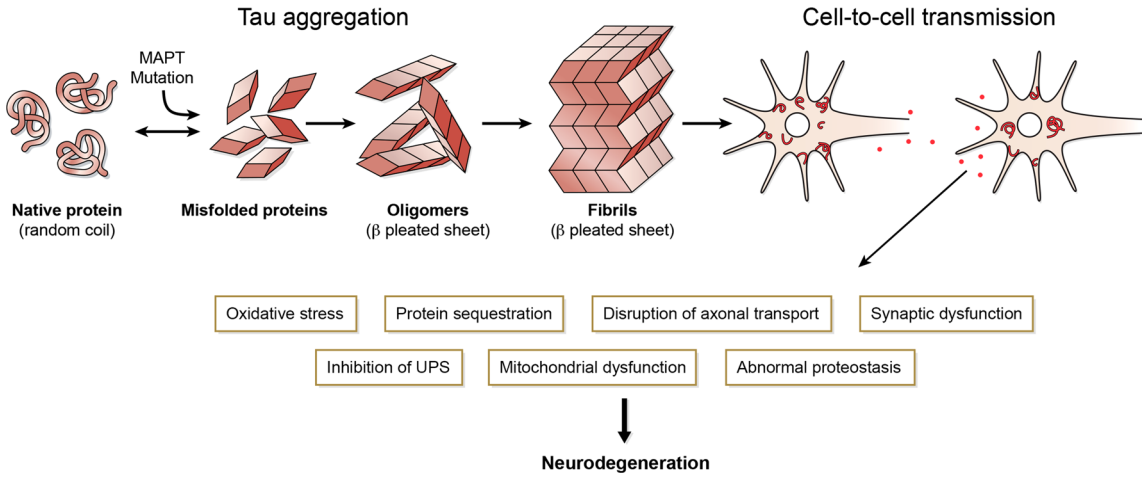

Fig. 5 Tau-mediated neurodegeneration in FTLD-Tau. Tau misfolding and aggregation into to beta-pleated sheet containing oligomers and fibrils occur in familial FTLD-Tau due to *MAPT* mutations and in FTLD-Tau. This process results in loss of microtubule-binding function and formation of cytosolic tau inclusions (*red*). Animal- and cell-model data suggest neuron-to-neuron transmission is central to disease pathogenesis and propagation. This process leads to multiple areas of cell dysfunction (*boxes*)

and increasing tau phosphorylation at multiple sites regulates MT binding [32]. More recently, tau has also been shown to be modified by acetylation [49, 156]. However, in both sporadic and familial tauopathies, tau is hyperphosphorylated and acetylated and it is this "abnormal" tau that is the principle component of the filamentous aggregates in neurons and glia that are the pathological hallmarks of these disorders. Similar to phosphorylation, acetylation of tau at the lysine 280 residue (i.e., acK280) in the second MT-binding motif of 4R tau also disrupts the MT-binding function of tau, but in addition also promotes tau aggregation in vitro [49]. Other lysine residues in the MT-binding motif may inhibit tau polymerization and phosphorylation at these residues [50] and may inhibit degradation of abnormal tau [156]. The acK280 modification is disease specific for pathological tau in tauopathies and is not present in normal control CNS tissue [49, 101, 102]. Comparison with multiple tau epitopes across various stages of AD neuropathology suggests a close association of acK280 modification with the amyloid properties (i.e., Thioflavin-S reactive) of AD tangles and also in Thioflavin-S-negative inclusions in FTLD-Tau [101, 102]. Thus, a potential interplay between phosphorylation and acetylation modifications in tau may perturb normal tau function and promote pathological aggregation in various tauopathies. Finally, in the disease state, tau also may be nitrated [91] and glycated [129] which may contribute to disease pathogenesis.

FTLD-Tau can be subdivided into several neuropathological diagnoses and classified based on the predominant tau isoforms that are present in the inclusion bodies (i.e., 3R, 4R or equal 3R:4R ratio).

