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TDP-43 in Neurodegenerative Disorders

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Abstract

Background: The number of neurodegenerative diseases associated with pathological aggregates of TAR DNA-binding protein 43 (TDP-43) has increased, leading to the new designation "TDP-43 proteinopathy." Biochemically, TDP-43 proteinopathies are characterized by decreased solubility, hyperphosphorylation, and cleavage of TDP-43 into 25- and 35-kD fragments, as well as altered cellular localization.

Objective: This review summarizes the extensive research characterizing the distribution of TDP-43 pathology in human postmortem brain tissue and discusses possible therapeutic strategies based on genetic and *in vitro* studies.

Methods: We reviewed recently published studies of TDP-43 proteinopathy in the following manuscript.

Results/conclusion: Given that several different genetic mutations can lead to TDP-43 proteinopathies, including mutations in progranulin and valosin-containing protein, research is needed to decipher and potentially exploit the link between these mutations and TDP-43 pathology.

Keywords

amyotrophic lateral sclerosis; frontotemporal dementia; progranulin; TAR DNA binding protein-43 (TDP-43); valosin-containing protein

1. Background

Neumann and colleagues discovered TAR DNA binding protein-43 (TDP-43) in the inclusions of frontotemporal lobar degeneration with ubiquitin-positive inclusions (FTLD-U) and amyotrophic lateral sclerosis (ALS) [2]. Subsequently, numerous retrospective studies have evaluated the frequency of TDP-43 in other neurodegenerative diseases. From the following collective review of these studies, including new insights into TDP-43 function and regulation, the mystery of TDP-43 proteinopathies is beginning to unravel, but this rapid progression of scientific understanding has generated additional questions that will be discussed within this review.

2. Genetics, protein structures, and biological functions of TDP-43

TDP-43 was identified from a genomic screen for novel transcriptional inactivators that bind to the TAR-DNA element of the HIV-1 virus, where it functions as a transcriptional repressor [3]. The human TDP-43 gene, which is located on chromosome 1 and contains 6 exons, is alternatively spliced to generate at least four isoforms that have been identified to

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date [4]. Given that the TDP-43 gene is highly conserved throughout evolution, it is likely that TDP-43 fulfills a crucial and vital role in maintaining cellular function and survival.

TDP-43, a 414-amino acid protein, has a theoretical molecular weight of 44.74 kDa (Figure 1). In addition to full-length TDP-43 (observed at 43 kDa), three isoforms of TDP-43 have also been detected in human brain and spinal cord tissue [5], but the functional significance of these isoforms is currently unknown. The expressed protein contains two highly conserved RNA recognition motifs (RRM1 and RRM2), as well as a glycine-rich C-terminal sequence. Little is known about the function of the N-terminal region, only that the RRM1 domain of TDP-43 binds single-stranded UG or TG repeat motifs with very high affinity [6,7]. Although not completely characterized, the RRM2 domain is believed to participate in RNA binding, and also contains a leucine-rich nuclear export signal located between the amino acid residues 239-250 of the human TDP-43 sequence [5,7,8]. The glycine-rich C-terminus, a region that mediates protein-protein interactions, is required for TDP-43 to participate in alternative splicing, and also enables TDP-43 to bind to several proteins of the heterogeneous nuclear ribonucleoprotein (hnRNP) family, a class of proteins involved in the biogenesis of mRNA [4,9]. Thus, given the role of TDP-43 in alternative splicing, it is not surprising that in cell culture models and human postmortem brain tissue, full-length TDP-43 has been localized predominately to the nuclear compartment. However, first reported by Buratti and Baralle as unpublished observations [10], a recent report has verified the presence of small amounts of cytosolic TDP-43 under normal, physiologic conditions [8].

