

REVIEW ARTICLE

ALS and FTLD: two faces of TDP-43 proteinopathy

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Keywords:

amyotrophic lateral sclerosis, frontotemporal dementia, frontotemporal lobar degeneration, granulin, motor neuron disease, *TARDBP*, TDP-43, ubiquitin, valosin-containing protein

Received 17 March 2008

Accepted 30 April 2008

Major discoveries have been made in the recent past in the genetics, biochemistry and neuropathology of frontotemporal lobar degeneration (FTLD). TAR DNA-binding protein 43 (TDP-43), encoded by the *TARDBP* gene, has been identified as the major pathological protein of FTLD with ubiquitin-immunoreactive (ub-ir) inclusions (FTLD-U) with or without amyotrophic lateral sclerosis (ALS) and sporadic ALS. Recently, mutations in the *TARDBP* gene in familial and sporadic ALS have been reported which demonstrate that abnormal TDP-43 alone is sufficient to cause neurodegeneration. Several familial cases of FTLD-U, however, are now known to have mutations in the *progranulin* (*GRN*) gene, but granulin is not a component of the TDP-43- and ub-ir inclusions. Further, TDP-43 is found to be a component of the inclusions of an increasing number of neurodegenerative diseases. Other FTLD-U entities with TDP-43 proteinopathy include: FTLD-U with *valosin-containing protein* (*VCP*) gene mutation and FTLD with ALS linked to chromosome 9p. In contrast, chromosome 3-linked dementia, FTLD-U with *chromatin modifying protein 2B* (*CHMP2B*) mutation, has ub-ir, TDP-43-negative inclusions. In summary, recent discoveries have generated new insights into the pathogenesis of a spectrum of disorders called TDP-43 proteinopathies including: FTLD-U, FTLD-U with ALS, ALS, and a broadening spectrum of other disorders. It is anticipated that these discoveries and a revised nosology of FTLD will contribute toward an accurate diagnosis, and facilitate the development of new diagnostic tests and therapeutics.

Introduction

Frontotemporal lobar degeneration (FTLD) is used here as an umbrella term to include both a clinical syndrome and one of the neuropathological entities [1–3]. FTLD is a focal, non-Alzheimer form of dementia, clinically characterized as either behavioral or aphasic variants [1,2,4]. Most commonly, the behavioral or frontal variant is characterized by behavioral dysfunction and change in personal and social conduct. The aphasic variant includes a non-fluent form called progressive non-fluent aphasia, and a fluent form called semantic dementia. Typically, the patient with FTLD does not have an amnesic syndrome, at least in the early stage of the disease, which distinguishes FTLD clinically from Alzheimer's disease (AD) [5], but there are exceptions [6]. Focal dementias account for up to 20% of presenile dementia cases [7], and FTLD is the

second most frequent form of dementia in people under the age of 65 years after AD [8]. FTLD may occur alone or in combination with amyotrophic lateral sclerosis (ALS), parkinsonism, or corticobasal syndrome during the course of the disease.

ALS is the most common adult-onset progressive and, ultimately fatal, motor neuron disease (MND). Like FTLD, ALS encompasses a range of clinicopathological entities [9]. ALS is used here to describe signs of upper and lower motor neuron degeneration with a progressive spread of signs within a region or to other regions as defined by the El Escorial World Federation of Neurology Criteria [10]. The overlap between dementia and ALS is demonstrated by the presence of cognitive and behavioral dysfunction in up to 50% of ALS patients [10–16], indicating a spectrum of clinical phenotypes that relate to common neuropathological lesions [17–19]. Further evidence for a clinical overlap between FTLD and ALS is the occurrence of progressive aphasia [20,21] and the presence of frontotemporal atrophy [22] in patients with ALS. Incidence rates of FTLD with ALS vary often as a consequence of referral bias and differing diagnostic criteria. Several studies

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have shown that ALS patients with frontotemporal impairment have significantly shorter survival compared with FTLN patients [23,24]. However, the clinical diagnosis of FTLN may only be considered after other potential causes of dementia (e.g. small and/or large vessel disease), systemic conditions (e.g. hypothyroidism, B-vitamin deficiency), tumors, and substance abuse have been excluded. This review will highlight a number of important advances in our understanding of the molecular genetics, biochemistry, and neuropathology of FTLN that have occurred within the recent past.

