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REVIEW

Frontotemporal lobar degeneration: Pathogenesis, pathology and pathways to phenotype

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Abstract

Frontotemporal Lobar Degeneration (FTLD) is a clinically, pathologically and genetically heterogeneous group of disorders that affect principally the frontal and temporal lobes of the brain. There are three major associated clinical syndromes, behavioral variant frontotemporal dementia (bvFTD), semantic dementia (SD) and progressive non-fluent aphasia (PNFA); three principal histologies, involving tau, TDP-43 and FUS proteins; and mutations in three major genes, *MAPT*, *GRN* and *C9orf72*, along with several other less common gene mutations. All three clinical syndromes can exist separately or in combination with Amyotrophic Lateral Sclerosis (ALS). SD is exclusively a TDP-43 proteinopathy, and PNFA may be so, with both showing tight clinical, histological and genetic inter-relationships. bvFTD is more of a challenge with overlapping histological and genetic features, involvement of any of the three aggregating proteins, and changes in any of the three major genes. However, when ALS is present, all cases show a clear histological phenotype with TDP-43 aggregated proteins, and familial forms are associated with expansions in *C9orf72*. TDP-43 and FUS are nuclear carrier proteins involved in the regulation of RNA metabolism, whereas tau protein – the product of *MAPT* – is responsible for the assembly/disassembly of microtubules, which are vital for intracellular transport. Mutations in TDP-43 and FUS genes are linked to clinical ALS rather than FTLD (with or without ALS), suggesting that clinical ALS may be a disorder of RNA metabolism. Conversely, the protein products of *GRN* and *C9orf72*, along with those of the other minor genes, appear to form part of the cellular protein degradation machinery. It is possible therefore that FTLD is a reflection of dysfunction within lysosomal/proteasomal systems resulting in failure to remove potentially neurotoxic (TDP-43 and tau) aggregates, which ultimately overwhelm capacity to function. Spread of aggregates along distinct pathways may account for the different clinical phenotypes, and patterns of progression of disease.

INTRODUCTION

Frontotemporal Lobar Degeneration (FTLD) refers to a clinically, pathologically and genetically heterogeneous group of disorders that affect principally the frontal and temporal lobes of the brain. After Alzheimer's disease, it is the second most common cause of dementia in younger people. Its prevalence has been estimated at 10.8 per 100 000 and lifetime risk at 1 in 742 (33). FTLD is a "disorder of threes": there are three major associated clinical syndromes, three principal histologies and three main genetic mutations.

CLINICAL SYNDROMES

The most common clinical syndrome, which accounts for more than half of cases (72, 77), is behavioral variant frontotemporal dementia (bvFTD), characterized by behavioral change and associated with atrophy of the frontal and anterior temporal lobes (116). Core behavioral features are social disinhibition, apathy, emotional blunting with loss of sympathy and empathy for others, repetitive, obsessive and stereotyped behaviors, and dietary changes such as gluttony and altered preference for sweet foods. These key characteristics form the basis for contemporary clinical diagnostic criteria (133). Patients vary in terms of the relative preponderance of these behaviors. Hence, some patients are profoundly apathetic whereas others are overactive and socially disinhibited (94). Other behavioral characteristics, seen in some patients, include hypersensitivity or hyposensitivity to pain, sounds and other sensory stimuli (10, 44, 45, 151). Moreover, although thought to be rare (106), it is now recognized that some bvFTD patients experience psychotic symptoms of delusions and hallucinations (92, 147, 158). Behavioral

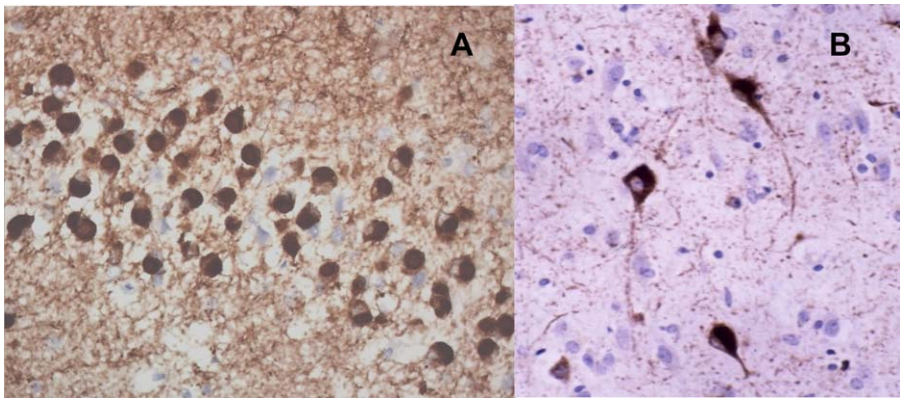

Figure 1. Tau inclusions (Pick bodies) (A) in missense *MAPT* mutations and sporadic bvFTD. Tangle-like inclusions in neurons (B) and glia associated with intronic mutations in *MAPT*.

changes are accompanied by cognitive impairments in "frontal" executive functions such as abstraction, planning, attention, reasoning and judgment. Distinct behavioral profiles within bvFTD have been attributed to differential vulnerability within functional brain networks (132).

A second, less common, clinical syndrome is semantic dementia (SD), a disorder of conceptual knowledge (116). It is characterized by impaired understanding of the meaning of words, faces, objects and other sensory stimuli. SD is also known as semantic variant primary progressive aphasia (54) because of the prominence of language-related problems. Neuroimaging shows bilateral, albeit often asymmetrical atrophy of the temporal lobes (65). Patients with predominantly left-sided atrophy have particular difficulties with the understanding of words whereas right-predominant patients show difficulties in face recognition (82, 153, 162), but in both there is a gradual loss of conceptual understanding that ultimately affects all sensory domains.

The third clinical syndrome, termed progressive non-fluent Aphasia (PNFA), (116) or non-fluent variant primary progressive aphasia (54), is a disorder of expressive language, associated with asymmetric atrophy of the left hemisphere. It is typically characterized by effortful speech and impaired use of grammar. The precise characteristics of the language disorder are not uniform across patients (58, 107, 138, 142). Some patients, for example, show effortful speech production with distortions of utterances (speech apraxia) whereas others do not.