Although the functions of TDP-43 are not completely characterized, we do know that TDP-43 possesses the capacity to regulate biological systems through multiple mechanisms due to its ability to bind to both single-stranded DNA and RNA, as well as various proteins. Currently, TDP-43 has been implicated in regulating gene transcription and alternative splicing, in addition to maintaining mRNA stability. As a transcriptional repressor, TDP-43 binds to a polypyrimidine-rich motif in TAR-DNA [3]. In mice, TDP-43 binds and regulates the expression of the proximal promoter of the SP-10 gene, which is involved in spermatogenesis [11]. TDP-43 also forms part of a complex involved in the alternative splicing of the cystic fibrosis transmembrane conductance regulator gene [12,13], as well as the apolipoprotein A2 gene [14]. In addition, Ayala and colleagues recently identified TDP-43 as a negative regulator of cdk6 expression, such that loss of TDP-43 led to a concomitant increase in cdk6 expression and phosphorylation of retinoblastoma protein (pRb), a substrate for cdk6 and apoptosis [15]. Further expanding the role of TDP-43 in cellular function, a recent study demonstrated that TDP-43 stabilizes the human low-molecular-weight neurofilament (hNFL) mRNA transcript through direct interactions with the 3′ untranslated region [5]. It has also been suggested to play a role as a neuronal activity-responsive factor by binding to mRNA species in P bodies near synaptic structures [16]. However, we still need to investigate the effects of posttranslational modifications of TDP-43, including phosphorylation, ubiquitination, and cleavage, on its regulation of various cellular processes. Thus given the diversity of physiological functions already ascribed to TDP-43, future research into the continued characterization of this protein is essential to fully appreciate the cellular consequences of TDP-43 pathology.

3. TDP-43 pathology in neurodegenerative disease

3.1 FTLD-U/MND

Frontotemporal lobar degeneration (FTLD) is the third most common cause of dementia in some series and one of the major causes of dementia in young adults [17,18]. FTLD encompasses a class of heterogeneous neurodegenerative disorders that are occasionally associated with motor neuron disease (MND) [19,20]. Neuropathologically, FTLD can be

subdivided into two major categories: tauopathies and non-tauopathies. Tauopathies include Pick's disease, corticobasal degeneration, progressive supranuclear palsy, and neurofibrillary tangle-only dementia, as well as frontotemporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17). The most common non-tauopathy is FTLD-U, a form of FTLD in which neuronal and sometimes glial inclusions are positive for ubiquitin and negative for tau and α-synuclein [21,22]. Cases of FTLD-U associated with motor neuron disease (MND), sometimes resembling ALS, are referred to as FTLDMND. Although TDP-43 appears to be the major constituent of inclusions in motor and non-motor neurons in ALS and FTLD-MND [2,23-26], some inclusions in ALS, particularly familial forms of ALS, show no TDP-43 immunoreactivity [27,28]. Other non-tauopathies include rare disorders associated with inclusions composed of neuronal intermediate filaments [29], disorders in which there are inclusions composed of yet-tobe-identified proteins [30], and disorders with no inclusions and only nonspecific neuronal loss and gliosis [31].

Two groups independently identified TDP-43 as the major constituent in FTLD-U by using similar yet distinctly different approaches. Sampathu and colleagues isolated the highly insoluble, high-molecular-weight material from brain extracts of FTLD-U patients and generated a series of antibodies that was subsequently used in histological studies [1]. A subset of these antibodies colocalized with ubiquitin inclusions solely in FTLD-U, with no immunoreactivity detected in other neurodegenerative diseases, demonstrating the specificity of these novel antibodies. In a subsequent study, two of those antibodies were used for immunoblotting to determine which protein species was being recognized; both antibodies detected 24-26-kDa bands only in FTLD-U patients [2]. When these 24-26-kDa bands were extracted and analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS), the C-terminal fragments of TDP-43 were identified. Simultaneously, Arai and colleagues isolated insoluble material from FTLD-U patients and performed LC-MS/MS on all bands, also identifying TDP-43 as the major protein component of ubiquitin inclusions in FTLD-U patients [23].