3R tauopathy: Pick's disease

The sole 3R predominant tauopathy is Pick's disease (PiD), which historically referred to clinical FTD in general but now this term is reserved for the neuropathological diagnosis described here due to the neuropathological heterogeneity of FTD (Fig. 4). On gross examination, there is often severe "knife-edge" atrophy of the frontotemporal neocortex. The diagnostic histological feature of PiD is the Pick body [164] (Fig. 2a). Pick bodies are well-circumscribed, spherical, argyrophilic, and tau-immunoreactive neuronal intracytoplasmic inclusions. In addition, there are swollen achromatic so-called "ballooned" neurons or Pick cells, neuronal loss, and astrocytosis. Pick bodies are found most abundantly in the granule cells of the dentate gyrus. Pick bodies are found at lower densities in the pyramidal neurons of the frontal and temporal neocortex. The distribution of Pick bodies may be uni- or bilaminar, and this difference may reflect the stage of progression of the disease [9]. A prominent band may be seen in layer II and upper layer III, and a band in layer IV. These neurons can be contrasted with those in AD, in which NFTs are found predominantly in the large pyramidal neurons of layers III and V, the major cortico-cortical projecting neurons. Spatial pattern analysis has shown that Pick bodies appear in regular clusters throughout affected cortical areas [7]. Pick bodies are best identified using tau-directed immunohistochemistry. They have a similar staining pattern to NFTs, but the immunohistochemical and biochemical profile of tau in Pick disease is different from that in AD: in Pick disease, IHC shows that 3R tau isoforms predominate in Pick bodies [16, 56] and biochemical Western blot studies support these IHC findings [222]. A subset of inclusions are thioflavin-S positive

and among these, are the ones that that contain 4R-tau immunoreactivity by IHC with acetylation-specific antibodies directed at K280 [101]. Ultrastructurally, Pick bodies contain 15-nm-diameter filaments and do not appear to have a limiting membrane [164]. Ballooned neurons can be labeled with antibodies specific for the heat shock protein, β-crystallin. The significance of ballooned neurons in the pathogenesis of PiD is unclear and they are not present in all cases. Finally, PiD also contains numerous tau-positive glial inclusions in gray and white matter.

4R tauopathies: corticobasal degeneration

Similar to PiD, current nomenclature of FTLD-Tau reserves the term corticobasal degeneration (CBD) for the neuropathological diagnosis of the 4R tauopathy [57] described below. Corticobasal syndrome (i.e. CBS) refers to the clinical diagnosis of patients who present with an asymmetric Parkinsonian disorder [6], which was originally linked to CBD neuropathology. This clinical syndrome is now known to encompass several potential underlying neuropathologies outside of CBD [133], which has necessitated the change in nomenclature (see below). On gross examination, the brain is atrophied asymmetrically in the posterior frontal and parietal lobes; both the pre- and postcentral gyri may be affected. There is also pallor of the substantia nigra in the majority of cases. Microscopically, neuron loss may be more severe in the outer cortical laminae and generate status spongiosus. The white matter underlying the affected areas of cortex may be rarefied and display a reactive astrocytosis. Ballooned neurons are often readily seen throughout the neocortex. There is usually severe neuronal loss and accompanying astrocytosis in the substantia nigra. A characteristic feature is the intraneuronal basophilic inclusion. These "corticobasal inclusions" are argyrophilic and fibrillar, and are labeled by anti-ubiquitin and anti-tau antibodies. Histologically, they resemble the NFTs of PSP. Ultrastructurally, the filaments in these CBD inclusions are mainly straight, with a diameter of 15 nm [213]. In addition to these corticobasal inclusions, small neuronal tau-positive inclusions and neuropil threads can be found in the superficial layers of the cortex.

The most prominent microscopic features of this disorder are clusters of astrocytic tau-positive processes that coalesce to form astrocytic plaques (Fig. 2c). There are also tau-positive inclusions in oligodendrocytes, referred to as "coiled bodies." Both the astrocytic and oligodendroglial inclusions in CBD are labeled by anti-ubiquitin and anti-tau antibodies. The tau protein in CBD is predominantly 4R tau, and these findings are supported by biochemical Western blot studies [65, 224]. Moreover, CBD inclusions are robustly reactive for the acK280 acetylation modification of tau [102]. Interestingly, CBD inclusions do not react with amyloid-binding dyes and lack several tau epitopes linked to more "mature" and extracellular ghost tangles in AD such as C-terminal truncation epitopes [17, 82]. These morphological and biochemical differences in tangle formation between CBD and PSP (see below) as well as with AD are currently unclear, but provide a possible avenue for future efforts in biomarker discovery to differentiate these tauopathies ante-mortem.