The clinical syndromes of bvFTD, PNFA and SD may present in relatively pure form. Symptoms may, however, overlap (59). Thus, some patients who meet criteria for bvFTD also exhibit language features of PNFA or SD, whereas those presenting with a language disorder may develop "frontal" behavioral changes.

HISTOLOGIES

The three histologies are characterized by abnormal neuronal, and sometimes glial, accumulations of aggregated proteins (Figures 1–3). In about 45% of cases, neuronal intracytoplasmic inclusions (NCI) are composed of the microtubule associated protein, tau (146). Such cases are termed **FTLD-tau**. In about half of these tau-positive cases, rounded bodies, known as Pick bodies, are seen (Figure 1A) and glial tau inclusions may also be present (146). In the remainder, the neuronal tau is present as neurofibrillary tangle-like structures (NFT) or more amorphous deposits (pre-tangles) (Figure 1B). Cases with Pick bodies and glial inclusions conform to the modern definition of Pick's disease.

In about 50% of FTLD cases, the RNA- and DNA-binding protein, TDP-43, is present within ubiquitinated NCI, neuritic processes (dystrophic neurites, DN) or neuronal intranuclear inclusions (NII) (35, 119, 146) (Figure 2). Such cases, formerly known as FTLD-U are now termed **FTLD-TDP**. The relative preponderance of pathological features varies, giving rise to a sub-classification of FTLD-TDP pathology (100). Subtype A is applied when NCI and DN are both commonly present (Figure 2A), type B when NCI predominate over DN (Figure 2B), type C when DN predominate over NCI (Figure 2C) and type D when NII (see Figure 2A) are most common type of histological change.

Most of the remaining 5% of cases show NCI, and sometimes NII, composed of the protein, Fused in Sarcoma (FUS) (also known

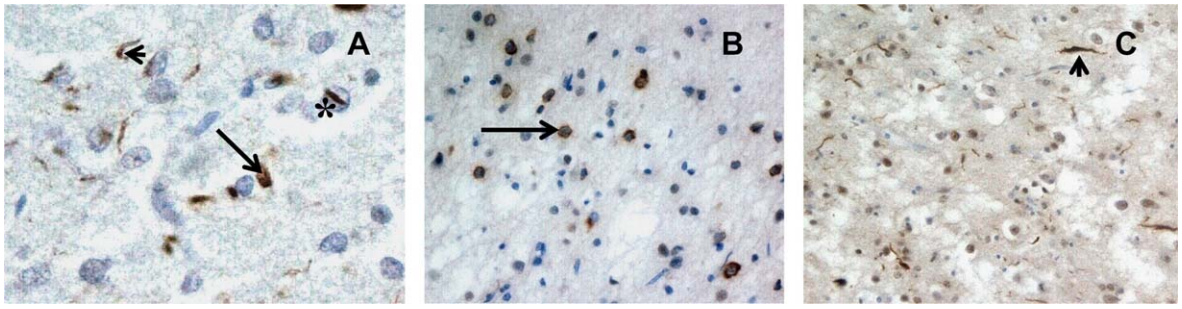

Figure 2. TDP-43 inclusions. Subtype A (A) is characterized by neuronal cytoplasmic inclusions (arrow) and dystrophic neurites (arrowhead), and neuronal intranuclear inclusions (*) when *GRN* mutation is present. In Subtype B, NCI predominate, and in Subtype C, DN are mostly present.

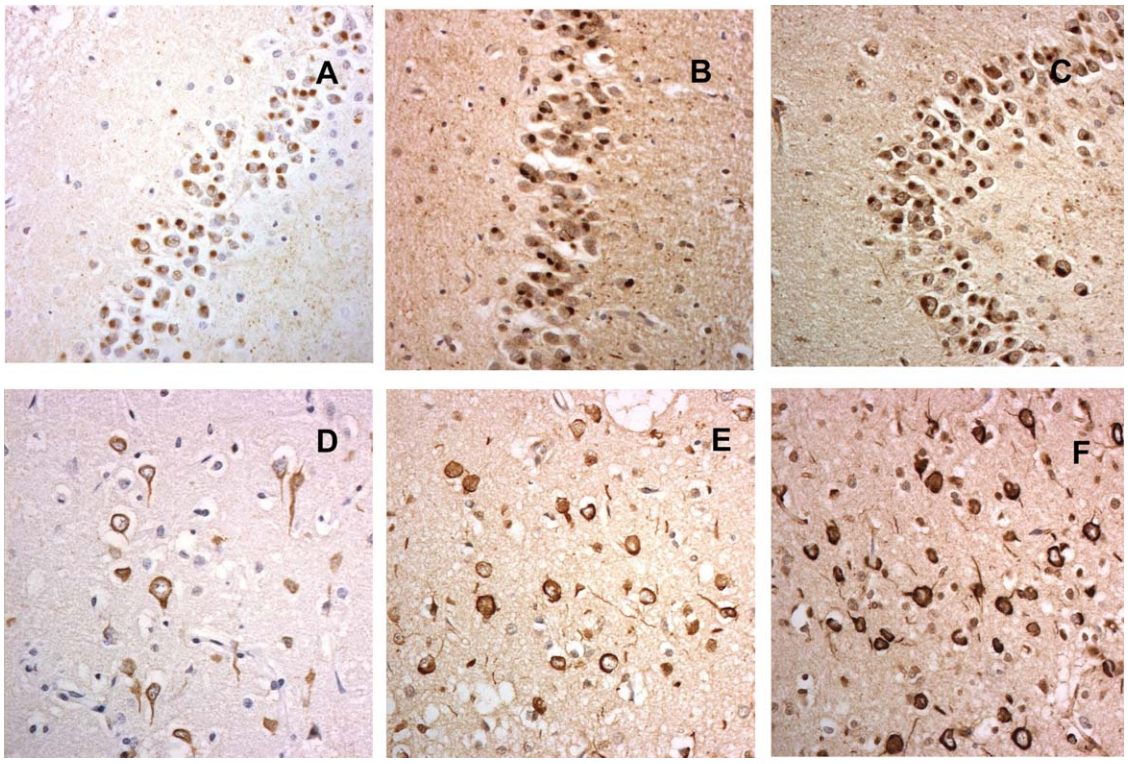

Figure 3. FUS pathology in aFTLD-U (A–C) and Neuronal Intermediate Filament Inclusion Body Disease (D–F), as shown by immunostaining for FUS protein (A,D), transportin-1 (B,E) and TAF15 (C,E).