Specific TDP-43 antibodies were used to histologically determine the localization and distribution of TDP-43 and ubiquitin pathology in FTLD-U patients, which has led to further subclassification of FTLD-U cases into 4 types (see Table 1) [1,24,32,33]. Although Mackenzie and colleagues and Sampathu and colleagues assigned different characteristics to subtypes 1-3, as demonstrated in Table 1 and Figure 2, the FTLD-U subtypes identified by each group are presumably the same. Given that most researchers utilized the Sampathu classification system, the remainder of this review will refer to the subtypes as defined by that group [1,32]. Briefly, type 1 is characterized by long, dystrophic neurites in superficial and middle cortical layers, with few to no neuronal cytosolic inclusions (NCI) or neuronal intranuclear inclusions (NII). In type 2, abundant NCIs are observed in both superficial and deep cortical layers, with few to no NII and fewer dystrophic neurites. In contrast, type 3 is characterized by numerous NCIs and short dystrophic neurites in superficial layers of the cortex. Rod-shaped (lentiform) NIIs are also present in affected regions, particularly in patients with a positive family history [33]. In all 3 subtypes NCIs are observed in the dentate gyrus of the hippocampus. Although NCIs are uncommon in the cortex in type 1, they are present in the dentate gyrus. Other consistent observations across subtypes are the nuclear localization of TDP-43 in unaffected cells and the absence of TDP-43 in the nuclear compartment of cells with cytosolic TDP-43 inclusions. Those observations indicate that in TDP-43 pathologies, TDP-43 is redistributed from the nuclear compartment to the cytosolic compartment. A potential mechanism by which this occurs is just beginning to be made clear by recent *in vitro* studies, as discussed below [34].

The genetic causes of FTLD have been studied extensively. Although mutations in tau are known to FTDP-17 [35,36], the most common familial tauopathy, an additional linkage to

chromosome 17 was observed for familial FTLD-U. Recently, mutations in progranulin (*PGRN*) were identified in FTLD-U patients [37-39]. The *PGRN* gene encodes a secreted growth factor involved in cell cycle regulation. Additional genetic mutations that have been linked to FTLD-U include valosin-containing protein (VCP) [40-42], charged multivesicular body protein 2B (CHMP2B) [43], as well as a newly identified genetic locus on chromosome 9p, which might result from mutations in intraflagellar transport protein 74 [44]. In addition, although a number of groups have evaluated the TDP-43 gene in FTLD patients, currently no pathogenic mutations in TDP-43 have been linked to FTLD-U [45-47].

Analysis of TDP-43 immunoreactivity in familial FTLD-U cases revealed that *PGRN* mutations are associated with type 3 pathology, whereas *VCP* mutations produce an atypical pattern of TDP-43 pathology that led to the designation of a fourth subtype (see Table 1) [32,40]. In type 4 FTLD-U, the characteristic findings are scarcity of NCIs in proportion to NIIs, and lack of inclusions in the dentate gyrus of the hippocampus. Although TDP-43 pathology was not detected in FTLD-U cases with CHMP2B mutations, chromosome 9p-linked FTLD-U cases were classified as type 2, with most of those cases also exhibiting ubiquitin-positive and TDP-43-positive inclusions in both upper and lower motor neurons [24]. This finding is consistent with the high incidence of MND in patients with FTLD-U type 2 pathology [24,33,48]. Cairns and colleagues also observed TDP-43 cytoplasmic immunoreactivity that was not immunoreactive for ubiquitin, which they hypothesized might represent an early stage of TDP-43 inclusion formation [24]. These ubiquitin-negative TDP-43 deposits also appear to be particularly common in motor neurons. Although further analysis of these deposits is needed, if they are in fact pre-inclusions, this finding could be exploited to characterize the different stages of TDP-43 inclusion formation. However, it is still unclear how three different genetic mutations result in a similar frontotemporal dementia yet have distinct pathological phenotypes.

