Frontotemporal Lobar Degeneration: Current Concepts in the Light of Recent Advances

Samir Kumar-Singh, Christine Van Broeckhoven

Neurodegenerative Brain Diseases Group, Department of Molecular Genetics, Laboratory of Neurogenetics, VIB, Institute Born-Bunge and University of Antwerp, Universiteitsplein 1, BE-2610 Antwerpen, Belgium.

Corresponding author: Samir Kumar-Singh, VIB—Department of Molecular Genetics, University of Antwerp, Universiteitsplein 1, BE-2610, Antwerpen, Belgium.
(E-mail: Samir.KumarSingh@ua.ac.be)

Work done over the past decade has led to a molecular understanding of frontotemporal lobar degeneration (FTLD), a deadly disease that afflicts patients in mid-life. It is a common cause of dementia, second only to Alzheimer’s disease in the population below 65 years of age. Neuroanatomical and neurobiological substrates have been identified for the three major subtypes of FTLD and these discoveries have broadened the FTLD spectrum to include amyotrophic lateral sclerosis (ALS). Mutations in MAPT were found to cause frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), a familial disorder with filamentous tau inclusions in nerve cells and glial cells. FTDP-17 can result in clinical syndromes that closely resemble progressive supranuclear palsy, corticobasal degeneration and Pick’s disease. More recently, mutations in three genes (VCP, CHMP2B and PGRN) have been found to cause FTLD with ubiquitin-positive, tau-negative neuronal inclusions (FTLD-U). They explain a large proportion of inherited FTLD-U. It remains to be seen whether dementia lacking distinctive histopathology (DLDH) constitutes a third disease category, as many of these cases are now being reclassified as FTLD-U. Recently, TAR DNA-binding protein-43 (TDP-43) has been identified as a key protein of the ubiquitin inclusions of FTLD-U and ALS. Thus, for familial forms of FTLD and related disorders, we now know the primary etiologies and accumulating proteins. These findings are pivotal for dissecting the pathways by which different etiologies lead to the varied clinicopathological presentations of FTLD.


INTRODUCTION

Frontotemporal lobar degeneration (FTLD) is the second most common form of cortical dementia in the population below the age of 65 years. Clinically, it is characterized by changes in personality/behavior and/or language dysfunction (aphasia), and results in at least three distinct clinical syndromes: frontotemporal dementia, semantic dementia and primary progressive aphasia (PPA). Extrapyramidal features can also be present and are an important component of corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP).

Over the past decade, much effort has gone into the histopathological characterization of FTLD and, based on the presence or absence of the microtubule-associated protein tau (MAPT) in neuronal inclusions, FTLD is now classified as either a tauopathy or a non-tauopathy disorder. Tauopathy disorders (FTLD-τ) include Pick’s disease, PSP, CBD, and frontotemporal dementia and parkinsonism linked to chromosome-17 (FTDP-17). The non-tauopathy disorders include FTLD with ubiquitin-positive neuronal inclusions (FTLD-U) and dementia lacking distinctive histopathology (DLDH). However, considerable heterogeneity is observed both clinically and neuropathologically and many of the neurobehavioral syndromes and pathologies overlap (Figure 1). This partly matches with the high genetic complexity observed in FTLD.

Despite this heterogeneity, the past few years have witnessed enormous progress, both in terms of understanding the pathological complexity and in identifying the genetic etiologies of FTLD. If a rapidly changing classification and a new terminology are a measure of increasing knowledge, then progress in FTLD has been rapid indeed. As a result, CBD and PSP are now grouped under the umbrella of FTLD-τ (62). Over the past 3 years, the first FTLD-U-causing genes have been identified. They are the valosin-containing protein gene or VCP on chromosome 9p21-p12 (109), the charged multisvesicular body protein 2B gene or CHMP2B on chromosome 3p13 (97) and the recently identified progranulin gene or PGRN on chromosome 17q21-22 (6, 16). Identification of PGRN was particularly exciting, as it provided an explanation for the amazing coincidence of the presence of two important genes linked with the same disease phenotype on chromosome 17q21-22. Moreover, TAR DNA-binding protein (TDP-43) has recently been identified as a key protein in the inclusions of FTLD-U and related disorders (75). It remains to be seen whether mutations in the TDP-43 gene can also cause FTLD-U. The central theme of this review is to identify commonalities and overlaps between the different clinicopathological entities, and to support the viewpoint that FTLD is part of a spectrum of diseases that includes amyotrophic lateral sclerosis (ALS).