4R tauopathies: progressive supranuclear palsy

PSP pathologically is also a 4R predominant tauopathy with significant white matter pathology predominantly in the brainstem and subcortical structures [221, 224]. Macroscopically, the substantia nigra and locus coeruleus often appear pale and cortical atrophy is variable. Histology reveals tangles, neuropil threads, glial inclusions, neuronal loss, and astrocytosis [57]. The predominant hallmarks of PSP are the 4R tau-positive tangles and tufted astrocytes (Fig. 2b). The NFTs are found in the substantia nigra, globus pallidus, subthalamic nucleus, nucleus basalis of Meynert, pretectal area, tegmentum of the midbrain and pons, locus coeruleus, raphé nuclei, and the nuclei of various cranial nerves as well as the cerebellar dentate nucleus. The tangles are readily seen by silver impregnation methods but are best visualized by tau IHC. Electron microscopy demonstrates that the tangles contain straight filaments of 12–15 nm, which in turn are composed of six or more protofilaments of 2–5 nm [160]. Paired helical filaments (PHFs) similar to those seen in AD, and intermediate forms have been described. Many astrocytes have inclusions called tufted astrocytes, and the cell bodies containing these inclusions may be tuft shaped or less frequently thorn shaped. Oligodendrocytes may also contain tau-positive "coiled-body" inclusions. PSP inclusions are largely negative for thioflavin-S and robustly positive for the acK280 acetylation modification in tau [102]. Similar to CBD, PSP cases lack several "late" C-terminal truncation tau epitopes seen in AD neuropathology [17, 81].

Recently, globular glial tauopathies (GGTs) have been described in 22 cases as a new neuropathological entity [1]. GGT is a 4R tauopathy with astrocytic and oligodendritic tau inclusions similar to PSP but they differ by the lack Gallyas reactivity. Further there is often minimal subcortical neuronal loss in the dentate and subthalamic nuclei and very extensive white matter pathology. Three GGT types have been delineated corresponding to involvement in frontotemporal (Type I), motor/corticospinal tract (Type II) or both (Type III) corresponding to a range of clinical syndromes including ALS, FTD and PSP [1].

4R tauopathies: argyrophilic grain disease (AGD)

The term 'argyrophilic grain' derives from its appearance using some (e.g., Gallyas), but not all, silver impregnation methods; however, they are best visualized using 4R isoform-specific anti-tau antibodies. Grains are small (4–8 μm diameter), round or spindle-shaped structures found mainly in the cortical neuropil (Fig. 2e) and to a lesser degree in the underlying white matter. Grains are found mainly in dendrites and dendritic branches and some axons. Other non-specific lesions include: pre-tangle neurons, coiled bodies, tau-immunoreactive astrocytes, swollen achromatic, or 'ballooned,' neurons, NFTs, and neuropil threads. The tau immunoreactivity in astrocytes is more diffuse than the compact fibrillar, tau-immunoreactive inclusions of tufted astrocytes of PSP. Ultrastructurally, grains contain straight filaments of 10–20 nm diameter and tubular structures of 25 nm diameter. Although AGD may be found in the absence of other diseases, as a 4R tauopathy [223, 224], it most frequently occurs with more common neurodegenerative disorders including AD, the 4-repeat (4R) tauopathies, PSP and CBD, and other molecular pathologies including dementia with Lewy bodies, Parkinson disease dementia, and Parkinson disease. AGD may also be found as a comorbidity in older patients with hippocampal sclerosis. Various staging schemes have been proposed based on the density and distribution of lesions in the medial temporal lobe, adjacent structures, neocortex and subcortical nuclei [60, 187]. Grains in AGD show reactivity with acK280 acetylation modification of tau [101], but may lack other potential acetylation epitopes [76].

3R/4R tauopathies: primary age-related tauopathy (PART)