Genetic studies

FTLN is a genetically complex disorder, with multiple genetic factors contributing to the disease. A positive family history with an autosomal dominant pattern of inheritance and high penetrance is usually found in one quarter to one half of patients [25–30]. Recently, several genes and a locus on chromosome 9p have been linked to familial FTLN with ubiquitin-immunoreactive, tau-negative inclusions (FTLN-U): genetic defects include mutations in the *chromatin modifying protein 2B* (*CHMP2B* gene), the cause of chromosome 3-linked FTLN [31], and mutations in the *valosin-containing protein* (*VCP*) gene, a cause of chromosome 9-linked FTLN [32,33]. Locus heterogeneity for FTLN and ALS is indicated by the presence of other genetic loci at 9p [34,35]. Recently, the major genetic cause of familial FTLN-U linked to chromosome 17 was identified as mutations in the *progranulin* (*GRN*) [36,37] gene. This discovery was soon replicated by the identification of other *GRN* mutations in the HDDD2 [38], PPA1 and PPA3 [39], and HDDD1 [40] families. Although null mutations, mainly nonsense and frameshift mutations resulting in premature stop codons, in *GRN* were the first to be identified and the causal mechanism underlying FTLN-U, some of the families described have missense mutations which are predicted to alter trafficking, protein folding, or processing leading to a *GRN* protein haploinsufficiency [36,37]. Thus, a spectrum of mutations in *GRN* leads to loss of functional protein, the primary etiology of FTLN with *GRN* mutation.

This genetic heterogeneity is also reflected in clinical variability. FTLN with *GRN* mutation has been described in families with corticobasal syndrome [41–43] and in familial and sporadic patients from large FTLN cohorts [44–48]. In 37 patients with a single gene defect, Arg493X, in 30 families with FTLN, there was a variable age at onset (range 44–69 years) and clinical diagnoses included: frontotemporal dementia, primary progressive aphasia, corticobasal syndrome, and Alzheimer's disease [47]. In contrast, there is phenotypical homogeneity in the PPA1 and PPA3 families, at least in

the initial stage of disease [39]. Also, FTLN with *GRN* A9D, a missense mutation located in the signal peptide, has been described in a family with corticobasal syndrome [43] as well as in another family (HDDD2) with prominent behavioral and language dysfunction [38]. Thus, FTLN with *GRN* mutation is both clinically, neuropathologically, and genetically heterogeneous [36–50]. Most of the mutations reported to date, but not all, lead to premature termination of the coding sequence and nonsense mediated decay (NMD) resulting in functional loss of one allele. The overall effect of these changes is likely to be a significant reduction in the growth modulator activity of *GRN*. The various *GRN* mutations predict at least two disease mechanisms – the partial loss of functional *GRN* (haploinsufficiency) [36,37] or functional loss caused by mis-trafficking of mutant protein [38,49]. Further studies are required to expand the spectrum of FTLN phenotypes with the several *GRN* mutations that have now been reported [36–50]. (For the current list of pathogenic mutations in FTLN refer to: <http://www.molgen.ua.ac.be/FTDMutations/>).

FTLN-U accounts for 5–15% of all dementia disorders [51]. Mutations in the *microtubule-associated protein tau* (*MAPT*) gene on chromosome 17q21 which, coincidentally, is in close proximity to the *GRN* gene, are known to be responsible for 10–20% of familial FTLN [52]. The progranulin gene (*GRN*) is mutated in 5–10% of patients with FTLN and in about 20% of patients with familial FTLN [53], similar to that of FTLN with *MAPT* mutation [52].