CLINICAL SYNDROMES COMPRISING FTLD

FTLD usually occurs between the ages of 35 and 75 years and is the second most common form of cortical dementia in the presenium, after Alzheimer’s disease (AD). The personality changes and aphasia observed in patients allow one to distinguish between the three prototypical
clinical syndromes of frontotemporal dementia, semantic dementia and PPA. Recently, highly specific (57, 74) and very sensitive (62) diagnostic criteria have been established for these disorders.

Frontotemporal dementia (FTD) is the most common clinical manifestation of FTLD, accounting for 5%–10% of all dementia patients, 10%–20% of which are younger than 65 years (31, 74, 89). In these patients, progressive deterioration in personality occurs, initially with a relative preservation of language and memory. Social and personal conduct is profoundly altered, accompanied by inertia and loss of volition. Repetitive, compulsive and stereotypic behavior is common. Although linguistically correct, speech output is reduced. Mutism may ensue later in the course of the disease. The absence of early neurological signs and findings of focal abnormalities in the frontotemporal lobes on neuroimaging contribute to the clinical diagnosis. However, in some patients, only behavioral changes are observed and these patients are referred to as having FTD-behavioral variant. FTD can also be accompanied by signs of parkinsonism, as in CBD, a clinical syndrome where progressive asymmetrical rigidity and apraxia, often accompanied by aphasia, are the most common symptoms. Similarly, progressive aphasia and behavioral features can also accompany PSP, which is the second most common cause of parkinsonism, after Parkinson’s disease. PSP is characterized by progressive axial rigidity, bradykinesia, vertical gaze palsy and dysarthria. Rarely, FTD is accompanied by motor neuron disease (FTD-MND), where patients have features of both ALS and FTD. Other complex forms of FTD associated with additional phenotypes have been described, especially in familial forms. Thus, families linked to chromosome 3p13 (CHMP2B gene) or to chromosome 9q21 have parkinsonism, as is often observed in FTDP-17; chromosome 20p-linked families have motor disturbances; and chromosome 9p21-p12-linked families (VCP) present with the unusual triad of inclusion body myopathy (IBM), Paget’s disease of the bone (PDB) and FTD (IBM-PDB-FTD) [reviewed in (82)].

Semantic dementia and PPA are alternative presentations of FTLD, where progressive changes in language function are an early and predominant feature that precedes behavioral symptoms. In semantic dementia, loss of verbal and nonverbal skills is the core feature, as evidenced by impairment in naming and word comprehension in the context of a fluent, effortless and grammatically correct speech output. An inability to recognize the meaning of visual stimuli is a striking feature; however, visuospatial skills and day-to-day memory are well preserved. Late in the course of the disease, patients may become mute. By contrast, PPA is a disorder of expressive language that is characterized by a progressive reduction in speech production, with phonological and grammatical errors and word retrieval difficulties, with preservation of daily life activities and evidence of relatively normal nonverbal abilities on neuropsychological testing. The understanding of word meaning is reasonably well preserved, while difficulties in reading and writing may occur. With the progression of disease, patients may become mute. These overlapping neurobehavioral syndromes have overlapping and heterogeneous pathological correlates.