3.2 Amyotrophic lateral sclerosis (ALS)

ALS is a rare neurodegenerative disorder that affects both upper and lower motor neurons, leading to progressive weakness and spasticity, with eventual paralysis and death within 3-5 years [49]. Although most ALS cases are sporadic, approximately 10% of patients have a positive family history [49]. The most common genetic cause of familial ALS, accounting for at least 20% of identified familial ALS cases, is missense mutations in the Cu/Zn superoxide dismutase gene (SOD1) [50,51]. Interestingly, 20% of ALS patients also develop clinical features suggestive of FTLD [52,53], and 50% of ALS patients have coincident deterioration of both motor and cognitive function [54,55]. Pathologically, ALS patients have tau-negative ubiquitin inclusions identical to those of FTLD-U patients [21]. Given the considerable overlap between these two very heterogeneous disorders, TDP-43 pathology was evaluated in ALS. Both reports that initially identified TDP-43 as a major protein component of ubiquitin inclusions in FTLD-U also found abnormal TDP-43 inclusions in the motor neurons of ALS patients [2,23]. Intriguingly, although no genetic mutations in TDP-43 have yet been linked to FTLD, two groups have independently identified several mutations in TDP-43 that segregate with disease in MND/ALS [56,57]. Specifically, Gitcho and colleagues detected a mutation at A315T that was present only in affected family members [56], and Sreedharan and colleagues identified the mutations Q331K and M337V that also segregated with disease [57]. Although this group also identified the additional mutations G294A and A90V, the G294A mutation has been detected in a single ALS patient to date, while the A90V mutation has only been observed in a young, healthy individual [57], thus future studies are needed to evaluate the pathogenicity of these additional mutations. However, expression of TDP-43 mutants Q331K and M337V in developing chick embryos led to impaired maturation and an increase in neuronal apoptosis compared to

wild-type TDP-43 expression, implying a toxic gain of function of these TDP-43 mutations [57].

Since the initial reports detecting the presence of TDP-43 in ubiquitin inclusions in motor neurons of ALS patients, TDP-43 pathology has been confirmed in both sporadic and non-SOD1-linked familial ALS cases. However, TDP-43 is not present in ubiquitin inclusions of familial ALS caused by SOD1 mutations [25-27]. From these findings, it has been hypothesized that different mechanisms control degeneration of motor neurons in SOD1-linked ALS compared with sporadic and non-SOD1-linked ALS [58]; however, it is also possible that TDP-43 pathology and mutant SOD1 produce or contribute to the same downstream consequences. In one mechanism, motor neuropathy with neurofilament (NF) aggregate formation results from disruption of the stoichiometry between the three NF isoforms, including the low-molecular-weight NF (NFL), middle-molecular-weight NF (NFM), and the high-molecular-weight NF (NFH) [59,60]. In addition, the MND induced in transgenic mice overexpressing NFH was dose-dependently rescued by overexpressing NFL [61]. Thus, since TDP-43 binds and stabilizes NFL mRNA [5] whereas mutant SOD1 binds but destabilizes NFL mRNA [62], it might explain how loss of normal TDP-43 function or mutations in SOD1 could produce a similar pathological phenotype.

Intriguingly, a recent study illustrated that phosphorylated Smad2/3, transcription factors phosphorylated in response to TGF-β signaling, colocalize with TDP-43 in round hyaline inclusions in sporadic ALS cases; while like TDP-43, there was no detection of Smad2/3 in inclusions from SOD-1 linked familial ALS cases [63]. Phosphorylation of Smad2/3 promotes association with Smad4, leading to the subsequent translocation of these factors into the nucleus [64]. Although Smad4 immunoreactivity was not assessed within this study, either the presence or absence of Smad4 in these inclusions could be enlightening and help to reveal the level of impairment in TGF-β-Smad signal transduction. Although the colocalization of Smad2/3 with TDP-43 in sporadic ALS is hypothesized to be indicative of a general impairment in the regulation of nuclear-cytosolic transport, it is unclear why the abnormal cytosolic colocalization of these proteins would only occur in sporadic ALS patients, highlighting the need for further research to more extensively evaluate this relationship.

In-depth analyses of the distribution of TDP-43 pathology in the brainstem of FTLDMND and ALS patients found that NCIs are present in nuclei of the facial, trigeminal, and hypoglossal cranial nerves [65,66], but not in nuclei of the oculomotor, trochlear, abducens, or vestibular nerves [65]. Because the nuclei of the cranial nerves are innervated directly (facial, trigeminal, and hypoglossal nuclei) or indirectly by the corticobulbar tract (a pathway that originates from the motor cortex and other areas of the frontal and parietal lobes), it is intriguing that TDP-43 pathology has only been observed in nuclei that receive direct projections from the cortex, and not in cranial nerve nuclei that are indirectly innervated by the cortex through interneurons of the reticular formation [67]. In addition, given that FTLD-MND is most commonly associated with type 2 pathology [24,48], which is characterized by TDP-43 inclusions in deep cortical layers, one might speculate that cortical output pathways, including the corticobulbar and corticospinal tracts originating from deep layers of the cortex, may be particularly affected in this subtype. This hypothesis awaits confirmation but might provide a link between selective vulnerability of distinct neuronal populations and clinical phenotype.