as Translocation in Liposarcoma, TLS) (Figure 3). Such cases are described as FTLD-FUS (99, 100), or FTLD-FET - in recognition that the NCI contain other members of the FET family of proteins, such as transportin-1 (Figure 3B,E), TAF15 (Figure 3C,F) and Ewing's Sarcoma protein (EWS) (17, 36, 122). FTLD-FUS encompasses 3 distinct histopathological variants; atypical FTLD-U (Figure 3A–C), Neuronal Intermediate Filament Inclusion Body Disease (NIFID) (Figure 3D–F) and Basophilic Inclusion Body Disease (BIBD) (22–24, 112, 120, 121). Although for purposes of classification it is logical to lump these together into the broad-brush category of FTLD-FUS, given the common presence of FUS protein within inclusions, these are distinct diseases and their development presumably reflects mechanistic differences. The disorders clearly differ in neuropathology – the NCI in NIFID and aFTLD-U do not contain RNA, NCI in NIFID contain internexin-1 whereas those in aFTLD-U and BIBD do not, vermiform NII are commonplace in NIFID and aFTLD-U, but rare or absent in BIBD, loss of lower motor neurons is frequent in BIBD but less common in aFTLD-U (22–24, 112, 120, 121) – all features pointing to distinctions in pathogenesis.

In a very small minority of cases no inclusions are seen (FTLD-ni), though it is still unclear whether these are true members of FTLD family or simply represent clinical phenocopies.

GENETIC MUTATIONS

FTLD is strongly familial, with up to 40% of patients having a history of a similar disorder within their family (137), indicating that genetic factors play a major role in its aetiology. A clearly autosomal dominant pattern of inheritance is documented in about 10% (137). Three major causal genes have been identified. Mutations in *MAPT* on chromosome 17 (71, 160), not unexpectedly, drive FTLD-tau pathology. FTLD-TDP pathology, by contrast, is not, or perhaps only rarely, associated with mutations in TDP-43 gene, *TARDBP*. Rather, it is represented by mutations in the progranulin gene (*GRN*) on chromosome 17 (9, 34) or expansions in *C9orf72* on chromosome 9 (40, 134). Mutations in other genes have also, less commonly, been associated with FTLD. Of these, most notable are *CHMP2B* mutations on chromosome 3 (20, 56, 148) occurring almost exclusively within a single pedigree within the Jutland region of Denmark (20, 56, 74). NCI are present in such cases, and although these are ubiquitinated the target protein remains to be identified (68). The classification, FTLD-UPS, has been applied in recognition of the involvement of the ubiquitin proteasome system in the disease. The great majority of cases with FTLD-FUS pathology appear to be sporadic. Interestingly, mutations in *FUS* do occur, but these are mostly associated with Amyotrophic Lateral Sclerosis (ALS) (90, 167), and isolated claims that these might be associated with bvFTD remain to be substantiated (57). Other rare genetic forms of FTLD involve mutations in valosin containing protein (*VCP*) (174), *SQSTMI* (also known as p62) (97), optineurin (*OPTN*) (104), ubiquilin 2 (*UBQLN2*) (41) and TANK binding-kinase 1 (*TBK1*) (129). Although, collectively, such cases are numerically few, they do provide important clues to pathogenesis since all involve TDP-43 proteinopathy and all have functions within the cell's protein degradation systems.

Table 1. Clinicopathological relationships.

Clinical phenotype	Pathology (type and subtype)								
	Tau		TDP-43				FUS		
			A	B	C	D	aFTLD-U	NIFID	BIBD
bvFTD	NFT	PB	NCI/DN	NCI	–	NII	NCI/NII	NCI	NCI
bvFTD/ALS	–	–	–	NCI	–	–	–	–	–
PNFA	–	PB	NCI/DN	–	–	–	–	–	–
SD	–	–	–	–	DN	–	–	–	–

bvFTD = behavioral variant frontotemporal dementia; ALS = Amyotrophic Lateral Sclerosis; PNFA = Progressive Non-Flent Aphasia; SD = Semantic dementia; aFTLD-U = atypical FTLD-U; NIFID = Neuronal Intermediate Filament Inclusion Body Disease; BIBD = Basophilic Inclusion Body Disease; NFT = neurofibrillary tangles; PB = Pick bodies; NCI = neuronal cytoplasmic inclusions; DN = dystrophic neurites; NII = neuronal intranuclear inclusions.

DEMOGRAPHICS AND NEUROLOGY

The distinct clinical syndromes, histologies and genetic mutations emphasize the heterogeneity within FTLD. There is variation too in demographic characteristics and neurological findings.

FTLD is typically thought of as an early-onset dementia, and indeed the average age at onset of disease is typically around 60 years (46, 94). There is, however, wide variation. There are published reports of patients presenting in their twenties (30, 75, 152). Conversely, between 25 and 30% of patients develop symptoms after the age of 65 years (88, 94, 124). The mean duration of symptoms from onset until death is around 8 years (5) but again there is wide variation (28, 33, 64) from less than 2 to more than 20 years. Progression can be rapid or very slow.

Patients presenting with clinical syndromes of FTLD are typically physically well, with signs of parkinsonism (slowing, limb rigidity) emerging only relatively late in the disease course. Importantly, however, some patients (around 15%) develop motor neuron disease (MND) (115), providing clinical evidence of the link between the disorders (22, 116, 117). The form of MND is that of ALS), characterized by weakness, wasting and fasciculations of the muscles. Onset may involve the bulbar muscles, affecting speech production and swallowing, or the limbs, affecting mobility. The presence of ALS attenuates the disease course (55, 64, 79, 86) and accounts for patients with very short duration of disease. The presence of ALS is also associated with differences in gender distribution. FTLD disorders as a whole affect men and women equally (124, 141). In patients with accompanying ALS, however, there is a significant male bias (143). Moreover, the presence of ALS influences the likelihood of one clinical syndrome rather than another. It is most often seen in combination with bvFTD. An association with SD and PNFA can occur but it is rare (143).