**NEUROPATHOLOGY OF FTLD**

The current consensus on the pathological classification of FTLD is based on (i) histopathological presence or absence of neuronal inclusions; (ii) immunohistochemical identification and biochemical characterization of proteins accumulating in the neuronal/glial inclusions; (iii) anatomical distribution of the underlying histopathology.

A first distinction is made based on the presence of tau inclusions (Figure 2). Tau is the MAPT gene product and adult human brain expresses six tau isoforms that are derived from a single gene by alternative mRNA splicing. Three isoforms contain three microtubule-binding repeats each (3R-tau); the other three isoforms have an additional repeat encoded by exon 10 of Tau (4R-tau). Thus, based on the presence or absence of filamentous tau inclusions, FTLD is differentiated into tauopathy and non-tauopathy. The tauopathy group is further divided into 3R-tau and 4R-tau subgroups, that is, 3R-tau in Pick’s disease, 4R-tau in CBD and PSP and all six isoforms in AD. However, this is only a rough guide, because overlaps frequently occur, especially in Pick’s disease.
Among the forms of FTLD without tau deposits, two overlapping pathologies are observed. The first type is characterized by the presence of ubiquitin-positive neuronal inclusions, also called FTD without motor neuron disease (MND), but with MND-type inclusions or, more commonly, FTLD-U. The second type is that without ubiquitin-positive inclusions and is referred to as DLDH.

**Tauopathy FTLD**

*Pick's disease.* The first form of FTLD was described by Arnold Pick in 1892 in patients with behavioral and aphasic clinical presentations and a severe circumscribed atrophy of the frontotemporal lobes at autopsy (79). Subsequently, many investigators, including Alzheimer, described the histopathological features of argyrophilic inclusions (later referred to as Pick bodies) and swollen achromatic cells (later referred to as Pick cells), and the eponym Pick's disease was suggested. This term is now restricted to cases of FTLD with Pick bodies. Pick's disease is often considered to be the prototypical FTLD; hence the concern that this might lead to the erroneous view that all cases of FTLD are tauopathies (46, 106).

The classical atrophy observed in patients with Pick's disease is a “knife-edge” atrophy of the frontal and temporal lobes of the cerebral cortex. The posterior part of the superior temporal lobe is typically spared. Affected brain regions show severe neuronal loss and astrogliosis, but the chief histological abnormality is the presence of Pick bodies in the dentate gyrus, pyramidal cells of the CA1 sector and subiculum of the hippocampus, the neocortex and several subcortical nuclei. In the neocortex, Pick bodies are frequently located in layers II and VI, in contrast to the predominance of neurofibrillary tangle...
many cases of FTDP-17 resemble sporadic Biochemically and neuropathologically, neuronal and spongiosis in the superficial cortical layers. Atrophy of the frontal and temporal lobes pathologically, FTDP-17 presents with age around 50 years (27, 70, 92). Neuroonset is also highly variable and ranges between mutations and within fami-
lies with the same mutation (27). Age at onset is also highly variable and ranges from the early 20s to late 70s, with a mean age around 50 years (27, 70, 92). Neuro-pathologically, FTDP-17 presents with atrophy of the frontal and temporal lobes with neuronal loss, astrocytic gliosis and spongiosis in the superficial cortical layers. Basal ganglia are also affected (27). Filamentous tau inclusions in neuronal and glial cells are a characteristic finding (98). Biochemically and neuropathologically, many cases of FTDP-17 resemble sporadic Pick's disease.

FTLD-U inclusions (82). A link between CBD and PSP is that they are both 4R-tauopathies (11, 71, 105).

A relatively new entity in the 4R-tau group is argyrophilic grain disease (AGD). Because the specific disease manifestations of AGD are currently unclear, it has so far remained a neuropathological entity (9, 103, 104). Argyrophilic grains are present in the hippocampal region and the amygdala, and are accompanied by coiled bodies in the underlying white matter and ballooned neurons in the limbic region. The frequency of AGD is estimated to be 5% at routine autopsy (65, 103).