The recent discovery of pathogenic missense mutations in a highly conserved glycine-rich, heterogeneous ribonucleoprotein interacting domain of the *TARDBP* gene (Fig. 1) in autosomal dominant ALS families and sporadic cases confirms the importance of TDP-43 in the pathogenesis of ALS and demonstrates that defects in *TARDBP* are sufficient to cause TDP-43 protein-

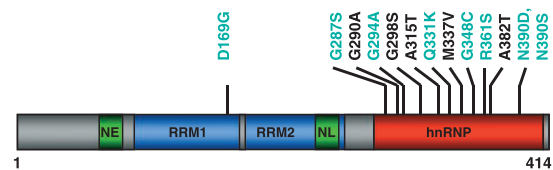


Figure 1 Mutations in the TAR DNA-binding protein 43 (TDP-43) encoded by the *TARDBP* gene in familial (FALS) and sporadic amyotrophic lateral sclerosis (SALS). Schematic diagram of functional domains and mutations in the coding region are indicated using the amino acid numbering of the 414 amino acid protein. RRM1, RNA recognition motif 1; RRM2, RNA recognition motif 2; NL, nuclear localization signal; NE, nuclear export signal; hnRNP, heterogeneous nuclear ribonucleoprotein interaction domain. *TARDBP* mutations: autosomal-dominant FALS (black), SALS (green).

pathy [54–57]. In none of these families, or in any of the sporadic cases, was there evidence of FTLN. As additional families are identified, more heterogeneous clinical phenotypes may emerge. As the glycine-rich domain (Fig. 1) is a ‘hot spot’ for the mutations reported so far, dysregulation of mRNA splicing may be the functional consequence of these gene defects. A great deal of work has yet to be done to elucidate the normal function of TDP-43 and the cellular pathways disrupted by abnormal protein caused by mutations in *TARDBP*. As some familial FTLN-U cases do not have *GRN*, *VCP*, *CHMP2B*, or *TARDBP* mutations, it is likely that additional causal genes and genetic risk factors for FTLN-U exist.

Neuropathology

FTLN comprises a neuropathologically heterogeneous group of neurodegenerative diseases, which share the common feature of preferential degeneration of the frontal and temporal lobes [1,4]. FTLN pathology can be broadly divided into two main classes, based on abnormal accumulation of hyperphosphorylated tau protein: those with tau-immunoreactive (tau-ir) neuronal and/or glial inclusions called tauopathies and those with ubiquitin-immunoreactive (ub-ir), tau-negative

inclusions, called FTLN-U. FTLN-U is the most common entity within this group [58]. ALS is also accompanied by a wide range of neuropathological features in which both cortical (upper motor neuron), and either brainstem motor neurons or anterior horn cells (lower motor neuron) are involved with a signature lesion: abnormal accumulation of insoluble proteins, which are ubiquitinated, in the cytoplasm of degenerating motor neurons [59]. Ub-ir inclusions are observed more commonly in sporadic ALS (SALS), but they are also seen in familial ALS (FALS) with *Cu/Zn superoxide dismutase (SOD1)* gene mutations [60,61]. Until recently, ubiquitin immunohistochemistry (IHC) was the only method to detect abnormal protein aggregates in FTLN-U, FTLN-U with ALS, and SALS. In this spectrum of diseases, the ubiquitinated inclusions contain neither tau, nor α -synuclein, nor neuronal intermediate filament protein epitopes.

