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REVIEW ARTICLE

The molecular basis of the frontotemporal lobar degeneration–amyotrophic lateral sclerosis spectrum

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There is increasing evidence that frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS) represent a continuum of neurodegenerative diseases. FTLD is complicated by ALS in a significant proportion of patients, and neuropsychological studies have demonstrated frontotemporal dysfunction in up to 50% of ALS patients. More recently, advances in neuropathology and molecular genetics have started to disclose the biological basis for the observed clinical concurrence. TDP-43 and FUS have been discovered as key pathological proteins in both FTLD and ALS. The most recent discovery of a pathological hexanucleotide repeat expansion in the gene *C9orf72* as a frequent cause of both FTLD and ALS has eventually confirmed the association of these two at first sight distinct neurodegenerative diseases. Mutations in the *TARDBP*, *FUS*, and *VCP* genes had previously been associated with different phenotypes of the FTLD–ALS spectrum, although in these cases one end of the spectrum predominates. Whilst on the one hand providing evidence for overlap, these discoveries have also highlighted that FTLD and ALS are etiologically diverse. In this review, we review the recent advances that support the existence of an FTLD–ALS spectrum, with particular emphasis on the molecular genetic aspect.

Key words: Amyotrophic lateral sclerosis, *C9orf72*, frontotemporal lobar degeneration, genotype–phenotype correlations, molecular genetics, pathology

Introduction

Frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS) are two related and devastating neurodegenerative diseases. FTLD is a form of dementia clinically characterized by progressive changes in behavior, personality, and/or language. ALS is a neurodegenerative disorder in which loss of motor neurons leads to progressive weakness of the voluntary muscles. While traditionally they were considered as two separate identities, it is now thought that FTLD and ALS form one clinical continuum, in which pure forms are linked by overlap syndromes. Neuropsychological testing shows normal cognition in the majority of ALS patients. However, in up to 50% of ALS patients some degree of cognitive or behavioral impairment

Key messages

- FTLD and ALS are considered as two extremes of a clinical continuum.
- TDP-43 and FUS are key pathological proteins in both FTLD and ALS.
- Common genetic factors underlie FTLD and ALS, most notably the gene *C9orf72*.

can be documented, which is in 15%–18% sufficient to meet the criteria of FTLD (1,2). Recent advances in neuropathology and molecular genetics have started to disclose the biological basis for this clinical overlap. Neuronal aggregations of dysfunctional proteins are a key neuropathological feature in many forms of neurodegenerative diseases. In both FTLD and ALS the proteins TDP-43 and FUS have been identified as the main components of these inclusions, thereby providing a strong molecular link between the two disorders. Insights into the underlying biological mechanisms have been provided by the identification and functional characterization of mutations in a small fraction of patients with autosomal dominant FTLD and/or ALS. While some genetic causes are specific for either FTLD or ALS, others were found to contribute to both ends of the disease continuum. In this review, we summarize the evidence for the overlap between FTLD and ALS at the different levels, with particular emphasis on the molecular genetic aspect.

Frontotemporal lobar degeneration

FTLD is defined by the focal neurodegeneration in the frontal and anterior temporal lobes of the brain. It is, after Alzheimer's disease (AD), one of the leading causes of dementia, particularly in patients with a disease onset before 65 years (3). FTLD occurs with an estimated prevalence of 10–20 per 100,000 and incidence of 3.5–4.1 per 100,000/y in the 45–64 year age-group (4–7). It can manifest as three clinically recognized subtypes, depending on the early and dominating symptoms: a behavioral variant FTLD

(bvFTD) and two language variants, progressive non-fluent aphasia (PNFA) and semantic dementia (SD). The bvFTD is the most frequent diagnosed variant, accounting for approximately two-thirds of FTLT patients, while PNFA and SD represent more rare forms (8). The distinct phenotypes are associated with specific areas of neurodegeneration in the brain, which can be revealed by neuroimaging; bvFTD shows predominant prefrontal neurodegeneration, SD atrophy affects mainly the anterior temporal lobes, and PNFA is associated with left perisylvian atrophy (9,10). Patients with bvFTD present clinically with marked changes in behavior and personality, displaying a combination of disinhibition, apathy, lack of emotional concern, hyperorality, and stereotypic behavior (11,12). Neuropsychological testing reveals deficits on frontal or executive tasks, with relative sparing of episodic memory and visuospatial abilities (13,14). Patients with SD develop progressive comprehension deficits and naming errors with otherwise spared speech production (11,15). In contrast, PNFA is characterized by loss of motor speech fluency and agrammatism, with relatively intact language comprehension (11,15). The clinical subtypes usually start to show overlap with the progression of the disease, likely reflecting the more diffuse spreading of the disease in the frontal and temporal regions (16). Besides the clinical overlap with ALS, symptoms of the atypical Parkinsonian disorders corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP) are not uncommon in FTLT (17). The median disease duration of FTLT is 6–8 years (18,19). Unfortunately, no cure exists for FTLT at the moment (20).