ALS is not the only possible physical accompaniment of FTLD syndromes. There is a clinical overlap between bvFTD and the neurological disorders of progressive supranuclear palsy (PSP), characterized by ophthalmoplegia and falls, and corticobasal syndrome (CBS), characterized by limb rigidity and apraxia (14, 81, 89).

The clinical, pathological and genetic heterogeneity within FTLD has led authors to highlight the need for biomarkers to enable the different pathologies to be distinguished in vivo (73). Whilst this is undoubtedly an important goal, there are already some clues. Close examination reveals certain predictabilities. Pathological subtypes do have clinical and genetic associations. These are important because they may inform understanding of the mechanics of neurodegeneration.

CLINICAL—PATHOLOGICAL CORRELATES

The behavioral disorder of bvFTD can be associated with FTLD-tau, FTLD-TDP or FTLD-FUS pathology (Table 1, Figure 5). Thus, the presence of a behavioral disorder *per se* does not distinguish between pathologies. However, when it occurs in combination with ALS, bvFTD is consistently associated with FTLD-TDP rather than tau pathology (84, 140, 157). Thus, the presence of ALS is a strong predictor of TDP rather than other pathologies. By contrast, neurological signs of PSP (vertical gaze palsy) and CBS predict tau pathology (46, 84). A very early onset of disease, before the age of 40 years is a strong predictor of FUS pathology (120, 145, 156, 166).

SD (in its pure form) is consistently linked to TDP pathology (84, 140, 157). PNFA may be underpinned by either FTLD-tau or FTLD-TDP pathology (84, 140, 157) yet there are specific characteristics of the language disorder that favor one pathological type over the other. In particular, effortful speech production and speech apraxia is a predictor of tau rather than TDP-43 pathology (80). Non-fluent speech production arising secondary to severe anomia has been linked to TDP-43 pathology (155).

BvFTD, PNFA and SD, as noted above, can all be associated with FTLD-TDP pathology. Yet, interestingly, the pathological characteristics are not identical. Clinical phenotype predicts a specific sub-type of TDP pathology (Table 1, Figure 5). PNFA is specifically associated with subtype A, in which there are numerous short DN and NCI, mostly in layer 2 of frontal and temporal cortex, associated with loss of neurones from that layer and a vacuolated appearance to the tissue (microvacuolation) (100). FTD, when combined clinically with ALS predicts subtype B histology, characterized by a predominance of NCI, again mostly in layer 2, but also involving those within deeper layers of the cortex. DN are relatively sparse (100). SD is associated with FTLD-TDP type C, where the predominant pathology is that of long neuritic profiles traversing the entire depth of the cerebral cortical ribbon (100).

The histological variants of FTLD-FUS are also associated with different clinical phenotypes. Patients with aFTLD-U pathology present with a prominent behavioral disorder of bvFTD (93, 140,

145, 156, 166), whereas in NIFID and BIBD motor symptoms predominate (93). Patients with aFTLD typically show obsessional and stereotyped behaviors, which are more marked than in other forms of bvFTD (139, 156). They may also show psychotic symptoms (156). Caudate atrophy is commonly reported (83, 156). It is the aFTLD-U form of FUS pathology that is particularly associated with very early onset of disease, in the 4th or 5th decade of life.

Familial vs. sporadic disease

FTLD may be familial or sporadic. The prevalence of familial disease differs according to clinical phenotype. bvFTD is most likely to be familial (137). SD, in its pure form, is rarely so (66, 137). There are, by implication, differences in type of pathology. TDP-43 types A and B pathology are more likely to be found in familial disease than type C, reflecting the fact that SD is unique to type C pathology.

In terms of tau pathology, familial forms of FTLD can be associated with either neurofibrillary or Pick type of tau pathology, depending on the location of the genetic mutation (Figure 5). Sporadic forms are mostly associated with Pick body histology. Just occasionally, apparently sporadic, forms show globular tau-immunoreactive oligodendroglial inclusions within white matter, leading to the pathological diagnosis of FTLD-tau with globular glial inclusions.

CLINICAL—GENETIC CORRELATES

Familial cases are most caused by mutation in one of 3 main genes, *MAPT*, *GRN* or *C9orf72*, although a proportion of cases still remains in whom there is a positive family history of dementia without known mutations. Clues to genotype can be deduced from clinical presentation.

bvFTD is commonly associated with mutations in each of the genes (159), so its presence, in itself, is non-discriminatory (Figure 5). However, in patients with *MAPT* mutations prominent behavioral disinhibition is characteristic (76, 127, 159) whereas in *GRN* and *C9orf72* cases apathy typically prevails (11, 159). Moreover, *MAPT* patients with intronic (splice site) mutations in exon 10 frequently exhibit semantic impairments in addition to their behavioral disorder (76, 127), a feature not seen in *GRN,* and only rarely in *C9orf72*, patients (159).

By contrast, mutations in *GRN* are associated with PNFA (26, 39, 95, 96, 128, 131, 168, 178) in up to a third of cases (Figure 5). The remaining two thirds presents with bvFTD. The distinct clinical presentations of bvFTD and PNFA may occur within the same family (11, 159) and there may be overlapping characteristics with disease progression. PNFA is absent in *MAPT* and rare in *C9orf72* cases (159).

FTD-ALS is associated with hexanucleotide expansions in the *C9orf72* gene (15, 70, 158, 169), but not with *MAPT* or *GRN* mutations (96, 159) (Figure 5). Psychotic features (delusions and hallucinations) too are common in patients with *C9orf72* expansions (43, 49, 87, 158). They occur to some degree in patients with *GRN* mutations (159, 170), but are rare or absent in sporadic FTD and in association with *MAPT* mutations (158, 159).