PART is a 3R/4R tauopathy that may readily be distinguished from AD by the presence of NFT in medial temporal lobe structures and the complete or nearly complete absence of Aβ plaques. This distinction is now recognized in the recent National Institute on Aging-Alzheimer's Association (NIA-AA) diagnostic criteria for AD [159] and thus, since the neuropathology can occur with minimal cognitive symptoms the term "tangle predominant senile dementia" has been replaced with PART [51]. The most characteristic finding is the presence of neuronal loss, gliosis, and frequent NFT, including extracellular NFT, called ghost tangles, in the hippocampus, parahippocampal gyrus, and entorhinal cortex (Fig. 2f). This is a common finding in patients of advanced age [51]. In more advanced disease, NFT may be seen in the nucleus basalis of Meynert, the amygdala, periaqueductal gray matter, locus coeruleus, and other regions; but NFTs are rare in the isocortex of PART. Biochemical studies indicate that fractions enriched for insoluble tau reveal no difference in the tau isoform ratio (3R:4R) in PART as is the case in AD [189] and tangles are similarly detected using phosphorylation-dependent tau-specific MAbs. Fine structural analysis of the NFT reveals mainly PHFs similar to those seen in AD. In addition, acK280 reactivity in PART is also similar to acetylation of tau in AD [101]. Tangle predominant senile dementia was previously categorized as FTLD-Tau [140] and there is considerable pathological overlap between PART, including lack of an association with APOE 4 genotype, suggesting a pathway of disease independent from AD [51]; however, these biochemical and topographic distribution similarities to AD, together with varying rates of progression of Aβ plaque and tau neurofibrillary pathology have suggested by some that PART is not a separate process from AD [31]. These discrepancies are a matter of ongoing study and debate.

Genetics

Risk factors in sporadic FTLD-Tau disease

Two extended haplotypes (H1, H2) cover the human *MAPT* gene, and there is complete disequilibrium between polymorphisms that span the gene (which covers approximately 100 kb of DNA). This suggests that the establishment of the two haplotypes was an ancient event, and that either recombination is suppressed in this region, or recombinant genes are selected against. The more common haplotype (H1) is significantly overrepresented in patients with PSP [12] and CBD [92], but there is no difference between the *MAPT* H2 haplotype or H2/H2 genotype frequency in PiD cases when compared with control subjects [162]. To date, no specific genetic locus has been associated with AGD. However, a 40-kb deletion at 17p13.2 encompassing the cystinosin, lysosomal cystine transporter (*CTNS*) gene has recently been described suggesting that this may be a candidate gene for AGD [212]. No mutation has been reported in *MAPT* in PART, but haplotype analysis demonstrates a strong association with the *MAPT* H1 haplotype. Next-generation re-sequencing of *MAPT* followed by association analysis showed an association between PART and two polymorphisms in the *MAPT* 3′ untranslated region (UTR). These results suggest that haplotype-specific variation in the *MAPT* 3′ UTR underlies an Aβ-independent mechanism for neurodegeneration in PART [189]. There are discrepant findings of an association of PART and APOE genotype and the potential overlap of PART with AD remains uncertain [31].

To identify common genetic variation contributing to PSP, a GWAS found significant signals associated with PSP risk in syntaxin 6 (STX6), eukaryotic translation initiation factor 2-α kinase 3 (EIF2AK3), and myelin-associated oligodendrocyte basic protein (MOBP) genes [89]. Two

independent variants in *MAPT* affect risk for PSP, one of which influences *MAPT* brain expression. The genes implicate proteins for vesicle–membrane fusion at the Golgi–endosomal interface, the endoplasmic reticulum unfolded protein response and, and a myelin structural component.

Hereditary FTLD-Tau: FTLD-Tau with a MAPT mutation

FTLD-Tau with *MAPT* mutations (Fig. 3), previously called FTDP-17, is now distinguished from chromosome 17-linked families who have a mutation in the GRN (Fig. 3). *MAPT* mutations, of which more than 40 have been identified as pathogenic, cause tau dysfunction by several mechanisms [63, 90]. First, intronic and some exonic mutations affect the alternative splicing of exon 10 and consequently alter the relative proportions of 3R and 4R tau which may disturb normal tau function and lead to increased cytoplasmic tau and inclusion formation. Missense mutations impair the ability of tau to bind MTs and to promote MT assembly. Finally, some mutations also promote the assembly of tau into pathological amyloid filaments.