3.3 TDP-43 pathology in other neurodegenerative diseases

Since the discovery of TDP-43 aggregate formation in FTLD-U and ALS, several other neurodegenerative diseases have been evaluated for the presence of TDP-43-positive lesions. Attesting to the specificity of the involvement of TDP-43 pathology in

neurodegenerative disease, Lee and associates recently demonstrated the lack of TDP-43 inclusion formation in both anoxic and ischemic lesions [68]. Although investigators have not detected TDP-43 pathology in classic tauopathies, including corticobasal degeneration and progressive supranuclear palsy, as well as familial FTLD cases with tau mutations [65], tau pathology associated with Alzheimer's disease (AD) is sometimes associated with TDP-43 pathology [69]. Amador-Ortiz and colleagues screened a large number of AD cases with and without hippocampal sclerosis (HpScl), which is characterized by neuronal loss and gliosis in the subiculum and CA1 region of the hippocampus. They detected TDP-43 pathology in approximately 75% of AD cases with HpScl and 30% of AD cases without HpScl [69]. Although Cairns and colleagues detected TDP-43 pathology in just 15% of AD patients, only 20 AD patients were included in the analysis, which due to small sample size may not be an accurate representation of the patient population [24]. In a subsequent study that evaluated the incidence of TDP-43 pathology in Lewy body disorders, TDP-43-positive inclusions were observed in 30% of AD cases with concomitant dementia with Lewy bodies (DLB), 7% of Parkinson disease (PD) cases, and 19% of PD cases with dementia [70]. Although a number of studies have failed to observe colocalization between TDP-43 and tau pathology, both Arai and colleagues as well as the aforementioned studies detected TDP-43 immunoreactivity in a small number of neurofibrillary tangles [23,69,70]. In addition, Nakashima-Yasuda and colleagues did not detect TDP-43 in Lewy bodies, but α-synuclein and TDP-43 were occasionally colocalized within dystrophic neurites [70]. These findings, along with the discovery of a *PGRN* mutation in individuals with heterogeneous pathology, including tau-related neurofibrillary pathology, α-synuclein-positive Lewy bodies, and TDP-43-positive NCIs and NIIs [71], show a common pathogenic link between a variety of neurodegenerative conditions. This link is further supported by the demonstration of TDP-43 pathology in neurodegenerative disorders of the Chamorro population of Guam, particularly Guamanian parkinsonism-dementia complex (G-PDC) and Guamanian ALS (G-ALS) cases [72,73]. Although the etiology of G-PDC and G-ALS remains unknown, we believe that a greater understanding of disease pathogenesis in these disorders could provide insight into the mechanisms of neurodegeneration in ALS, AD, and PD. Thus, the detection of TDP-43 pathology in GPDC and G-ALS indicates that this protein will have far-reaching pathophysiologic ramifications on the field of neurodegeneration.