Non-tauopathy FTLD

FTLD with tau-negative, ubiquitin-positive inclusions (FTLD-U). Recent esti-
mates have suggested that patients lacking tau pathology account for more than 50% of autopsy-confirmed FTLD (25, 41, 43, 45, 56). This proportion will grow even larger as many patients previously thought to be having DLDH show FTLD-U pathology on re-examination (see later). FTLD-U occurs as both familial and spo-
radic forms. To date, 20 families have been described with non-tauopathy FTLD linked to defined genetic loci and newly identified genes on various chromosomes, including FTLD-U families linked to chromosome 17q21-22.

FTLD-U is characterized by the presence of ubiquitin-positive neuronal cytoplasmic inclusions (NCIs) and lentiform intranuclear inclusions (NIIs) in layer II of frontal and temporal cortex, in striatum and in the dentate fascia of the hippocampus (56, 58, 63, 102). Because these inclusions were first described in patients with MND (76), they are sometimes referred to as FTLD with MND-type inclusions but without MND. Besides inclusions, superficial laminar spongiosis and chronic degenerative changes of the frontotemporal and, sometimes, parietal regions are the most consistent features. Ultrastructural analysis of the inclusions has shown the presence of tubofilamentous structures with a diameter of 10–18 nm (82). Patients with sporadic FTLD-U have a similar pathology, except that NIIs are only rarely present (7). Moreover, FTLD-MND is characterized by only a few or no inclusions in caudate nucleus and frontotemporal cortex, but with ubiquitin-positive granular inclusions in the dentate fascia and lower motor neurons (66, 110). The latter features are reminiscent of ALS.

For a long time, the nature of the protein components of tau-negative, ubiquitin-positive inclusions remained unknown; however, recent studies have shed important light on this issue. In a type of FTLD-U called neuronal intermediate filament inclusion dementia (NIFID), neurofilaments have been identified as the major component of the inclusions (42). NIFID patients present relatively early with FTD and may also suffer from parkinsonism and MND. Atrophy of frontotemporal cortex and caudate nucleus is a common feature (13, 42). For other cases of familial FTLD-U, a number of minor proteins has been recognized. For instance, p62 was reported to be present in the inclusions (82), similar to AD, Pick’s disease and Lewy body dementia (2, 50). HSP70 has also been found in some FTLD-U inclusions (82).

Recently, TDP-43, a nuclear protein that functions in the regulation of transcrip-
tion and alternative splicing, has been identified in some FTLD-U families. Interestingly, TDP-43 mutations have occurred in the context of FTDP-17 (93), as well as in the context of familial FTLD-U (82). TDP-43 is a ubiquitin-binding protein and is a component of nuclear inclusions in FTLD-U (82). The presence of TDP-43 in nuclear inclusions suggests that it may play a role in the formation of these inclusions. This is consistent with the observation that TDP-43 is involved in the degradation of ubiquitinated proteins (2).

Corticobasal degeneration, progressive supranuclear palsy and argyrophilic grain disease. CBD and PSP are two clinical manifestations of FTLD-τ. CBD has diverse clinical presentations, such as progressive asymmetrical rigidity and apraxia, progressive aphasia and frontal lobe dementia. Because of this diversity, a diagnosis of CBD is not dependent on a specific clinical presentation, but rather on a defined neuropathology. The minimal pathologic features for CBD are cortical and striatal tau-positive neuronal and glial lesions, especially astrocytic plaques and thread-like lesions in both white and gray matter, alongside neuronal loss in focal cortical regions and substantia nigra (22).

PSP has early behavioral manifestations, rendering differentiation from FTD difficult. Pathologically, it is characterized by atrophy of brainstem and basal ganglia, with corresponding neuronal loss, gliosis, and a high density of tangle-like tau pathology, neuropil threads and glial fibrillary tangles in both astrocytes (tufted astrocytes) and oligodendrocytes (coiled bodies) (32). However, atypical or variant PSP, where the severity and distribution of abnormalities deviate from the above, is also common (32). A link between CBD and PSP is that they are both 4R-tauopathies (11, 71, 105).