Consistent with the clinical differences *MAPT*, *GRN* and *C9orf72* are associated with different patterns of atrophy can be detected on neuroimaging (176).

Genetic—pathological correlates

The tau gene (MAPT)

The tau gene (*MAPT*) has 15 coding regions (exons), and transcripts are alternatively spliced to produce 6 different isoforms ranging from 352 to 441 amino acids in length. Tau is normally located in axons and regulates microtubule assembly/disassembly, and axonal transport of proteins and organelles. All six isoforms play a role in maintenance of microtubular structure. If one or more fails, or if there is a stoichiometric imbalance in the different variants, microtubule formation will become more difficult or the stability of microtubules formed will become compromised. Any excess of tau (of any isoform composition) can be bundled into indigestible residues (neurofibrillary tangles or Pick bodies) that choke the cell, but may also induce neurotoxicity. All patients with *MAPT* mutations are characterized by the deposition of insoluble, aggregated tau proteins within neurons and glial cells in the cerebral cortex and other brain regions. Nevertheless, there are two histological patterns depending on the location of the mutational change in the gene.

Most of the *MAPT* mutations are missense, deletion or silent mutations within coding regions of exons 1, 9, 11, 12 and 13, and affect all 6 isoforms of tau generating mutated tau molecules that (variably) lose their ability to interact with microtubules and promote axonal transport (60, 61, 67, 69, 113, 135, 136). Some also increase the propensity of the mutated tau to self-aggregate into fibrils that form characteristic pathological structures, usually Pick-like bodies (Figure 1A) within the brain (52, 60, 61, 114, 118, 135). Conversely, those with mutations in and around the stem loop structure produce an excess of 4R tau; hence, the insoluble tau aggregates are composed predominantly of 4R tau isoforms (29, 42, 69, 127), appearing as neurofibrillary tangle-like structures within large and smaller pyramidal cells of cortical layers III and V, and also prominent within glial cells in the deep white matter, globus pallidus and internal capsule (42, 127) (Figure 1B).

The progranulin gene (GRN)

GRN contains 13 exons and encodes a full-length protein (PGRN, predicted molecular weight 68 kDa) secreted as a glycosylated 85 kDa precursor which can be cleaved by elastase-like activity into a series of 6 kDa cysteine-rich fragments called granulins (GRNs) (63, 180). Both PGRN and the GRNs are biologically active with roles in tissue remodeling processes (4, 170). In peripheral tissues, PGRN is involved in development, wound repair and inflammation, activating signaling cascades that control cell cycle progression and cell motility (62). In the brain, PGRN is expressed in both neurons and microglia, particularly so in the latter following brain injury. *GRN* mutations in FTLD include missense mutations generating premature stop codons, insertion or deletion mutations resulting in frameshifts, or changes within initiation codons precluding transcription (9, 34). Nonetheless, all mutations, irrespective of type, ultimately generate the same functional effect – a null allele – with at least 50% loss of translated protein, causing haploinsufficiency. Most transcripts are immediately destroyed through nonsense-mediated decay, and it is likely that none, or perhaps only a small proportion, is ever translated into mutant protein, thereby explaining the lack of mutated PGRN protein within NCI and DN (9).

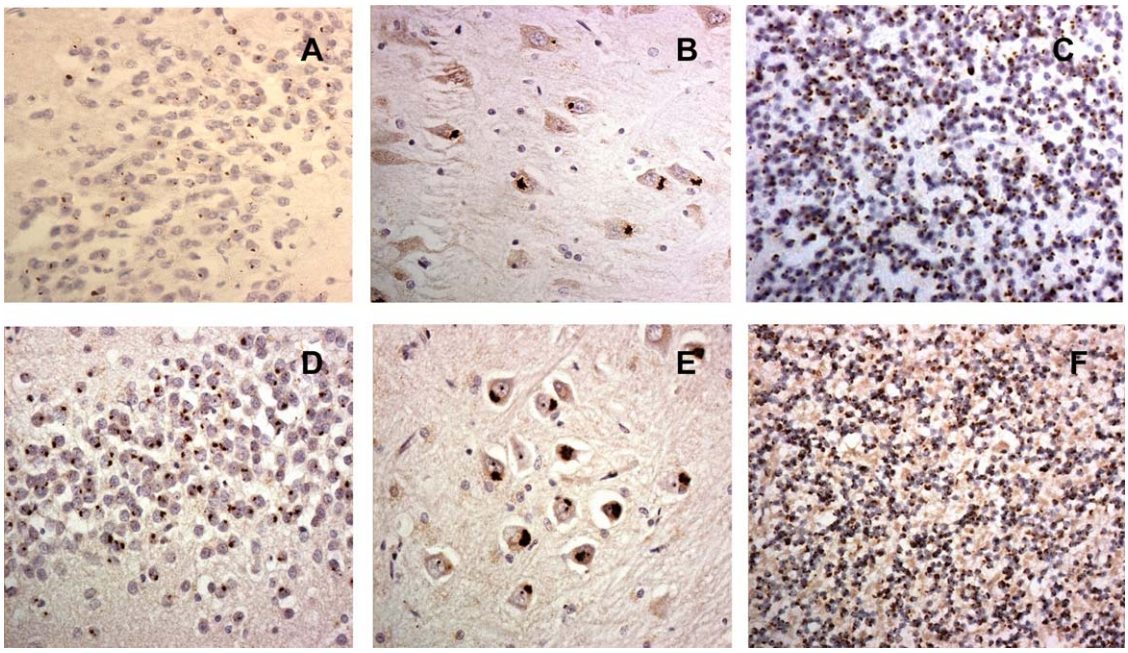

Figure 4. Dipeptide repeat proteins in hippocampus (A,B,D,E) and cerebellum (C,F) as observed in p62 immunostaining (A–C) and with antibody against poly (GA) (D–F).

Intriguingly, whilst heterozygous mutations in *GRN* result in FTLD, homozygous *GRN* mutations are associated with the lysosomal storage disease, Neuronal Ceroid Lipofuscinosis (NCL) (150), implying a role for PGRN in endosomal/lysosomal/autophagosomal pathways.