Recently, TAR DNA-binding protein 43 (TDP-43) [18,19], was identified as the major component of inclusions of sporadic and familial FTLN-U, with and without ALS, and SALS (Fig. 2) [60,62]. However, the absence of pathological TDP-43 in familial cases harboring *SOD1* gene mutations implies that motor neuron degeneration may result from a different mechanism in those cases [60]. It remains to be seen if

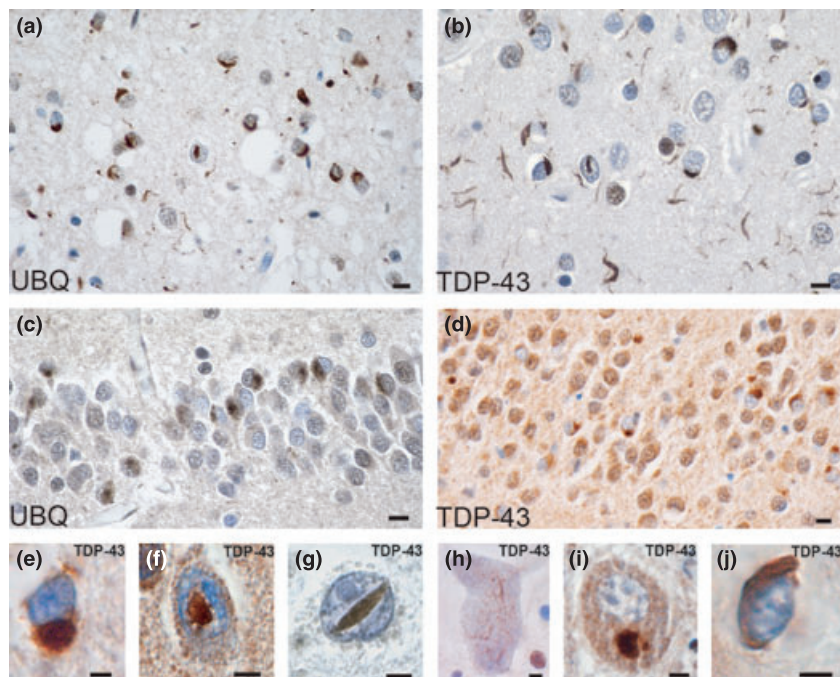


Figure 2 TDP-43 proteinopathy in FTLN-U. Adjacent sections of superficial frontal neocortex showing neuronal cytoplasmic inclusions (NCIs), dystrophic neurites (DNs), and isolated neuronal intranuclear inclusions (NIIs), stained for both ubiquitin (a) and TDP-43 (b). NCIs in the dentate granule cells stain for ubiquitin (c) and TDP-43 (d). Neuronal and glial inclusions include: NCI (e), round and lentiform NIIs (f, g); skein-like (h) and compact round (i) NCIs in lower motor neurons; and a glial cytoplasmic inclusion (GCI) (j). (a, c) ubiquitin immunohistochemistry; (b, d, e–j) TDP-43 immunohistochemistry. Bars 10 μ m (a–d); 5 μ m (e–j). *Source:* Cairns *et al.* [60] with permission from the American Society for Investigative Pathology.

TDP-43 may be useful in differentiating SOD1-related ALS from SALS [60].

Neuropathologically, the TDP-43 proteinopathies are characterized by ubiquitin- and TDP-43-ir neuronal cytoplasmic inclusions (NCIs), neuronal intranuclear inclusions (NIIs), dystrophic neurites (DNs) and, in cases of MND, glial cytoplasmic inclusions (GCIs) [18,19,63–67]. The pathological inclusions of these disorders may be distinguished from other protein folding diseases which are characterized by abnormal aggregates of tau, α -synuclein, β -amyloid, neuronal intermediate filament proteins, or expanded polyglutamine repeats. TDP-43 proteinopathy is characterized biochemically by the presence of relatively insoluble ubiquitinated TDP-43-containing inclusions of which TDP-43 is abnormally phosphorylated and cleaved to produce C-terminal fragments [18,19,62,64–66]. The variability in the distribution and morphology of ub-ir or TDP-43-ir inclusions in FTLD-U has led to the development of a classification of FTLD-U into four pathological subtypes based on the morphology of the inclusion, its location within the cell, and the density and distribution in the frontal and/or temporal lobes (Fig. 3) [3,62,67]. These different pathological subtypes correlate, although imperfectly, with the molecular genetic and clinical phenotype [68]. Alternative schemes have been proposed and additional studies are required to determine