Frontotemporal dementia and Parkinsonism linked to chromosome 17 (FTDP-17). An autosomal-dominantly inherited form of frontotemporal dementia with parkinsonism was linked to chromosome 17q21-22 in 1994 (111). In the following years, additional families with FTD and parkinsonism were linked to 17q21-22 were identified. In 1997, a consensus conference introduced the term FTDP-17 to describe these patients (27) and the following year mutations in MAPT were reported in the majority of these families (38, 84, 99). At present, 39 mutations in MAPT have been identified in 115 families. Interestingly, MAPT mutations have also been identified in cases with CBD and with PSP (53, 87, 91). For a complete update, visit (http://www.molgen.ua.ac.be/FTDMutations).

Clinically, MAPT mutation carriers present with disinhibition, loss of initiative, obsessive-compulsive behavior and/or psychosis, followed by cognitive decline. In most patients, extrapyramidal symptoms occur only late in the clinical course, but considerable heterogeneity is observed both between mutations and within families with the same mutation (27). Age at onset is also highly variable and ranges from the early 20s to late 70s, with a mean age around 50 years (27, 70, 92). Neuro-pathologically, FTDP-17 presents with atrophy of the frontal and temporal lobes with neuronal loss, astrocytic gliosis and spongiosis in the superficial cortical layers. Basal ganglia are also affected (27). Filamentous tau inclusions in neuronal and glial cells are a characteristic finding (98). Biochemically and neuropathologically, many cases of FTDP-17 resemble sporadic Pick's disease.

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identifying as a major inclusion protein in FTLD-U and ALS (3, 75). In the inclu-
sions, TDP-43 is hyperphosphorylated and ubiqui-
tinylated. It constitutes a common pathologic substrate that links sporadic and familial FTLD-U with ALS.

Dementia lacking distinctive histopath-
ology. The third subtype of FTLD, for which sporadic and familial forms have been described, is characterized by neuronal cell loss and gliosis in the absence of protein inclusions (47). DLDH is less common than previously thought, as many patients are now being reclassified as having FTLD-U (44, 61). Thus, until recently, hereditary dysphasic disinhibition dementia 2 (HDDD2) was considered to be a classical form of inherited DLDH. However, recent work (72) has shown that it is caused by a PGRN mutation and that ubiquitin-positive inclusions are present in brain. Earlier, a selective loss of all six tau iso-
forms, with no corresponding change in protein abundance, was reported in DLDH and HDDD2 brains, but the significance of these findings remains uncertain (116).

**GENETICS AND MOLECULAR PATHOLOGY OF FTLD**

**Tauopathy FTLD.** Following the identi-

fication of mutations in MAPT in FTDP-17, considerable progress has been made in genotype-phenotype analysis and many types of tau pathology have been identified. It is now clear that MAPT mutations give rise to FTLD-τ pathology. Similarly, sporadic forms of PSP and CBD are also linked to MAPT in some populations, where inheritance of the H1 haplotype of MAPT is a risk factor (5, 20, 36, 69, 88).