Amyotrophic lateral sclerosis

ALS is a progressive neurodegenerative condition affecting the motor neurons of the cerebral cortex (the upper motor neurons (UMN)), brain-stem, and the anterior horn of the spinal cord (the lower motor neurons (LMN)). ALS has, similar to FTLT, a peak incidence around the age of 60 years. The incidence of ALS is reported to be 1.5–2.7 per 100,000/y in Western countries (21). The prevalence ranges from 2.7 to 7.4 per 100,000 (21). The clinical picture of ALS consists of a characteristic combination of signs of UMN degeneration, which include muscular spasticity and hyperreflexia, together with signs of LMN degeneration, which comprise muscular atrophy and fasciculations. In about two-thirds of ALS patients the disease starts in the muscles of the arms or legs and in one-third of patients in those required for swallowing or speech production (bulbar onset) (22). A respiratory onset ALS is considered rare (23). The motor symptoms progressively spread to include other anatomical regions; a diagnosis of ‘clinical definite ALS’ according to the revised El Escorial criteria requires the presence of UMN and LMN signs in three of four anatomical regions (24). Electromyographic studies in patients suspected for ALS allow documentation of the LMN degeneration and exclusion of other disease processes that may result in muscular weakness. Clinical variants of ALS include progressive muscular atrophy (pure LMN disorder) (25) and primary lateral sclerosis (pure UMN disorder) (26). The majority of ALS patients die within a few years after onset of first symptoms, mostly due to aspiration pneumonia (27). The drug riluzole has been shown to slow down the progression of the disease by a few months (28).

Clinical continuum between FTLT and ALS

Reports of dementia or psychiatric disturbances in association with clinical features of ALS date back to the late nineteenth century (29,30). However, it was only together with the increased recognition of FTLT as a separate form of dementia in the early

1990s that the cognitive and behavioral abnormalities that occur in ALS started to gain more detailed attention. Currently it is estimated that approximately 15% of FTLT patients have motor dysfunction meeting the criteria of ALS (31,32). Similarly, in two large ALS patient series, the prevalence of FTLT was 15% and 18% (1,2). The pattern of cognitive changes in patients with both FTLT and ALS (FTLT-ALS) usually closely resembles that of bvFTD, and the motor neuron disease is similar to that of classic ALS (33,34). FTLT-ALS patients sometimes develop delusions or hallucinations, features that are relatively uncommon in pure FTLT (34–36). A few reports describing a PNFA or SD phenotype in association with ALS have also been published (37–39). The first symptoms in FTLT-ALS patients occur on average in the late 50s, and progress is rapid with death occurring within 2–3 years (18,40). In most of cases, the FTLT symptoms precede those of ALS (41).

Adding further to the evidence of a clinical overlap is the observation in ALS patients without dementia of specific difficulties in performing cognitive tasks sensitive to frontal lobe dysfunction, suggesting a continuum of involvement (Table I, Figure 1). Neuropsychological studies in series of ALS patients have most frequently documented abnormalities in the executive functions, which are higher-order mental processes implicated in planning, problem-solving, shifting of attention, and inhibiting behavior and thought to be located in the frontal lobes. Rates of executive function deficits in ALS patients without dementia have ranged from 22% to 36% (1,42). Impaired verbal fluency, related to executive dysfunction, has been a frequent finding in cognitively impaired ALS and has in consequence been proposed as a relatively sensitive screening method (43). The performance on these tests may, however, be confounded by the reduced motor abilities in ALS, and adaptations have been developed to eliminate this effect, for example, through performing a written instead of an oral fluency task in ALS patients with impairment of bulbar musculature (44). Language abnormalities in non-demented ALS also occur but less frequently. Difficulties have been described on naming and comprehension tests, and several reports have been published of ALS patients with spelling and writing errors (45–48). The spectrum of frontotemporal syndromes in ALS further includes mild neurobehavioral impairment, which may occur independent of the cognitive dysfunction (49). Patients with ALS have been reported with increased frequency of a mild to moderate degree of apathy that was mood-independent, with disinhibition, lack of emotional concern or stereotypic behavior (50,51). Imaging studies in

Table I. Diagnostic categories of the FTLT-ALS disease spectrum.