Familial cases with MAPT mutations typically have atrophy of the frontal and temporal lobes and microscopically show neuronal loss, astrocytosis, microvacuolation, and swollen neurons. There is a spectrum of tau pathology associated with *MAPT* mutations, including intraneuronal neurofibrillary tangle-like inclusions (Fig. 2d), neuronal globose tangle-like inclusions, intraneuronal Pick body-like inclusions, astrocytic tangle-like inclusions, and oligodendroglial inclusions resembling coiled bodies and dystrophic neurites. Mutations in *MAPT* generate a heterogeneous biochemical phenotype as well: mutations may generate predominantly either 3R or 4R tau, or a combination of the two. Thus, an extraordinarily wide range of tau pathology has been observed in these familial cases and aside from tau inclusion pathology, there is no unifying or distinct neuropathological finding to diagnose these familial conditions at autopsy [63]. Indeed, on occasion cases may appear pathologically consistent with sporadic tauopathies (i.e., PiD, CBD. PSP) and require genetic testing for diagnosis as disorders caused by *MAPT* mutations. Tau inclusions are similarly hyperphosphorylated in hereditary tauopathies as in sporadic disease (i.e., PiD, CBD, PSP). In addition, p.P301L and IVS10 + 16 mutation cases, which contain predominantly 4R tau isoforms, have robust reactivity for ack280, despite the absence of thioflavin-S-reactive amyloid tau inclusions [101].

Clinicopathological correlations

FTLD-Tau comprises approximately half of all cases with a bvFTD clinical syndrome [64, 88, 183] (Fig. 4) and this includes PiD and FTLD-Tau with a *MAPT* mutation, and less commonly CBD and PSP. Further, PiD most often presents clinically with bvFTD but also has been reported in association with PPA and CBS phenotypes [183]. In a large autopsy series of patients with clinical CBS, CBD comprised only 35 % of cases, with 13 % having PSP neuropathology and 23 % with AD (in addition to the aforementioned ~15 % with FTLD-TDP) [133]. Conversely, CBD neuropathology can often present with cognitive syndromes in the absence of motor features of CBS [166]. Thus, CBS is a very heterogeneous clinical syndrome and recent clinical criteria have been proposed to help identify clinical features that may identify underlying CBD neuropathology [6]. In contrast, the clinical syndrome of PSP, and in particular the supranuclear vertical gaze palsy and presence of early postural instability, is highly associated with PSP neuropathology [135, 183]. As such, PSP patients are an attractive patient population for emerging tau-directed therapies; however, despite the specificity of these clinical features, the criteria are not very sensitive and patients with PSP neuropathology may have other clinical manifestations. Indeed, CBS and PSP patients may present with behavioral changes consistent with bvFTD or non-fluent motor speech difficulties consistent with naPPA, prior to, or after the development of the movement disorder. Therefore, the presence of extrapyramidal symptoms suggestive of CBS/PSP in bvFTD or naPPA likely reflects an underlying tauopathy in most cases [64]. Finally, the majority of naPPA patients are found to have underlying FTLD-Tau in most autopsy series [78, 88, 109, 120, 154, 183] but a significant proportion may have underlying FTLD-TDP [78, 120, 154, 197] or AD at autopsy [3, 78, 120, 154]. FTLD-Tau with *MAPT* mutations is extremely heterogeneous and has been associated largely with bvFTD and PPA, but PSP and CBS clinical phenotypes have also been described [63].

The associations of PART and AGD with specific clinical symptoms of dementia are less defined. AGD has a varied clinical presentation with episodic memory loss observed in most subjects, but behavioral abnormalities, personality changes and emotional and mood imbalance similar to bvFTD have also been described [60]. Finally, PART is usually a late-onset (>80 years) amnestic disorder [107] although some cases may have bvFTD clinical features as well or be clinically silent [51].

Other forms of FTLD including FTLD-FUS, FTLD-U and dementia lacking distinctive histopathology (DLDH)

Following the discovery of mutations in *TARDBP* in FALS, the search for other RNA/DNA-binding proteins led to the discovery of mutations in *FUS* in other FALS kindreds

and that the ubiquitinated inclusion bodies in these cases contained FUS protein [123, 210]. Interestingly, the inclusion bodies of another group of FTLD-U entities were also found to be characterized by inclusion bodies containing FUS protein, but in the absence of FUS mutations, these include: basophilic inclusion body disease (BIBD) [165], neuronal intermediate filament (IF) inclusion disease (NIFID) [172], and atypical FTLD-U [204]. Collectively FTLD-FUS accounts for <5 % of all FTLD (Fig. 3). Both FUS and TDP-43 are RNA-binding proteins and have similar structures and both are involved in transcriptional regulation. Neuropathologically, there are similarities; TDP-43 and FUS migrate from their normal nuclear location to the cytoplasm where they form relatively insoluble aggregates. In vitro, several of the mutations appear to disrupt the import of TDP-43 or FUS into the nucleus which may result in its nuclear loss of function as well as a potential gain of toxic function as FUS aggregates in the cytoplasm. The family of three FET (FUS, EWS1, and TAF15) RNA-binding proteins which are expressed in all tissues and almost all cell types are all components of the inclusions in these sporadic FUS diseases [170]. Clinically FTLD-FUS with atypical FTLD-U often presents with bvFTD at a younger with atypical neuropsychological features [198, 204] while rare reports of FTLD-FUS with NIFID and BIBD include a more varied age at onset and clinical phenotype [126, 131, 198].