Consistent with observations that *GRN* mutations do not result in the translation of mutated PGRN protein, the pathological changes in FTLD are witnessed as brain accumulations of TDP-43, principally in the cerebral cortex and hippocampus, in the form of NCI and DN (9, 34) (Figure 2). NII of a "cat's eye" or "lentiform" appearance (Figure 2) have also been described (9, 34, 98, 128, 154).

C9orf72 expansion

The third major genetic cause of familial FTLD with or without ALS in combination, or familial ALS itself, is a hexanucleotide repeat expansion in *C9orf72* gene (40, 134). Little is known about the normal function of C9orf72 protein, though homology suggests it may be part of the DENN (Differentially Expressed in Normal and Neoplastic cells) family of proteins which are GTD/GDP exchange factors that activate Rab-GTPases. Consequently, the exact pathological mechanism(s) underlying the expansion in *C9orf72* remains uncertain. A loss of function effect (haploinsufficiency) consequent on a reduced output of C9orf72 protein has been suggested (40, 173). Alternatively, the formation of both sense and antisense nuclear RNA foci has been demonstrated, both in human disease (31, 32, 40, 108) and in fly models (108). These may sequester RNA transcripts (40, 108), or other endogenous RNA binding proteins (31, 32), thereby interfering with the transcriptome. Lastly, a non-ATG mediated (RAN) sense and antisense translation of the expansion itself leads to formation and cellular (usually cytoplasmic) accumulation of the dipeptide repeat proteins (DPR), poly-GA, poly-GR, poly-GP, poly-PA and poly-PR, of presumed variable length (6, 37, 103, 110, 111, 181), any, or all, of which could confer neurotoxicity (91, 105, 109, 144, 175, 179). None of these three possible mechanisms is likely to be mutually exclusive and all could play some part in driving the TDP-43 proteinopathy that characterizes the disorder.

Expansions in *C9orf72* are invariably associated with two histopathological changes. Firstly, there is TDP-43 proteinopathy, type A in patients with bvFTD alone or type B when bvFTD is combined with MND (Figure 5). Secondly, RAN translation of the expansion results in the deposition of aggregates of p62-positive, TDP-43-negative dipeptide repeat proteins (DPR) within the cytoplasm, and sometimes nucleus, of affected cells (Figure 4). DPR derived from sense translation (poly-GA, poly-GP and poly-GR) seem to be more abundant than those derived from antisense translation (poly-PA and poly-PR) (38, 101). The presence of the pathognomonic p62-containing DPR in *C9orf72* expansion bearers

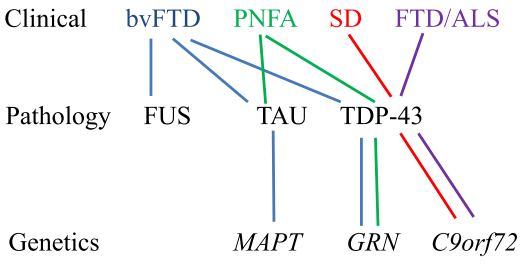

Figure 5. Clinicopathological-genetic relationships.
[Correction added on 26 April 2017, after first online publication: Figure 5 has been replaced to correct an error in the alignment of the figure labels in the originally published version.]

suggests an underlying dysfunction of the ubiquitin-proteasome system (UPS), which accords well with observations that mutations in genes coding for other members of this system (ie *SQSTM1*, *UBQLN2*, *OPTN*, *VCP*, *TBK1* and *CHMP2B*) are all associated with bvFTD, and all except *CHMP2B* (68) with TDP-43 proteinopathy. Indeed, *TMEM106B*, variations in which have been associated with bvFTD and TDP-43 pathology (168), is also claimed to have functions within lysosome/endosome system. Hence, FTLD associated with TDP-43 proteinopathy may reflect dysfunctions within protein degradation systems of the brain and failure to clear neurotoxic TDP-43 aggregates. Whilst mutations in *MAPT* are clearly not associated with TDP-43 proteinopathy, and no clear role in regulation of protein degradation pathways has been assigned to tau protein, this form of FTLD could, as with Alzheimer's disease and other tauopathies, again derive from failures of the lysosomal/proteasomal system to clear neurotoxic (phosphorylated, oligomeric) species of tau, which eventually overwhelm the neuron leading to its demise.

How, or indeed whether, DPR are related to TDP-43 proteinopathy remains unclear. Despite strong experimental evidence pointing the finger at DPR, especially those containing arginine residues, poly-GR and poly-PR (109), the clinical phenotype of bvFTD, bvFTD with ALS or ALS itself seems more closely related to the presence and brain distribution of TDP-43 pathological changes than of DPR (37, 38, 53, 101). DPR are present in similar brain distributions in patients with bvFTD, bvFTD with ALS or ALS alone, and are widely present in affected and unaffected (by TDP-43) regions of cerebral cortex, and numerous in granule cells of the cerebellum, CA subregions of the hippocampus and subcortical structures such as thalamus (Figure 4) (38, 53). Such a widespread distribution in "clinically silent" regions argues against a pathogenic role. Moreover, the extent of TDP-43 pathological changes in bearers of *C9orf72* expansion is identical in degree and distribution to that in patients with *GRN* mutation or no known mutation at all (38). Thus DPR may simply be pathological bystanders with no functional consequence. Nevertheless, as with other aggregating proteins such as Aβ or α-synuclein, it remains possible that more soluble, and potentially neurotoxic, forms of DPR exist, and that the aggregated proteins seen in neurons represents a "neuroprotective" action on the part of the neuron in an attempt to package these out of harm's way. In this context the absence of DPR in spinal neurone with TDP-43 proteinopathy in ALS (38, 53) may be relevant. However, the presence of such soluble (oligomeric) forms of DPR in human brain tissue has not been substantiated by western blotting. This may not be surprising given the extremely hydrophobic nature of the DPR which would "naturally" lead them to rapidly aggregate rapidly.