their validity [62,68]. The discovery of TDP-43 as a novel misfolded protein links a spectrum of diseases including FTLD, ALS, Alzheimer's disease [69], Lewy body disease [70] and Guam parkinsonism-dementia complex [71] by a common molecular pathology called TDP-43 proteinopathy. The identification of this protein as a major or minor component of the pathological inclusions of a spectrum of neurodegenerative disease provides new clues into the pathogenesis of protein aggregation, and it presents new targets for therapeutic intervention where none exists.

TDP-43 proteinopathy is also a signature feature of other rare familial diseases. Inclusion body myopathy associated with Paget's disease of bone and frontotemporal dementia (IBMPFD) is a rare autosomal dominant disorder caused by a mutation in the *VCP* gene [32,33,62]. IBMPFD is a distinct subtype of FTLD-U with numerous DN and NIIs [33,62]. As with cases of FTLD-U with *GRN* mutation, the ubiquitinated inclusions are not primarily composed of the mutated protein VCP, but rather TDP-43 [62]. Recently, a new genetic locus on chromosome 9p for familial ALS with or without FTLD has been described [34,35]. Neuropathology of some of these families reveals the characteristic lesions of FTLD-U: ub-ir and TDP-43-ir NCIs, DN, and NIIs indicating that another gene locus on chromosome 9 may precipitate TDP-43 proteinopathy [3].

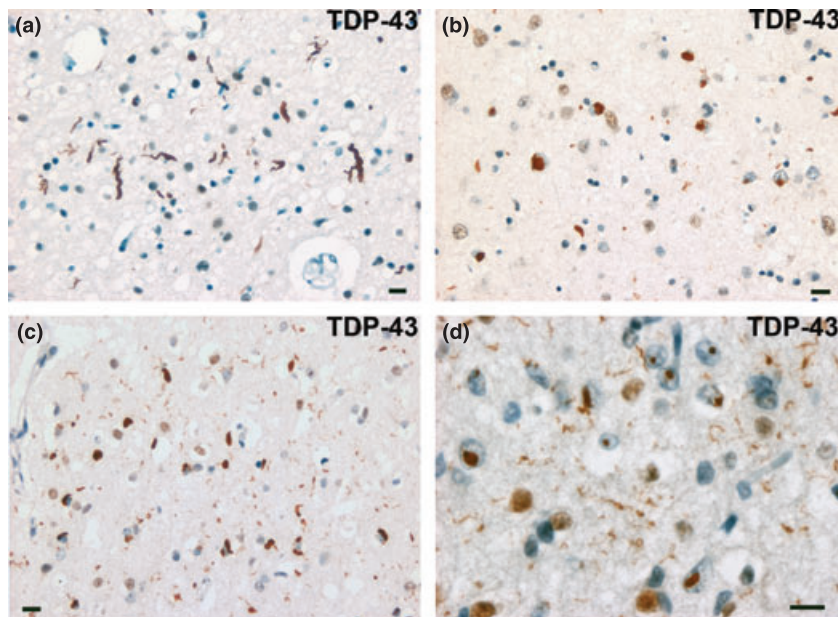


Figure 3 FTLD-U subtypes 1–4. (a) Type 1 is characterized by long dystrophic neurites (DNs) in laminae II/III with relatively few neuronal cytoplasmic inclusions (NCIs) and no neuronal intranuclear inclusion (NII). (b) Type 2 has numerous NCIs, relatively few DN, and no NII. (c) Type 3 has numerous NCIs and DN and an occasional NII. (d) Type 4 pathology is characterized by numerous NIIs and DN but few NCIs. TDP-43 immunohistochemistry. Bar 10 μ m (a–d). Source: Cairns *et al.* [60] with permission from the American Society for Investigative Pathology.