Advances in the genetics and molecular pathology of FTLD have consigned most cases previously described as FTLD-U (which was formerly known as DLDH) or FTLD-U plus ALS to FTLD-FUS or FTLD-TDP proteinopathy [140]. Today, very few cases in autopsy series have FTLD with inclusions containing proteins of the ubiquitin–proteasome system (FTLD-UPS) that are tau TDP-43 or FUS-negative inclusions. At present, only one rare disease entity is assigned to this entity and that is FTLD-UPS with charged multivesicular body protein 2B (*CHMP2B*) gene mutation. Human CHMP2B is a component of the endosomal secretory complex, which becomes dysregulated by the gene defects. There have been very few neuropathologic studies of this rare autosomal dominantly inherited disease.

FTLD not otherwise specified (FTLD-NOS) is an entity reserved for cases where the molecular pathology is not known, or that the case has not been investigated using anti-ubiquitin, tau, FUS, or TDP-43 antibodies [140]. Historically, this entity included dementia lacking distinctive histology DLDH cases [121]. Most of these cases have now been screened with molecular pathology-specific antibodies and most cases now have been re-assigned to one of the FTLD entities described above. There remain, however, rare cases with the stereotypical features of FTLD, but without any inclusions having been detected. The nosology of these cases remains uncertain. A recent entity referred to as FTD "phenocopy" has emerged to describe minimally progressive FTD cases that may represent decompensated psychiatric disorders or other non-neurodegenerative disease etiologies but autopsy studies are lacking [118].

Ftld biomarker studies

Due to the complex clinicopathologic relationships in FTLD (Fig. 4), there is an urgent need for disease-specific biomarkers to improve ante-mortem diagnostics. Several modalities have been employed for FTLD biomarker development including neuroimaging, biofluid, genetic and clinical measures. A desirable biomarker will have sufficient sensitivity and specificity for FTLD-specific neuropathology and optimally have low cost and minimal invasiveness.

As mentioned, differentiation of FTLD neuropathology from atypical AD is a critical first step, as this would change current clinical management since approved AD therapies may worsen FTD [26]. Clinical features of early episodic memory loss and visuospatial impairment are suggestive of underlying AD in patients with an FTD behavioral disorder [179] or PPA [75]; however, clinical measures require extensive training and have ceiling effects which may limit use in clinical trials. Biofluid and neuroimaging biomarkers would be advantageous to follow as surrogate end points of potential disease-modifying therapies. Well-studied cerebrospinal fluid (CSF) biomarkers such as total-tau (t-tau) and amyloid beta ($A\beta_{1–42}$) can accurately distinguish autopsy-confirmed AD from controls [192] and FTLD [19, 105, 203], with AD cases having higher t-tau: $A\beta_{1–42}$ ratio. Indeed, CSF t-tau: $A\beta_{1–42}$ ratio may provide a substantial improvement over clinical diagnosis in differentiating atypical AD from FTD [105, 203]. Further, AD is predominantly a gray matter (GM) disease, compared with the significant white matter (WM) involvement in FTLD, and as such, diffusion tensor imaging (DTI) approaches appear to approach meaningful levels of diagnostic accuracy in differentiating AD from FTLD in autopsied cases [150–152]. There are still limitations in the widespread use of CSF biomarkers for AD in clinical practice based on intra- and inter-lab sources of variation at pre-analytical, analytical and post-analytical stages [116, 193, 211], but there are international cooperative efforts to standardize these assays [147]. In vivo imaging of amyloid beta [47] may also be a useful tool to identify atypical cases of AD with an FTD clinical phenotype; however, this is not specific and a significant proportion of FTLD cases may have low levels of comorbid AD neuropathology [203]. Thus, FTLD-specific biomarkers are crucial.