Some support for a pathogenic role of DPR comes from the observation that brains of preclinical *C9orf72* expansion carriers and people with psychiatric or systemic disease in whom disease has been prematurely terminated due to accident or physical illness, show widespread DPR and RNA foci in the absence or near absence of TDP-43 pathology (8, 50, 130, 171). The presence of DPR within the brain may predate that of TDP-43 by many years (171). Rare cases such as these are useful in confirming that DPR accumulation precedes TDP-43 pathology, but do not provide irrefutable evidence for a pathogenic role of DPR, especially in the most clinically common *C9orf72* phenotypes. It remains possible that DPR are evidence of a functional/physiological deficit brought about by the effects of the gene expansion *per se*.

A possible explanation for these discrepancies between experimental and human studies may lie with the simplistic model systems that have been used to date in which transient over-expression of DPR in cell cultures artificially elevates the rate of DPR production, thereby quickly overwhelming the cells. In human disease, DPR accumulation proceeds at a much slower rate, possibly over decades as is likely with Aβ accumulation in Alzheimer's disease, so that the neurons are able to manage this effectively, and counteract any detrimental effect. In this regard, some recent studies using mammalian models may be relevant. Transgenic mice carrying a bacterial artificial chromosome (BAC) containing the human *C9orf72* gene with a disease-relevant expansion were found to develop DPR pathology and RNA foci though no behavioral abnormalities developed and no neurodegeneration or TDP-43 pathology was present (125, 126). In contrast, when an adeno-associated virus was used to express the expanded repeat mice did develop behavioral abnormalities and neurodegeneration and showed TDP-43 pathology in addition to DPR pathology and RNA foci (27). Taken together, these observations from mammalian models support the conclusion that RNA foci and DPR develop early but are insufficient to drive neurodegeneration in the absence of TDP-43 pathology.

One way of reconciling these apparently anomalous findings would be to regard the effects of the expansion as a "gatekeeper" to disease whose physiological/metabolic effects make key regions of brain, such as the frontal and temporal cortex, vulnerable to the same factors that induce TDP-43 proteinopathy in sporadic forms of FTLD-TDP. This concept is in keeping with observations that the expansion in *C9orf72* has no direct bearing on the specific histological or biochemical subtype, those patients with *C9orf72* expansion bearing type A histology showing a TDP-43 C-terminal banding pattern indistinguishable from that in patients with *GRN* mutation, or without known mutation, with type A histology, and those *C9orf72* patients with type B histology a pattern akin to that in patients with sporadic bvFTD with ALS (164). However, such a mechanism would require expansions in *C9orf72* essentially to exert a loss of function effect, and that sporadic forms of bvFTD and bvFTD with ALS displaying TDP-43 type A and type B histologies, respectively, would also suffer loss of C9orf72 function. While there is some evidence to suggest this is so in *C9orf72* expansion carriers at least (40, 173), the absence of well-characterized antibodies to the protein has hindered our lack of understanding of the normal role of C9orf72, and how changes in expression may affect protein degradation and influence disease risk. Although RAN translation in *C9orf72* expansions may drive DPR formation unambiguous evidence that these latter molecules are anything other than pathological bystanders, and are capable of inducing pathogenic effects and contributing to the generation of clinical change, in the context of human disease, is still lacking.

Functional consequences

TDP-43 is a 43 kDa nuclear protein, 414 amino acids long, first identified as a binding partner to the TAR DNA element of the human immunodeficiency virus. The TDP-43 gene (*TARDBP*), located on chromosome 1p36.2, contains 6 exons and is

ubiquitously expressed. It has 2 highly conserved RNA recognition motifs (RRM1 and RRM2) and a C-terminal, glycine rich tail, which mediates protein-protein interactions, including interactions with other heterogeneous ribonuclear protein (hnRNP) family members. Under physiological conditions, TDP-43 is mostly present within the nucleus, though low levels occur within the cytoplasm (7, 21, 163, 165, 177). It is believed that TDP-43 shuttles continuously between nucleus and cytoplasm, a process regulated by nuclear localization, and nuclear export, signal motifs. When NCI are present in the cell, TDP-43 is no longer detectable immunohistochemically in the nucleus, possibly having been sequestered into NCI (Figure 2). Perturbation of trafficking of TDP-43 between nucleus and cytoplasm may be a functional consequence of its incorporation into these cytoplasmic aggregates (177), though it is still unclear whether disease is due to a toxic gain of function relating to these pathological aggregates or stems from loss of normal nuclear functions, or some combination of the two.

In some cases, ubiquitinated, Pick-body-like inclusions are present in neurons of frontal and temporal cortex, and basal ganglia. These inclusions are negative for tau, TDP-43 and α-synuclein but (variably) immunopositive for all class IV intermediate filaments (IF), light, medium and heavy neurofilament subunits (13, 22–24, 78) and α-internexin (25, 121). Consequently, the disorder is known as neuronal intermediate filament inclusion disease, NIFID, and classified as FTLD-IF (109).

TDP-43 and FUS are both transcription factors involved in the transport of mRNA to dendritic spines for local translation in relation to synaptic activity. This process requires the involvement of several types of RNA-containing granules – ribonuclear protein particles (RNP), processing bodies (PB) and stress granules (SG) (16). However, whereas TDP-43 appears to be associated with PB, FUS relates to SG (16, 172). PB are associated with mRNA decay processes and decapping enzyme1 protein – a marker for PB – is absent from NCI in BIBD (47), explaining the lack of TDP-43 in such inclusions. In contrast, NCI in BIBD contain mRNA-binding proteins poly(A) binding protein 1 and T cell intracellular antigen 1, indicating their association with SG rather than RNP or PB (47). Hence, TDP-43 and FUS play different, through complementary, roles in the processing of RNA. The fact that mutations in *TARDBP* and *FUS* are associated with ALS and not bvFTD, alone or in combination with MND (12, 51, 57, 85, 90, 161), suggests that pure ALS, when characterized by TDP-43 or FUS proteinopathy, is driven by functional changes in RNA metabolism – a notion put forward many years ago (102)