FTLD linked to chromosome 3 is an FTLD-U with mutation in the *CHMP2B* gene and is an exception to the FTLD-U entities described above [31]. Early reports of this kindred described the neuropathology as 'dementia lacking distinctive histopathology' (DLDH). Subsequently, improved IHC methods revealed ub-ir, but TDP-43-negative, granular NCIs in frontal neocortex and hippocampus [62,72]. Thus, rarely, FTLD-U may not be a TDP-43 proteinopathy. In the light of these recent immunohistochemical, biochemical, and genetic advances, the Consortium for Frontotemporal Lobar Degeneration has developed an algorithm to facilitate diagnosis and revised neuropathological diagnostic criteria (Table 1) [3]. These criteria will be of value to the practicing clinician and provide a foundation for clinical, clinico-pathological, and mechanistic studies and *in vivo* models of the pathogenesis of FTLD.

Clinical evaluation

In addition to being the causative gene defect in autosomal dominantly inherited FTLD with *GRN* mutation, a mutation in *GRN* may rarely occur in supposedly

sporadic FTLD-U. Both behavioral and aphasic forms of FTLD can be associated with these gene defects [45–47,68], although the behavioral variant is the most common clinical phenotype associated with FTLD with *GRN* mutation [46,47]. Magnetic resonance imaging and 18-fluoro-deoxyglucose positron emission tomography helps discriminate AD from FTLD [73–77]. Patients with *GRN* mutations have predominant frontal, temporal and, to lesser extent, parietal atrophy and hypometabolism with a right-sided predominance and this probably relates to the predominance of behavioral symptoms [74]. However, language dysfunction in patients with FTLD with *GRN* mutation show a left-sided predominance of atrophy on imaging [45,78].

Several FTLD with *GRN* mutation families have been described: hereditary dysphasic disinhibition dementia families 1 and 2 (HDDD1 and 2) [79,80] and other kindreds with a similar clinical phenotype [37,75], UBC-17 [50,81], and aphasic families described by Mesulam *et al.* [39] and Snowden *et al.* [82]. Interestingly, the HDDD1 and HDDD2 kindreds are characterized pathologically by FTLD-U and additional AD-type pathology, which distinguishes them from other reported families with no

Table 1 Neuropathologic diagnostic criteria for FTLD

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1. Tauopathy (with associated neuron loss and gliosis) and insoluble tau with a predominance of 3R tau, the most likely diagnoses are:
 - FTLD with Pick bodies
 - FTLD with *MAPT* mutation
 2. Tauopathy (with associated neuron loss and gliosis) and insoluble tau with a predominance of 4R tau, the most likely diagnoses are:
 - Corticobasal degeneration
 - Progressive supranuclear palsy
 - Argyrophilic grain disease
 - Sporadic multiple system tauopathy with dementia
 - FTLD with *MAPT* mutation
 3. Tauopathy (with associated neuron loss and gliosis) and insoluble tau with a predominance of 3R and 4R tau, the most likely diagnoses are:
 - Neurofibrillary tangle dementia
 - FTLD with *MAPT* mutation
 4. Frontotemporal neuronal loss and gliosis without tau- or ubiquitin/p62- positive inclusions, the most likely diagnoses is:
 - FTLD (also known as dementia lacking distinctive histologic features)
 5. TDP-43 proteinopathy with associated neuronal loss and ubiquitin-positive/p62-positive, tau-negative inclusions, with MND or without MND but with MND-type inclusions, the most likely diagnoses are:
 - FTLD-U with MND (FTLD-U types 1–3)
 - FTLD-U but without MND (FTLD-U types 1–3)
 - FTLD-U with *GRN* mutation (FTLD-U type 3)
 - FTLD-U with *VCP* mutation (FTLD-U type 4)
 - FTLD-U linked to chromosome 9p (FTLD-U type 2)
 - Other as yet unidentified TDP-43 proteinopathies
 6. Frontotemporal neuronal loss and gliosis with ubiquitin-positive/p62-positive, TDP-43- and tau-negative inclusions, the most likely diagnoses are:
 - FTLD-U with *CHMP2B* mutation
 - Basophilic inclusion body disease (BIBD)
 - Other as yet unidentified FTLD-U, non-TDP-43 proteinopathies
 7. Frontotemporal neuronal loss and gliosis with ubiquitin/p62 and α -internexin-positive inclusions, the most likely diagnosis is:
 - Neuronal intermediate filament inclusion disease (NIFID)
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CHMP2B, charged multivesicular body protein 2B gene; FTLD, frontotemporal lobar degeneration; FTLD-U, FTLD with ubiquitin-positive, tau-, α -synuclein-, TDP-43-, and neuronal intermediate filament protein-negative inclusions; *MAPT*, microtubule-associated protein tau gene; MND, motor neuron disease; neurofibrillary tangle dementia, also called tangle predominant form of senile dementia; *GRN*, granulin gene; TDP-43, TAR DNA-binding protein 43; *VCP*, valosin-containing protein gene. Reprinted from Ref. [3] with permission of the Editor.