After exclusion of atypical AD cases, there is still considerable heterogeneity of FTLD neuropathology and a

reasonable next step in diagnostic algorithm would be differentiation of the two main classes of FTLD neuropathology: FTLD-Tau from FTLD-TDP, as disease protein-targeted therapies are already in development such as those targeting tau [37, 219]. Since FTLD-TDP does not have significant phospho-tau pathology there may be less phosphorylated tau (p-tau) released into the CSF compared to FTLD-Tau. Indeed, although both FTLD-Tau and FTLD-TDP have lower levels of p-tau and t-tau compared to controls, FTLD-TDP and ALS have lower levels of p-tau and p-tau:t-tau ratio compared with FTLD-Tau [79, 97]. CSF measurements of neurofilament light chains, a marker of axonal injury and neuronal loss, have found elevated levels in clinical FTD cohorts compared with controls and other neurodegenerative diseases [190, 195], with potential prognostic utility suggested by association with FTD disease severity in one study [190]. Further, exploratory proteomics-based approach has identified several other potential CSF biomarker candidates for FTLD-TDP [94] and others have developed assays to detect specific forms of tau [23, 24, 137] which may be helpful in differentiating FTLD-Tau and subtypes within this group. Plasma [66] and CSF [200] measurements of TDP-43 pathology have yet to find specificity to differentiate TDP-43 proteinopathies from controls; however, novel MAbs directed at various epitopes on TDP-43 [125] may prove useful for future biomarker studies. Novel biofluid analytes will require further validation in future studies with large autopsy-confirmed samples and require efforts for reducing inter-lab sources of variability before widespread clinical use.

Both FTLD-Tau and FTLD-TDP are associated with widespread ventromedial and dorsolateral frontal and anterior temporal GM loss compared with healthy control patients using magnetic resonance imaging (MRI). Direct comparison of neuropathological groups finds subtle differences in MRI cortical atrophy patterns that may be helpful in diagnosis (reviewed by [216]). Based on neuropathological observations of higher relative WM burden in FTLD-Tau compared to FTLD-TDP, comparisons of DTI imaging in autopsy-confirmed cases finds diagnostic accuracy for FTLD-Tau and the WM degeneration was confirmed on neuropathological examination of subjects who were imaged ante-mortem [149]. Finally, the recent development of tau-specific radioligands [46, 146] holds great promise for a non-invasive method to identify FTLD-Tau cases and studies to demonstrate this are currently ongoing. Since the current clinical definitions of bvFTD, CBS and PPA variants do not correspond to a particular neuropathology (Fig. 4) it is not possible to compare clinical diagnostic accuracy with FTLD-Tau or FTLD-TDP specific biomarkers. Instead, prospective studies using these emerging biomarkers will be critical in refining clinical criteria to develop endophenotypes through identification of key clinical features that predict FTLD-Tau or FTLD-TDP neuropathology (e.g., bvFTD-Tau vs bvFTD-TDP).

Hereditary forms of FTLD provide a unique opportunity for biomarker discovery as pathogenic mutations do reliably predict underlying neuropathology, in contrast to clinical syndrome. Detection of hereditary cases is aided using of a formal pedigree analysis to identify symptomatic individuals with a high likelihood of having an underlying FTLD-pathogenic mutation [218]. Further, study of pre-symptomatic individuals within families that harbor pathogenic mutations may be useful to understand the longitudinal progression of biomarkers in early stages of disease [26]. Indeed, there are signs of network dysfunction in pre-symptomatic *GRN* [58] and *C9orf72* mutation carriers [132]. As aforementioned, serum progranulin levels [196] and CSF DPR levels [202] may prove to be useful biomarkers for *GRN* and *C9orf72* mutation cases, respectively. While these hereditary forms of FTLD may be attractive for clinical trial development for therapeutics specific for the mutation (e.g., progranulin-restorative therapy), it is unclear if inclusion of hereditary cases with sporadic disease would influence disease outcome measurements for more broad tau- or TDP-directed therapies. For example, *C9orf72* disease contains additional protein inclusions [2, 10, 36, 161], additional clinical symptoms [148, 199] and possibly a worse prognosis compared with sporadic forms of the disease [39, 103]. Further, FTLD-Tau with *MAPT* mutations usually has a much earlier age at onset. Thus, disease-modifying therapeutic trials targeting tau or TDP would most likely benefit from a stratified analytic approach, similar to *APOE* genotype in AD clinical trials. Finally, SNPs may also provide a potential non-invasive method to help improve diagnostics in sporadic disease. Simultaneous evaluation of multiple SNPs from autopsy-confirmed FTLD GWAS [89, 208] finds several SNPs over-expressed in FTLD-Tau or FTLD-TDP in a clinically mixed group of sporadic autopsy-confirmed cases [153]. In a study of sporadic bvFTD, the risk allele in FTLD-Tau-associated SNP in *MOBP* was associated with a shorter disease duration and WM loss on DTI in the midbrain and long association fibers [104]. These studies highlight the potential usefulness of SNP genotyping as diagnostic and prognostic markers, although future studies in large populations of FTD patients with known pathology from diverse ethnic backgrounds are needed for confirmation of these associations. In addition, next-generation sequencing advancements will most likely reveal multiple new variants associated with forms of FTLD for future studies.