		Main clinical characteristics
FTLT	bvFTD	Disinhibition, apathy, lack of emotional concern, hyperorality, stereotypic behavior and executive dysfunction
	PNFA	Labored speech, agrammatism with relatively spared comprehension
	SD	Comprehension deficits, naming errors with fluent speech
FTLT-MND-like		FTLT with minor motor system dysfunction
FTLT-ALS		Meeting the diagnostic criteria of both FTLT and ALS
ALSci		ALS with minor cognitive impairment
ALSbi		ALS with minor behavioral impairment
ALS		Muscle weakness, hyperreflexia, spasticity, atrophy and fasciculations

ALSbi = ALS with a mild behavioral impairment; ALSci = ALS with a mild cognitive impairment; bvFTD = behavioral variant FTLT; LMN = lower motor neuron; PNFA = progressive non-fluent aphasia; SD = semantic dementia; UMN = upper motor neuron; MND = motor neuron disease.

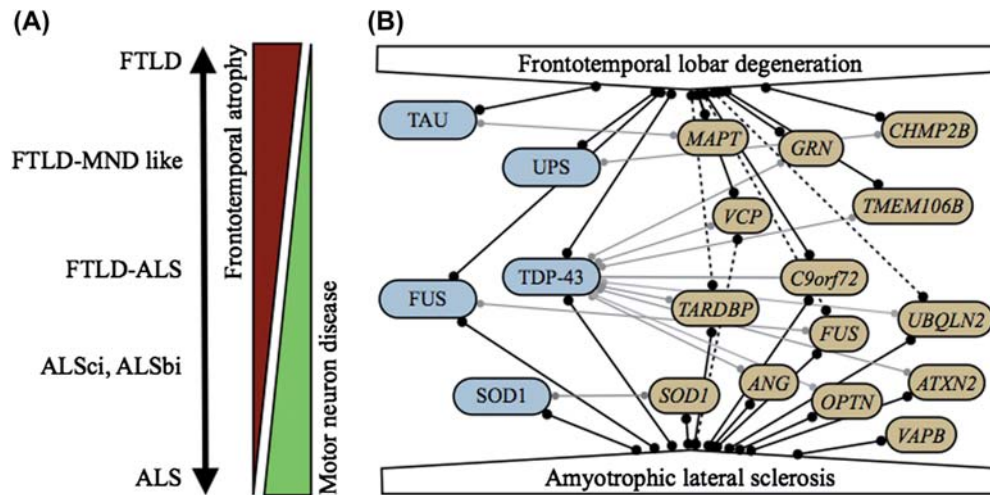


Figure 1. A: FTLD and ALS form a clinical disease continuum. B: Molecular relationships between FTLD and ALS. Pathological proteins are indicated in blue, causal genes in yellow. Full lines indicate strong correlations; dotted lines represent putative correlations. Correlations between genes and pathological proteins are indicated by light gray lines.

non-demented ALS patients have correlated the presence of cognitive or behavioral impairment with dysfunction in the frontal and temporal cortices (49,52–54). When considering a clinical continuum between ALS and FTLD, it is noteworthy that so far no clear progression of minor cognitive or behavioral impairment to FTLD-ALS has been documented in longitudinal studies (55,56). Recently, consensus criteria have been proposed for the diagnosis of frontotemporal dysfunction in ALS, which include the classes FTLD-ALS, ALSci (ALS with mild cognitive impairment), and ALSbi (ALS with minor behavioral impairment) (43).

The reverse phenomenon of subtle and pre-symptomatic motor abnormalities in FTLD has also been investigated, although less extensively. One prospective study reported that while 14% of FTLD patients met the criteria for clinical definite ALS, another 36% had possible features of ALS such as occasional fasciculations, evidence for neurogenic changes in one limb on EMG, or troubles with swallowing (31). A similar rate of minor motor system dysfunction in FTLD was reported in a second study (32).