or little coexisting neurodegenerative disease [36,37]. Another family with the same *GRN* A9D mutation has been reported in an individual with corticobasal syndrome [43] indicating, again, clinical heterogeneity associated with the same mutation. Unlike most other FTL-D-U with *GRN* mutation families [47], the HDDD1 mutation carriers also had AD-type early-memory loss which correlated with coexisting AD pathology [40]. The overlap between FTL-D-U and AD in familial cases is important as 23% of AD cases show FTL-D-U type TDP-43 pathology [67].

Recent discoveries in the molecular genetics, biochemistry, and neuropathology of FTL-D have transformed our understanding of this hitherto enigmatic group of diseases. TDP-43 has been identified as the major pathological protein of a spectrum of diseases which includes FTL-D-U, FTL-D-U with ALS, and sporadic ALS, and a minor component of the inclusions of a widening spectrum of other diseases. The physiological function of TDP-43 in the brain is currently unknown; however, it is normally localized to the nucleus of neurons and some glial cells [19,64,65]. Although the specific role of TDP-43 in neurodegeneration remains speculative, some studies indicate that this protein is directly involved in the pathogenesis of SALS, ALS with dementia and FTL-D-U [18,19,60,61]. The most common FTL-D is FTL-D-U and accounts for more than one half of all FTL-D entities in most studies [51,52]. Ubiquitin and TDP-43 immunohistochemistry may be used to distinguish four subtypes of FTL-D-U which correlate with genotype and neuropathological phenotype [62,67], but mutation analysis will be required to determine the genetic cause in familial cases. Additional studies of larger groups of cases are required to determine the utility of the FTL-D-U subtypes that have been described. The identification of different mutations in the *GRN* gene in HDDD kindreds [38,40] links these families to other FTL-D-U families in which *GRN* mutations have been identified [36,37,43,50,68], but the HDDD kindreds appear to be distinctive both clinically and pathologically. Further studies are required to describe more accurately the clinical and neuropathological heterogeneity associated with different gene defects that result in FTL-D-U.

The identification of the causative gene defect in a patient with FTL-D and/or ALS may provide some insight into clinical and neuropathological variation that may be present. Clinical studies of ALS, FTL-D and FTL-D with ALS have found significant clinical overlap, indicating a spectrum of phenotypes, suggesting that they represent different manifestations of the same neurodegenerative disorder [17,83]. The clinical overlap between ALS and FTL-D has also been illustrated in a study of 36 FTL-D patients, five of whom met clinical

and electrophysiological criteria for definite ALS and an additional one-third met criteria for possible ALS [15]. In contrast, in 100 consecutive ALS patients, frontal executive deficits were present in half of ALS patients, many of whom met research criteria for FTL-D [16]. In patients with bulbar onset ALS, however, the incidence of FTL-D has been reported as high as 48% [14]. The presence of TDP-43 proteinopathy in cases with sporadic ALS, ALS with FTL-D, and FTL-D links clinical phenotypes by a common molecular pathology. The absence of pathological TDP-43, however, in ALS with *SOD1* mutation may partially explain why therapeutic strategies, shown to be effective in *SOD1* mouse models, have not been effective in clinical trials of patients with sporadic ALS [83–85].