Only rarely have MAPT variants been reported to be associated with “non-tauopathy” (80, 100). Recently, these patients have been shown to harbor mutations in PGRN, indicating that the reported MAPT variants were benign polymorphisms (81). Similarly, a family with the presenilin 1 (PSEN1) insArg352 change (1, 8, 94) was shown to have a PGRN mutation (81). In contrast, the PSEN1 Gly183Val mutation associated with “Pick’s disease tauopathy”, which we reported earlier (19), does not carry a mutation in PGRN. This mutation affects a splice donor signal and is predicted to produce, apart from the full-length mis-
sense transcript, at least two other aberrantly spliced transcripts that, when not degraded, would lead to short C-truncated proteins (19). Although the precise disease mechanism remains unidentified, preseni-
lin 1 protein is reduced by ~20% in brain of a Gly183Val carrier. There is also an experimental amyloid precursor protein-independent reduction in γ-secretase activity in presenilin null mouse fibroblasts. The involvement of a splice donor signal and the reduced protein suggest that the Gly183Val mutation is a more complicated mutation than initially believed (Tolia et al, unpub. data). Interestingly, another PSEN1 mutation associated with FTD, Leu113Pro, is also affecting a splice donor site (90). Association of these splice-site mutations with FT is interesting in the light of the presence of alternative PSEN1 transcripts in FTD brain (24), the loss of presenilin function associated with AD-causing mutations (49) and the finding that PSEN conditional knock-out mice show tau-like neurodegeneration (95). Future studies will address whether and how presenilin loss contributes to neurode-

generation involving tau.

**Non-tauopathy FTLD.** The study of FTLD-U is presently at a particularly exciting stage. The remainder of this review will therefore focus on the recent advances. As mentioned above, approximately 20 families with non-tauopathy FTLD have been linked genetically to loci on chromosomes 3p13, 9q21, 9p21, 17q21-22 and 20p (6, 16, 97, 109). To date, pathogenic mutations in three genes have been identified: Mutations in a fourth gene, dynactin (DCTN1), have been identified mainly in ALS patients, but with some overlap in FTD (85) (Table 1).

<table>
<thead>
<tr>
<th>Mutated gene</th>
<th>Pheno-typen</th>
<th>Locus</th>
<th>References</th>
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<tbody>
<tr>
<td>Microtubule-associated protein tau (MAPT)</td>
<td>FTDP-17</td>
<td>17q21-q22</td>
<td>(38, 84, 99)</td>
</tr>
<tr>
<td>Charged multivesicular body protein 2B (CHMP2B)</td>
<td>FTLD</td>
<td>3p13-3p12</td>
<td>(97)</td>
</tr>
<tr>
<td>Valosin-containing protein gene (VCP)</td>
<td>IBM-FTD</td>
<td>9q21-p12</td>
<td>(109)</td>
</tr>
<tr>
<td>Programuin (PGRN)</td>
<td>FTLD</td>
<td>17q21-q22</td>
<td>(6, 16)</td>
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**Table 1. Genes involved in FTLD.**
activity is observed only rarely in the ubiquitin inclusions in these patients (26, 82).

_**CHMP2B mutations cause a small subset of FTLD-U.**_ In an autosomal-dominant form of FTD in a large family of Danish descent and linked to a locus on chromosome 3p13 (10), a complex C-truncating mutation in _CHMP2B_ was identified (97). In addition, a Gly442Thr missense mutation was also identified in one individual with semantic dementia from a large European FTD series (97). A large screen of patients with familial FTD from the US, the UK and the Netherlands failed to reveal additional mutations, suggesting that _CHMP2B_ mutations are not a common cause of FTLD (14, 93).

Neuropathologically, the Danish family was initially reported to have DLDH, but subsequent studies showed the presence of ubiquitin-positive NCIs (35). Besides giving rise to FTD, _CHMP2B_ mutations may also cause additional phenotypes. For instance, mutations have been identified in two ALS patients, one of whom had also FTD (78). However, the sequence change in the latter was also present in a control individual, rendering its significance uncertain.