Molecular pathology of FTLD and ALS

The histopathological characteristics of FTLD and ALS include, as for most neurodegenerative diseases, abnormal accumulation of protein aggregations in the affected parts of the nervous system. In contrast to the near-uniform nature of the aggregates in case of, for example, AD (amyloid- β plaques and intracellular tau neurofibrillary tangles), the molecular pathology of FTLD and ALS is notably heterogeneous (Figure 1). Nevertheless, similar molecular inclusions are being observed in FTLD and ALS, which suggests that they share common pathogenic mechanisms leading to neurodegeneration and aggregation of the specific inclusion proteins.

Approximately 35% of the FTLD patients who come to autopsy show intraneuronal and glial aggregations of the microtubule-associated protein tau (indicated as FTLD-tau) (57,58). The prototype of FTLD-tau is Pick's disease, where round inclusions of tau filaments are observed in ballooned neurons, which can be visualized by silver staining (Pick bodies).

In most FTLD brains, however, tau deposits cannot be detected. In the majority of these cases, neuronal intracytoplasmic and intranuclear inclusions are present that are immunoreactive to ubiquitin (FTLD-U) (59). Similar ubiquitin-positive inclusions

were also observed in the degenerating motor neurons of ALS patients (60). Moreover, further research demonstrated that a significant fraction of ALS patients, including those without overt cognitive changes, also have extra motor neuron ubiquitin pathology, which is mostly located in the limbic and frontotemporal brain regions reminiscent of FTLD (61). In 2006, the protein TDP-43 was identified as the main component of the ubiquitinated inclusions in both FTLD-U (Figure 2) (renamed FTLD-TDP) and in the majority (>90%) of ALS (ALS-TDP) (62,63). Following this discovery, it was proposed that FTLD and ALS form a clinico-pathological spectrum of TDP-43 proteinopathies (64).

In 2009, aggregations of the FUS protein were demonstrated in rare ALS patients with a mutation in the *FUS* gene (ALS-FUS) (65,66). These FUS inclusions were negative for TDP-43, which implies the involvement of mutually distinct pathways that lead to neurodegeneration. For FTLD, a small number of FTLD-U cases remained (10%–20%) that could not be explained by TDP-43 (67,68). When analyzed, almost all these atypical FTLD-U (aFTLD-U) brains appeared to harbor FUS inclusions (69–72). In addition, abundant FUS pathology has been demonstrated in two related rare neurodegenerative disorders: basophilic inclusion body disease (BIBD) (73) and neuronal inclusion filament disease (NIFID) (74). Current pathological nomenclature considers aFTLD-U, NIFID, and BIBD as the three distinct forms of FTLD-FUS (75). Together, ALS-FUS and FTLD-FUS form a new class of FUS proteinopathies (64).

In rare FTLD patients that have been linked to the *CHMP2B* gene, cellular inclusions are present that are ubiquitin-positive but TDP-43- and FUS-negative (FTLD-UPS) (71). Likewise, in ALS, a third molecular class exists without clear TDP-43 or FUS pathology, ALS-SOD, which is observed in ALS patients with a *SOD1* mutation (76).

Notably, TDP-43 and FUS are not specific to FTLD and ALS. Concomitant TDP-43 pathology is also found in several other forms of neurodegenerative diseases, such as AD (20%–26% of patients) (77,78), dementia with Lewy bodies (DLB) (18%–45% of patients) (79,80), or corticobasal degeneration (CBD) (15% of patients) (78) (for review see (81)). The relevance of this phenomenon of concomitant TDP-43 pathology remains unclear, and attempts to correlate the concurrent TDP-43 pathology with the clinical phenotype has given mixed results (78,82). In neurologically healthy elderly, a limited number of studies indicated that