4. TDP-43 in disease

Biochemical analyses of human postmortem brain and spinal cord from patients with various neurodegenerative diseases showed a similar pattern of TDP-43 immunoreactivity. Specifically, in cases with TDP-43 inclusions, biochemical evaluation revealed decreased solubility of TDP-43, as well as ubiquitination, phosphorylation, and cleavage into 35-kDa and 25-kDa fragments in affected regions [2,22,23,26,[34],40,69,72,73]. Although the effects of ubiquitination or phosphorylation on TDP-43 function and cellular localization have not been determined, a recent report demonstrates that caspase-dependent cleavage of TDP-43 mediates abnormal redistribution of TDP-43 to the cytosol and thus loss of nuclear TDP-43 [34]. In addition, siRNA-mediated knockdown of *PGRN* led to a decrease in the solubility of TDP-43, as well as an increase in cleavage that paralleled caspase-3 activation [34]. Because *PGRN* mutations associated with FTLD-U are hypothesized to lead to a loss of functional PGRN [37-39], the demonstration that decreased PGRN expression *in vitro* increases TDP-43 cleavage via caspase activation provides the first mechanistic link between PGRN haploinsufficiency and TDP-43 pathology; however a subsequent study reported an inability to replicate these findings [74], A parsimonious explanation to account for these differences could be the influence of variations in methods (e.g. extraction buffers, knockdown efficiency between various targeted PGRN siRNA, and treatment duration). Regardless, strategies to promote the overexpression or inhibit degradation of *PGRN* could potentially yield a very promising therapeutic approach to either prevent or alleviate TDP-43 pathology.

Another approach to treat TDP-43 proteinopathies might be to accelerate the clearance of TDP-43 inclusions. Recent data have demonstrated that TDP-43 pathology increased when either proteasomal or autophagic pathways were inhibited *in vitro* [34,75]. Because the precise cellular mechanism(s) of TDP-43 degradation are unknown, these findings suggest that TDP-43 aggregates might be cleared by stimulating either the ubiquitin-proteasome system (UPS) or autophagy. Stimulation of autophagy by overexpressing histone deacetylase 6 (HDAC6) in *Drosophila* suppressed degenerative phenotypes caused by UPS impairment resulting from the overexpression of either Aβ fragments (unpublished observations reported in [76]) or polyQ-expanded proteins [76]. Other inducers of autophagy, including treatment with trehalose and rapamycin, alleviated toxicity and enhanced clearance of mutant huntingtin and α-synuclein in both *in vitro* and *in vivo* models [77,78]. Thus the UPS and lysosomal/autophagy pathways might regulate the clearance of pathological aggregates. Stimulation of either pathway could increase degradation of TDP-43 pathology. To evaluate the utility of this approach in TDP-43 proteinopathies, future studies to determine how TDP-43 expression is regulated, in particular the mechanism(s) of TDP-43 degradation, will be imperative.

5. Expert opinion

As the list of TDP-43 proteinopathies expands, it is becoming increasingly necessary to study normal and pathological functions of TDP-43. Although several studies have investigated the physiological functions of TDP-43, the role of TDP-43 in cellular function is still not completely characterized. The effects of posttranslational modifications, such as ubiquitination, phosphorylation, and cleavage, on TDP-43 function are also unclear. Given that the cleaved 25-kDa and 35-kDa fragments of TDP-43 do not contain the N-terminus, which has an RNA-binding domain and a nuclear localization signal, cleavage most likely results in altered function of TDP-43 through loss of the N-terminus and nuclear localization, although future studies will need to investigate this hypothesis. In addition, the identification of a putative nuclear export signal in the RRM2 domain [8], which upon cleavage of TDP-43 would remain intact in C-terminal fragments, may explain how caspase-mediated cleavage of TDP-43 leads to a cytosolic localization. The recent demonstration that siRNA-mediated knockdown of TDP-43 leads to an increase in both cdk6 expression and phosphorylation of the cdk6 substrate pRb, as well as an increase in apoptosis and disruption of the nuclear membrane, further emphasizes the dramatic effects of loss of normal TDP-43 function in disease [15].

Evidence from histological studies suggests that there is heterogeneity in the morphology, distribution, and biochemical correlates of TDP-43 immunoreactive inclusions. Specific monoclonal antibodies recognize the 25-kDa fragment of TDP-43 [2]. Although these antibodies detected ubiquitinated inclusions in cases of FTLD-U types 1 and 2, they failed to recognize ubiquitinated inclusions from type 3 cases [1]. The full implications of this are not yet completely understood, but it is possible that in FTLD-U type 3 cases, the TDP-43 present in inclusions has been modified to block a critical epitope that is otherwise exposed in inclusions from type 1 and 2 cases. Thus additional research is needed to characterize the spectrum of TDP-43 inclusions, in order to fully understand the mechanism(s) by which TDP-43 inclusions form, and to identify specific kinases, phosphatases, and ubiquitin ligases/hydrolases that regulate the phosphorylation and ubiquitination state of TDP-43. It will also be important to determine if and how these modifications are linked and if phosphorylation alters the biological function of TDP-43. Whether these post-translational modifications are preferential to full-length or cleaved fragments of TDP-43 also remains to be determined.