Most likely a combination of markers, rather than a single marker alone will have sufficient sensitivity and specificity to accurately diagnose the underlying molecular etiology of FTLD. Indeed, a combination of neuropsychological measures with neuroimaging data improves

diagnostic accuracy in PPA [95]. Further, AD-associated biofluid analytes are highly correlated with regional GM density on MRI in FTLD/ALS; Low p-tau levels correlate with degeneration in motor area GM and WM in ALS [79] and low t-tau levels are associated with frontal and temporal regional atrophy in FTLD patients [80]. Indeed, in a mixed AD and FTLD cohort, GM density was predictive of CSF t-tau:Aβ levels, and predicted CSF values based on GM density in ventromedial prefrontal (low t-tau:Aβ) and posterior neocortical regions (high t-tau:Aβ) were accurate in identifying underlying neuropathology, suggesting quantitative MRI could potentially serve as a surrogate for CSF biomarker measures [150].

Finally, FTLD-associated GWAS-derived SNPs predictive of FTLD-Tau or FTLD-TDP were found to correlate with measures of GM and WM degeneration, suggesting that genetic variants may influence anatomic degeneration [153]. Thus, multimodal assessments provide converging evidence for biomarker validation. Future work integrating multiple modalities in large datasets of well-annotated autopsy-confirmed cases will be critical for defining clinically useful diagnostic algorithms for FTLD. Due to the relative rarity of these disorders compared with AD, large multi-center efforts will be necessary. Recent international multi-center clinical trials of bvFTD [27] and PSP [28] have proven the feasibility of such efforts. Indeed, longitudinal observational studies are currently underway in Europe (i.e., Genetic Frontotemporal Dementia Initiative, GENFI) and the US (i.e. Advancing Research and Treatment for Frontotemporal Lobar Degeneration Consortium, ARTFL and Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects, LEFFTDS).

Conclusions

The accumulation of different pathologically misfolded proteins in diverse inclusion bodies is a common feature of both FTLD-Tau and FTLD-TDP that comprise the sporadic and familial neurodegenerative disorders presenting with the clinical spectrum of FTLD/ALS. The discovery of mutations in *MAPT*, leading to abnormal filamentous inclusions, demonstrates that tau dysfunction is sufficient to produce neurodegenerative disease. Similarly, the discovery of mutations in *TARDBP* in familial ALS indicate that TDP-43 dysfunction is sufficient to cause disease. The causal links between *GRN*, *VCP*, and *C9orf72* mutations and TDP-43 proteinopathy are indirect and require further research to be elucidated. The identification of additional gene mutations in FTLD or polymorphisms, such as *TMEM106B*, at distinct genetic loci that either cause or are risk factors for disease will provide additional insights into disease pathogenesis, as well as the development of novel strategies for treatment and prevention. Notably, the evidence that tau pathology can be transmitted in animal models opens up new avenues to pursue mechanistic studies of disease progression as well as novel strategies to block the spread of tau pathology and it will be interesting to determine if TDP-43, FUS and other FET pathologies can be transmitted in laboratory animals to create compelling model systems to study the pathogenesis of these FTLD pathologies [83, 112].

Finally, since a current limitation in clinical practice is the inability to reliably diagnose specific FTLD neuropathologies prior to autopsy, we expect that a multimodal approach utilizing, clinical, genetic, neuroimaging and biofluid FTLD-specific biomarkers will be central to accurately diagnose FTLD-spectrum pathology ante-mortem [25, 26, 77, 106]. This approach will require discovery of new more informative biomarkers for FTLD, but this will certainly enhance power for clinical trials focused on slowing or preventing transmission of tau, TDP-43 and other FTLD-associated pathologies and work toward the goal of defining clinical endophenotypes of FTD.

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