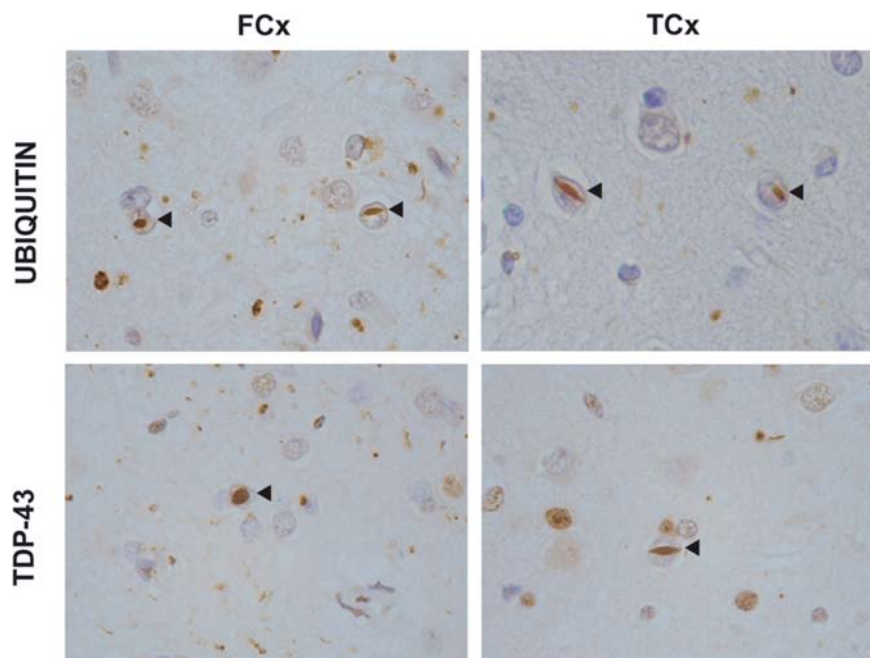


Figure 2. TDP-43 proteinopathy in FTLD. Ubiquitin and TDP-43 immunohistochemistry of sections from the superficial frontal cortex (FCx) and temporal cortex (TCx) of a patient with a *VCP* mutation (176). Frequent intranuclear inclusions (arrow-heads) are seen that stain positive for ubiquitin and TDP-43.

TDP-43 pathology is rare in normal aging (3% or less) (83). As in the case of TDP-43, concomitant FUS inclusions have been described in several other diseases, including disorders with expanded polyglutamine stretches such as Huntington's disease (84) and several forms of spinocerebellar ataxia (85).

FTLD-ALS mutation spectrum

FTLD is known to be a principally familial disorder, with the incidence of FTLD-ALS spectrum disorders in a patient's relative being 38%–47% (86–88). Similarly, a positive familial history has been found in 36%–59% of patients with FTLD-ALS (86–88). In ALS, however, most patients are isolated cases, but 5%–10% have a familial history of the disease (89). The notion of a shared genetic susceptibility between FTLD and ALS is also supported by findings of epidemiological studies. First-degree and second-degree relatives of ALS patients have a 2-fold increased risk for dementia (90,91).

Major progress has been made in the last 20 years in unraveling the genetic basis of FTLD and/or ALS. Together, FTLD-ALS disorders have been linked to at least 14 different genes. While some genetic causes are largely specific for either FTLD or ALS, others contribute to different phenotypes of the FTLD-ALS disease spectrum (Figure 1, Table II).

Autosomal dominant mutations in two genes, *MAPT* and *GRN*, account for about 10%–20% of all FTLD patients (87, 92–94). ALS has only very rarely been part of the clinical spectrum within *MAPT* or *GRN* segregating FTLD families (95–99). Other rare genetic causes of FTLD include mutations in the *CHMP2B* gene, in which pathogenic nonsense mutations have so far been identified in one large Danish FTLD pedigree (100) and one familial Belgian FTLD patient (101). A small number of *CHMP2B* missense mutations have also been described in FTLD and ALS patients; however, the pathogenicity of this type of *CHMP2B* mutations still remains uncertain (101–104). Mutations affecting the gene *VCP* were previously known to cause a rare multi-system disorder that includes FTLD (105). Recently,

the phenotypic spectrum associated with *VCP* has been extended also to include ALS.

Mutations in the *SOD1* gene are being found in about 20% of familial and 3% of sporadic ALS patients (106,107). There are very few reports of dementia in association with *SOD1* mutations (108). Further, neuropsychological assessment in series of *SOD1* mutation carriers failed to detect significant cognitive impairment (109). Mutations have been detected in the genes that encode the key pathological proteins of the FTLD-ALS spectrum, FUS and TDP-43 (65,66,110,111). Unexpectedly, however, mutations in the respective genes, *FUS* and *TARDBP*, appear to occur mostly at the ALS end of the disease spectrum. Occasionally, mutations in these genes have also been reported in FTLD-ALS or FTLD patients. While expansions of a polyglutamine tract in *ATXN2* have been associated with ALS (112), screening of this gene in FTLD and FTLD-ALS cohorts has so far been negative (113,114). Lastly, rare genetic causes of ALS include mutations in the *ANG*, *OPTN*, *UBQLN2*, and *VAPB* genes (Table II) (115–118). In *UBQLN2* families, the phenotype was mostly ALS, with a few patients reported as FTLD-ALS (118). The *ANG* gene has also been associated to FTLD-ALS, but this was based on the observation of a mutation in a single FTLD-ALS pedigree (119).