Like VCP, _CHMP2B_ is widely expressed in brain and although the exact function of _CHMP2B_ is unknown, its yeast ortholog Vsp2 is part of the ESCRTIII complex (endosomal secretory complex required for transport). This process enables the sorting of transmembrane proteins and trafficking along late endosomes to multisvesicular bodies (MVBs) and lysosomes. Dysfunction of these components results in the inability of the MVB to internalize membrane-bound cargo and results in poor protein turnover (4). Accordingly, epitope-tagged mutant isoforms of _CHMP2B_ cause aberrant late endosomal trafficking in PC12 cells (97), although it is not known whether this is through a gain of function or (dominant) loss-of-function mechanism. The Danish _CHMP2B_ mutation causes altered splicing, resulting in two aberrant transcripts that lead to a protein lacking the 36 C-terminal amino acids of _CHMP2B_. In one of these transcripts, there is addition of a non-physiological C-terminal 29 amino acid sequence, which may cause an aberrant gain of toxic function (67, 97).

_PGRN loss-of-function mutations cause FTLDU-17._ The identification of mutations in _PGRN_ was an exciting event in the study of FTLD. Previously, FTLD-U had been shown to be linked to the chromosome 17q21—MAPT region in a number of families, including ours (54, 60, 86, 115). However, extensive analysis of the 140 kb MAPT genomic region, including intronic and regulatory sequences, failed to detect any pathogenic mutation (15). At the same time, biochemical analysis of tau from frozen brain did not reveal any abnormalities in the distribution of tau isoforms at either protein or mRNA level (60). An extensive mutational analysis of genes near MAPT, which was carried out in parallel to the above work, led to the identification of _PGRN_ as the FTLDU-17 gene (6, 16). Subsequent studies in other FTLDU-17 families and in the HDDD2 family confirmed this finding (6, 16, 28, 37, 52, 72). _PGRN_ encodes a 68.5 kDa secreted precursor glycoprotein composed of a signal peptide followed by 7.5 tandem repeats of a 12-cysteinyl granulin motifs that can be proteolytically cleaved to form a family of 6 kDa granulin peptides (33). _PGRN_ is a widely expressed multifunctional growth factor and both _PGRN_ and granulins have important roles in development, cell cycle progression, cell motility, wound repair and inflammation (17, 33, 34). _PGRN_ is expressed in neurons of cerebral cortex, hippocampus and cerebellum. A high expression of _PGRN_ is associated with a variety of tumors, including glioblastoma (17, 33, 55).

So far, seven unique _PGRN_ null mutations have been identified in 67 FTD patients (AD&FTD Mutation database: http://www.molgen.ua.ac.be/ADmutations). Their frequency is estimated to be 5%–11% in the sporadic, and 13%–25% in the familial FTD population from Belgium, the USA and France, indicating that (null) mutations in _PGRN_ are a major cause of FTD (16, 28, 52). Four classes of _PGRN_ mutations have been identified. The first class includes mutations where the transcripts do not leave the nucleus, that is, the splice-donor site mutation of the _PGRN_ exon 0 (IVS0 + 5G > C), where nuclear retention signals remain in the unspliced transcript and prevent it from leaving the nucleus, where it is destroyed (16). Although this is so far the only mutation in this class, it provides one of the most convincing pieces of evidence in support of the notion that _PGRN_ mutations are loss-of-function mutations. The second class of mutations is where the transcript reaches the cytoplasm, but the protein is not produced efficiently. It includes additional splice site, frameshift and nonsense mutations that result in nonsense-mediated decay of the mutant transcripts (6, 16, 64). This class also includes mutations in the Met start codon, which disrupt the Kozak sequence and result in a substantial reduction in _PGRN_ expression (6, 16, 28). A third class is where the protein is mislocalized; this includes the missense mutation in the signal peptide identified in the HDDD2 family (72). It abolishes recognition of the signal peptide by the signal recognition particle and hampers its translocation into the endoplasmic reticulum. The final class includes coding variants, the significance of which is currently not understood (28).