Conclusion

FTL-D and ALS are clinically, genetically, and neuropathologically heterogeneous. FTL-D can no longer be considered a rare group of disorders as it accounts for 5–10% of dementia cases in most dementia centers. Although ALS and FTL-D phenotypes may be distinguished in the clinic, it is not usually possible to determine which neuropathological entity is responsible for the clinical presentation. In familial cases, molecular genetics may identify the causative gene but, at present, there is no effective treatment. Two distinct FTL-D entities have been linked to chromosome 17: FTL-D-U with *GRN* mutation and FTL-D with *microtubule-associated protein tau (MAPT)* mutation. TDP-43 is the major pathological protein of the motor neuron inclusions found in FTL-D-U, FTL-D-U with ALS, SALS, FALS, but not FALS with *SOD1* mutation, and G-PDC, and is a minor component of the inclusions of other disorders including the neurofibrillary tangles of AD, Lewy bodies of Parkinson's disease and dementia with Lewy bodies, and the ubiquitinated inclusions of some cases of hippocampal sclerosis. TDP-43 proteinopathies are distinct from most other neurodegenerative disorders in which protein misfolding leads to brain amyloidosis, as pathologic TDP-43 forms neuronal and glial inclusions lacking the features of brain amyloid deposits [62]. Both HDDD kindreds are examples of FTL-D-U with *GRN* mutation which links them to other FTL-D-U with *GRN* mutation families. However, the HDDD kindreds appear to have coexisting memory deficits and AD-type pathology and as many as 20% AD cases have pathology similar to FTL-D-U indicating that these coexisting diseases may be more frequent than previously realized. Also, TDP-43 proteinopathy may be a component of a growing number of inclusions of different neurodegenerative diseases and further studies are needed to determine the prevalence of this

proteinopathy. Additional clinicopathological correlations are required to discern the relationship between genotype, neuropathology, and clinical phenotype more closely.

A rare form of familial FTL-D-U is caused by mutations in the *VCP* gene, while other cases of FTL-D with ALS are linked to chromosome 9p. The majority of inclusions of sporadic and familial FTL-D-U with *GRN* and *VCP* mutations contain TDP-43 protein, but FTL-D-U with *CHMP2B* mutation appears to be an exception with ub-ir positive and TDP-43-negative inclusions. Also, familial cases of ALS with *SOD1* mutations have ub-ir, but TDP-43-negative inclusions. These data indicate that most, but not all, familial cases of FTL-D or ALS are TDP-43 proteinopathies. Thus, FTL-D-U and SALS represent two ends of a spectrum of disorders that are united by a common pathogenic mechanism TDP-43 proteinopathy which is reinforced by recent discoveries of pathogenic mutations in *TARDBP* in some FALS. These dramatic new insights into the molecular genetics and neuropathology of FTL-D-U and ALS have led to a revised nosology of FTL-D. These advances will contribute toward an accurate diagnosis, foster clinicopathological studies, and facilitate the quest for biomarkers and rational therapeutics.

Acknowledgements

We thank the clinical, genetic, pathology, and technical staff of the collaborating centers for making information and tissue samples available for this study and we thank the families of patients whose generosity made this research possible. This work was supported by NIH (National Institute on Aging) grants (P01-AG03991, P50-AG05681, U01-AG16976), Fulbright Grant 68428174 (RML) and CAPES.

Disclosure

The authors report no conflicts of interest.

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