The strongest evidence for a shared genetic etiology between FTLD and ALS came from multiple linkage and genome-wide association (GWA) studies that established a shared disease locus on chromosome 9p (120–131). Most recently, three research groups have independently identified pathological expansions of a hexanucleotide repeat (GGGGCC) in the gene *C9orf72* as the underlying genetic cause of chromosome 9p-linked FTLD and ALS (132–134).

A pathological repeat expansion in *C9orf72* results in both FTLD and ALS

Since 2006, several large families in which FTLD and ALS co-segregated were reported with linkage to a region on chromosome 9p (120–127). The shared chromosomal region between

Table II. Genes associated with FTLN and ALS.

Gene	Locus	Inheritance	Mutation type	Mutation frequency FTLD	Mutation frequency ALS	Molecular pathology	Comment
<i>MAPT</i> (94)	17q21	AD	Missense, splice site, deletion	5%–10%	–	Tau	
<i>PGRN</i> (92,93)	17q21	AD	Nonsense, splice site, frameshift, deletion, met1, missense	5%–10%	–	TDP-43	FTLD-TDP type A
<i>VCP</i> (105)	9p13	AD	Missense	< 1%	< 1%	TDP-43	In combination with IBM and PDB; FTLD- TDP type D
<i>CHMP2B</i> (100)	3p11	AD	Nonsense	< 1%	–	UPS	
<i>TMEM106B</i> (131)	7p21	Risk factor	/	/	/	TDP-43	
<i>C9orf72</i> (132–134)	9p21	AD	GGGGCC expansion	5%–10%?	5%–10%?	TDP-43, UPS	FTLD-TDP type B?
<i>SOD1</i> (106)	21q22	AD and AR	Missense, frameshift nonsense	–	~5%	SOD1	
<i>TARDBP</i> (110,111)	1p36	AD	Missense, nonsense	< 1%	~1%	TDP-43	
<i>FUS</i> (65,66)	16q12	AD and AR	Missense, nonsense, splice site, frameshift	< 1%	~1%	FUS	Also associated with juvenile ALS with BIBD
<i>ATXN2</i> (112)	12q24	AD and risk factor	GAG expansion	–	~1%	TDP-43	Intermediate expanded alleles cause ALS, longer alleles cause SCA2
<i>ANG</i> (115)	14q11	AD and risk factor	Missense	–	< 1%	TDP-43	
<i>OPTN</i> (117)	10p13	AD and AR	Missense, exon- deletion nonsense	–	< 1%	TDP-43	
<i>VAPB</i> (116)	20q13	AD	Missense	–	< 1%	?	Classic ALS, slow-progressive ALS, late onset SMA
<i>UBQLN2</i> (118)	Xp11	AD	Missense	< 1%	< 1%	TDP-43	

Sub-classification of FTLD-TDP is according to (135).

AD = autosomal dominant; AR = autosomal recessive; BIBD = basophilic inclusion body disease; IBM = inclusion body myositis; met1 = mutation of Met1 translation initiation codon; PDB = Paget's disease of the bone; SCA2 = spinocerebellar ataxia type 2; SMA = spinal muscular atrophy.

the linked families was 3.6 Mb in size and was located at 9p21.2-p21.1. The same chromosome 9p region was independently identified in several large population-based GWA studies in cohorts of unrelated ALS patients and control individuals. A trend for association with the same region was also observed in a FTLD GWA study, in a cohort of patients enriched for TDP-43 neuropathology (128–131). Fine mapping in the GWA studies delineated the association signal to a 106.5 Kb sized region at 9p21.2. In spite of extensive genetic analyses of all known and predicted coding and RNA genes within the candidate region, no simple sequence mutation or copy number variation could be identified explaining the established linkage and associations (125–127).

The clinical phenotype both between and within the chromosome 9p-linked families was variable (Table III); 31% of all patients presented with bvFTD only, 35% ALS only, and 34% a combination of both disorders. Additional clinical features included frequent hallucinations and delusions (120,122,124,126,127). Further, Parkinsonism was common in these families, and a CBS phenotype was reported in one patient (122,125–127). One patient had prominent cerebellar ataxia (127). The mean disease onset age in these families was 53 years, ranging from 31 to 84 years, with some risk haplotype carriers remaining disease-free until late in life (> 75 years) (120,122,125). The disease duration was 5 years on average, with shorter survival for ALS patients (3 years) than for FTLD-ALS (4 years) or bvFTD patients (7 years).