Neuropathologically, cases with _PGRN_ mutations show numerous lentiform NCIs in neocortex and striatum, as well as less well-formed NCIs, especially in the hippocampus (59) (Kumar-Singh et al, unpub. data). Thus, both _PGRN_ and VCP mutation carriers have abundant NCIs, which is an infrequent finding in patients with sporadic FTLD-U. _PGRN_ staining showed that, although immunoreactivity was localized to a subset of cortical neurons and up-regulated in activated microglia, ubiquitin inclusions were not stained (6, 16). By contrast, anti-TDP-43 antibodies stained a substantial number of inclusions in _PGRN_ mutation carriers (75) (Kumar-Singh et al, unpub. data). The mechanisms by which _PGRN_ loss-of-function causes FTLD-U are unclear, but parallels might be drawn from cell culture work, where _PGRN_ has been shown to abrogate the requirement for insulin-like growth factor 1 receptor for growth (112), perhaps by promoting the activation of phosphatidylinositol 3’-kinase and mitogen-activated protein kinase pathways with sustained expression of cyclin B (113).

TDP-43 may define the underlying proteopathy. TDP-43 is a major component of
ubiquitin-positive NIs and NCIs of sporadic and familial FTLD-U (3, 75). TDP-43-positive deposits were also identified in ALS, suggesting that their formation is a common downstream denominator of FTLD-U/ALS ubiquitinopathies. TDP-43 was first identified as a ubiquitously expressed 43-kD nuclear protein that binds to the TAR DNA in the human immunodeficiency virus 1 long terminal repeat, where it functions as a transcriptional repressor (77). A second function as an activator of exon skipping was identified later (12). The primary transcript of the human TARDBP gene undergoes alternative splicing to generate 8 distinct mRNAs (108) and the protein undergoes phosphorylation. The levels of nuclear TDP-43 are reduced in neurons in FTLD, especially those with inclusions (75). It is presently not known whether a loss of TDP-43 function contributes to the FTLD-U phenotype.

CONCLUSION

From the large body of clinical, neuropathological, biochemical and genetic data discussed here, it is clear that FTLD is heterogeneous, as indicated by the existence of FTLD-t, FTLD-U, DLDH, FTD-MND and ALS. Not only is heterogeneity observed between disease forms, but it is also seen between families with the same mutation and even within families. Thus, these diseases most likely represent a clinicopathological spectrum. DLDH is becoming less common and a number of findings suggest that FTLD-U and ALS are at two ends of the same spectrum. Thus, they have overlapping clinical features, that is, ALS patients can develop dementia and, conversely, patients with FTLD frequently develop ALS. FTLD and ALS also have an overlapping spectrum of pathology. Furthermore, they share common etiologies, that is, ALS is associated with mutations in CHMP2B (78) and PGRN (60) and a mutation in DCTN1—an ALS gene—may cause FTD in some family members (73). Interestingly, two recent reports have identified an FTLD-ALS locus on chromosome 9p13.2-21.3 (68, 107). Even where common etiologies of ALS and FTLD are not directly evident, common disease pathways may be involved, that is, PGRN stimulates the expression of vascular endothelial growth factor (VEGF) (101) and mutations in angiogenin or polymorphisms in VEGF are associated with ALS (29, 51). Another example is that VCP can bind to Dorfin (an E3 ligase) and contributes to its ability to ubiquitinate superoxide dismutase 1, which, when mutant, causes ALS (39). And lastly, TDP-43 is a component of the ubiquitin-positive inclusions of both FTLD-U and ALS.

The cellular pathways that the currently known FTLD-U gene products are involved in are protein turnover—that is, the endosomal-lysosomal system (CHMP2B), the unfolded protein response and the Ub-Pr system (VCP) and cell signaling (PGRN). It is presently unclear how disruption of these pathways can lead to FTLD-U and the accumulation of TDP-43. The latter contains two RNA-binding domains and it is well documented that such domains can also be involved in protein–protein interactions (23). Could this mean that other proteins are also sequestered in the inclusions and that the resultant loss of their function is an even more proximate event? Judging by the recent progress, it appears likely that in times to come we will learn how different triggering factors can lead to FTLD and related disorders.

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