Despite the failure to identify mutations in TDP-43 linked to FTLD-U, the recent detection of genetic mutations in TDP-43 associated with ALS and MND have already yielded extremely enlightening findings regarding disease pathogenesis [56,57]. Given the precedent from other neurodegenerative disorders characterized by the detection of genetic mutations in genes encoding proteins that accumulate aberrantly, such continued efforts are considerably important, especially in familial cases. Furthermore, genetic engineering of TDP-43 will illuminate TDP-43 biology. For example, mutations in residues critical for phosphorylation or ubiquitination of TDP-43 might alter its function and subcellular localization, as would mutations or deletions in the nuclear localization signal and putative caspase cleavage sites Deletion constructs composed of the 25-kDa and 35-kDa fragments can be used to characterize and differentiate the properties of these fragments and to determine whether full-length TDP-43 or these fragments might form insoluble aggregates similar to fibrillar aggregates that are characteristic of tauopathies, synucleinopathies, and amyloidoses. To conduct such research, we will need to generate animal models that will help advance the current understanding of TDP-43 pathobiology. In addition, given the link between TDP-43 proteinopathies and mutations in *PGRN* and *VCP*, evaluating TDP-43 expression, function, and localization in various mutant and knockout models of *PGRN* and *VCP* might explain the link between these proteins. The effects of both a loss and overexpression of PGRN and VCP on TDP-43 should also be investigated to determine whether manipulation of either PGRN or VCP levels may be a suitable therapeutic strategy to treat TDP-43 proteinopathies.

Acknowledgments

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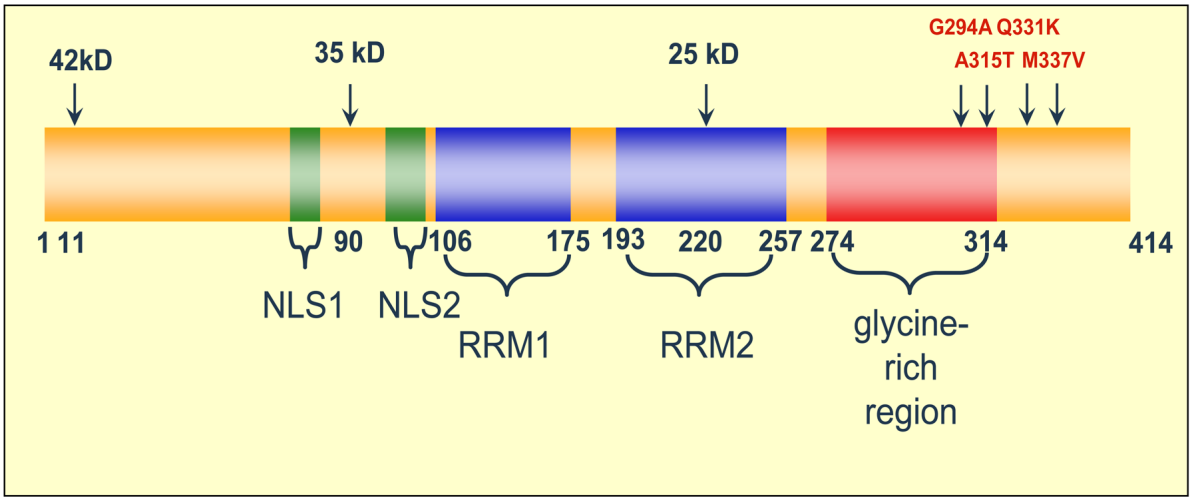