Mechanistic considerations

Apart from being diagnostically relevant, and of clear value in the classification of disease, the histopathological changes in TDP-43 that characterize many cases of FTLD may also inform pathogenesis. Although the use of "generic" antibodies to TDP-43 have proved helpful in characterizing the morphological changes of FTLD-TDP to subtype TDP-43 proteinopathy, they may mask subtle biochemical and proteolytic differences that could provide clues to neural pathways involved in the disease, and highlight mechanistic differences between disorders. Hence, while immunoblotting of sarkosyl-insoluble fractions from FTLD-TDP and ALS cases demonstrates hyperphosphorylated full-length TDP-43 at 45 kDa, smearing substances, and fragments at 18–25 and 35 kDa in common across all histological subtypes, the use of phosphospecific antibodies, enables at least three C-terminal banding patterns to be distinguished, which correspond to pathological phenotypes (164). Moreover, the insoluble TDP-43 aggregates appear to have prion-like properties, whereby TDP-43 can induce aggregates characteristic of its own particular C-terminal subtype via a proposed templated self-seeding mechanism (48, 123, 149). Indeed, TDP-43 pathology in ALS, at least, appears to progress in a hierarchical fashion that permits the recognition of 4 neuropathological stages (18, 19), consistent with the hypothesis that TDP-43 pathology is propagated along axonal pathways, Collectively, these observations raise the possibility that each histopathological subtype may be associated with a specific pattern of TDP-43 mismetabolism and proteolysis, and that each clinical syndrome develops from the templating and spread of such aggregates along its own discrete series of pathways.

The different morphological appearances and topographic patterns associated with each histological subtype have neuroanatomical implications. Subtype A, in which there is widespread NCI and DN within layer 2 of the cortex (Figure 2A) suggests degeneration within connecting corticocortical pathways, this being the layer where nerve terminal from intracortical projection fibres terminate. Type B histology, where NCI within cells of origin in layers 2, 3 and 5 predominate over DN (Figure 2B), implies involvement of cortical efferent pathways to subcortical regions. In type C histology (Figure 2C), the predominance of DN as long neuritic profiles could reflect damage to cortical afferents originating in the bilaterally damaged temporal lobes.

Such interpretations have relevance in terms of clinical phenotype. Sub-type A is particularly associated with PNFA, which affects the left hemisphere extensively and is accompanied by loss of white matter connectivity in dorsal pathways (2, 3). There is prominent involvement of arcuate fasciculus, the traditional language pathways associated with phonological processing. PNFA patients may know a word but have difficulty accessing the pattern of sounds with which it is associated, in keeping with lack of cortico-cortical connections. In sub-type B, the involvement of cortical efferent pathways to subcortical regions is consistent with the specific association of this subtype with FTD-ALS. It could be argued that FTD-ALS represents a "cortical" extension of MND-type pathology. Type C histology is specifically linked to SD. From a clinical perspective, SD might be construed as a disorder of "connectivity." Patients with SD hear words, perceive objects and experience other sensory inputs normally. The problem is that those normal percepts have lost their connotative associations: they no longer "connect up" to convey meaning. The anterior temporal lobes are thought to be crucial for the integration of information from different modalities. Neuroimaging studies in SD using tractography (1, 2) also provide evidence of impaired connectivity. They have shown extensive loss of white matter connectivity from ventrorostral temporal lobes, affecting uncinate and inferior longitudinal fasciculus and including pathways to the supramarginal gyrus and the posterior superior temporal gyrus, classical language areas. The imaging findings have been interpreted (1) in terms of degeneration of axons whose cell bodies arise in the anterior temporal lobe and project to posterior language areas. The findings suggest a mechanism whereby a primary ventrorostral temporal lesion may result in a loss of input to language areas that are not themselves damaged.

Diagnostic and therapeutic issues

As summarized above, certain forms of FTLD, particularly the language variants, "obey" strict rules as regards their clinical, histological and genetic characteristics. SD and some forms of PNFA reflect TDP-43 proteinopathy. Where there is autosomal inheritance of disease in PNFA, this relates to mutations in *GRN*. Similarly, when MND is present combined with bvFTD (and rarely SD or PNFA), TDP-43 underlies this, and inherited forms are always associated with expansions in *C9orf72*. Should therapeutic options based on a correction of TDP-43 abnormalities become available, choice of treatment could be based on these clinical and/or genetic features. The major challenge to diagnosis and therapy lies with bvFTD, since here there are potentially three histologies, and 3 genes (at least), that could drive the disease process. Distinguishing which might be responsible to direct treatment is not easy, unless there is a genetic cause. Whilst a validated clinical genetic test for *C9orf72* is now widespread and relatively inexpensive, screening for *MAPT* or *GRN* mutations is more challenging, both in time and cost, given that a mutation could putatively exist in most of 15 exons in *MAPT* or 13 exons in *GRN*. FTLD-FUS is essentially non-genetic, ruling out one line of diagnostic enquiry. Better ways of predicting disease, either employing patterns of atrophy based on MRI image, or PET ligands that specifically bind to the relevant aggregated protein, would help reduce diagnostic uncertainty for bvFTD at least, though in this respect more precise neuropsychological profiling may help refine diagnosis and point to relevant therapy. Clues like the association between *MAPT* mutations and semantic impairment, very early onset with FUS pathology, psychosis and ALS with *C9orf72* expansion with TDP-43 proteinopathy, can provide helpful pointers.

CONCLUSION

While it is clear that FTLD is a beast with many heads, their faces bear distinguishing features that point to distinctive origins and properties. SD (especially) and PNFA have tight clinical, histological and genetic inter-relationships, which ease diagnostic uncertainty and facilitate potential therapeutic strategy. BvFTD remains a challenge, where the overlapping clinical and histological properties are as yet only partially resolved by genetic analysis or neuropsychological assessment. Future advances in blood biomarkers and brain imaging may help to dissect underlying processes and direct therapy. It remains to be seen whether we can devise a single magic bullet that will slay the heart of the beast, and in so doing unselectively take with it all of its varying heads, irrespective of their complexion, or whether a more targeted approach will be required to identify and take out the individual malign elements that cripple the beast as a whole.

CONFLICT OF INTEREST

The authors have no Conflicts of Interest to declare.

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