Figure 1.
Schematic of TDP-43 Molecule

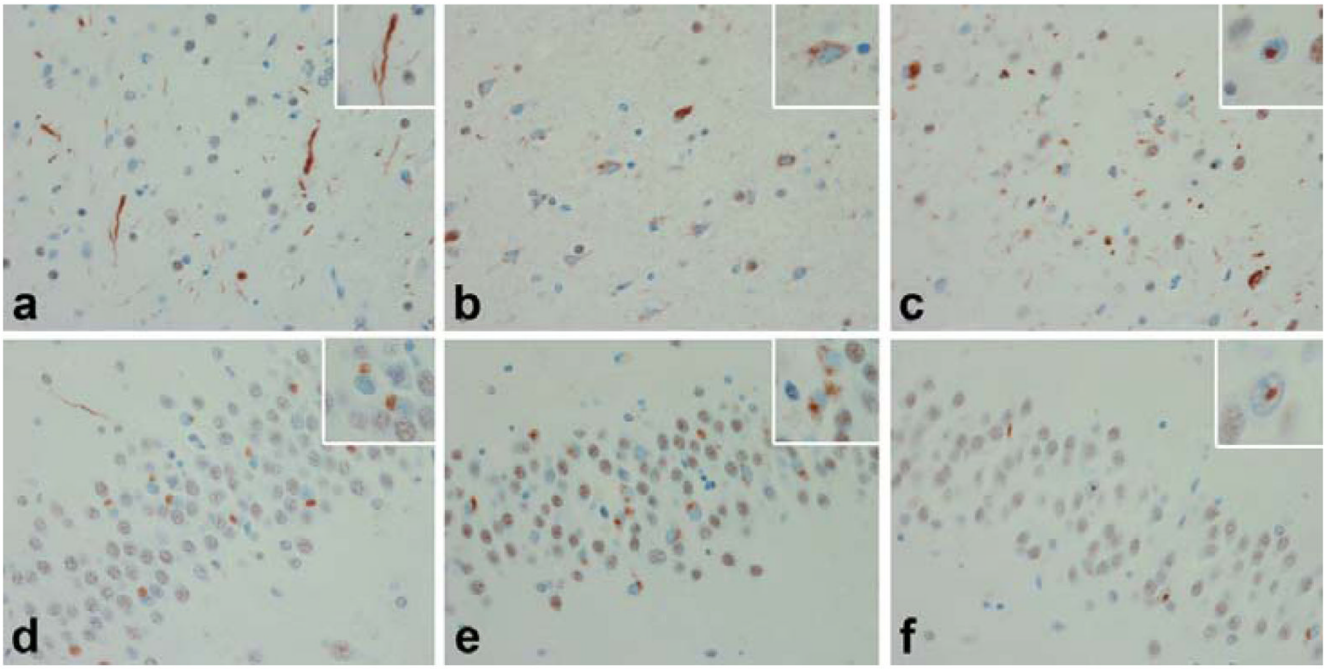

Figure 2.

Cortex (a, b & c) and dentate gyrus (d, e & f) of Type 1 (a & d), Type 2 (b & e), and Type 3 (c & f) FTLD-U according to Sampathu & Cairns [1]. **Type 1.** Predominance of dystrophic neurites (DN) (a, inset) in cortex with round neuronal cytoplasmic inclusions (NCI) (d, inset) in the dentate gyrus. **Type 2.** Predominance of NCI, including granular cytoplasmic TDP-43 immunoreactivity, with sparse DN in cortex (b, inset) and dentate gyrus (e, inset). **Type 3.** NCI, DN & neuronal intranuclear inclusions (NII) (c, inset) and NCI and NII in dentate gyrus (f, inset).

Table 1

FTLD-U Subtypes according to Cairns et al [32].

	Type I	Type II	Type III	Type IV
Characteristic histology	Long dystrophic neurites	NCI, including granular "pre-inclusions"	NCI and short neurites; NII in some	Many NII
Cortical layers most affected	Superficial and middle	Superficial and deep	Superficial	Superficial and middle
Dentate gyrus	Round NCI	Variable granular, crescent or round NCI	Variable crescent or round NCI	No NCI
Clinical feature	Many patients have semantic dementia	Some patients have motor neuron disease	Most patients have frontotemporal dementia	Most patients have frontotemporal dementia
Genetic linkage	None known	9p chromosome linkage	PGRN	VCP