The neuropathology of the chromosome 9p-linked FTLD-ALS patients was, in case of FTLD, characterized by TDP-43 inclusions, showing a specific pattern of abundant neuronal cytoplasmatic inclusions with few neurites and intranuclear inclusions (a subtype of FTLD with TDP-43 pathology denoted as FTLD-TDP type B) (135). This FTLD-TDP subtype is typical for FTLD-ALS and has also been observed in familial FTLD-ALS patients not linked to chromosome 9p and in sporadic FTLD-ALS patients (136–138). The ALS pathology has been described as classical ALS-TDP. Often, chromosome 9p-linked patients with exclusively clinical FTLD or ALS showed a combined pathology at autopsy.

Most recently, others and we independently demonstrated that a pathological expansion of a GGGGCC hexanucleotide repeat within the promoter region of *C9orf72* is at the basis of chromosome 9p-linked FTLD and ALS (132–134). The expanded repeat was shown to co-segregate with disease in several of the linked families. Further screening for GGGGCC repeat expansions in FTLD and ALS patient cohorts resulted in high mutation frequencies. Depending on the study, in patients with familial disease, 80% of FTLD-ALS, 25%–50% of ALS patients, and 10%–30% of FTLD patients had a pathological repeat expansion. The majority of the autopsy-confirmed mutation carrier patients had TDP-43 inclusions in brain or spinal cord. However, also ubiquitin-positive and TDP-43-negative inclusions were observed, suggesting that proteins other than TDP-43 were accumulating (132,139). The identification of a pathological repeat expansion in *C9orf72*

Table III. Characteristics of chromosome 9p-linked FTLN-ALS families.

Reference	No. families (<i>n</i> patients)	FTLD or dementia	FTLD- ALS	ALS	Mean AAO (range)	Mean DD (range)	Molecular pathology (<i>n</i> patients)
Morita et al. 2006	1 (14)	9 (64%)	0 (0%)	5 (36%)	55.3 (45–64)	4.3 (1–9)	NK (2)
Vance et al. 2006	1 (12)	2 (17%)	3 (25%)	7 (58%)	60.3 (39–72)	3.0 (1–8)	Ub + (5)
Valdmanis et al. 2007	2 (16)	3 (19%)	3 (19%)	10 (63%)	55.1 (45–63)	3.6 (1–9)	0
Luty et al. 2008	1 (11)	7 (64%)	2 (18%)	2 (18%)	52.9 (43–68)	8.6 (1–18)	Ub +, TDP-43 +, FUS + (3)
Le Ber et al. 2009	6 (31)	10 (32%)	12 (39%)	9 (29%)	57.9 (41–84)	3.6 (1–9)	Ub +, TDP-43 + (3)
Gijssels et al. 2010	1 (9)	8 (89%)	0 (0%)	1 (11%)	58.1 (51–65)	6.4 (1–17)	Ub +, TDP-43 + (1)
Boxer et al. 2010	1 (10)	5 (50%)	3 (30%)	2 (20%)	45.7 (35–57)	5.8 (3–10)	Ub +, TDP-43 +, FUS- (3)
Pearson et al. 2010	1 (9)	0 (0%)	6 (67%)	3 (33%)	42.2 (31–52)	3.6 (1–13)	Ub +, TDP-43 + (3)
All families	12 (112)	35 (31%)	38 (34%)	39 (35%)	53.4 (31–84)	4.9 (1–18)	

No. = number; AAO = age at onset; DD = disease duration; NK = not known.

as a major cause of both FTLN and ALS provided the ultimate evidence that these two diseases are indeed biologically related.

Genotype–phenotype correlations in other FTLN-ALS spectrum genes

TARDBP

Sequencing of the *TARDBP* gene in FTLN and ALS patients was motivated by the discovery of underlying TDP-43 pathology. By early 2008, the first mutations in *TARDBP* were reported in ALS, providing conclusive evidence that TDP-43 itself can trigger TDP-43-associated neurodegeneration (110,111). To date, over 40 mutations have been identified in *TARDBP*, 7 of which were found in FTLN or FTLN-ALS patients (<http://www.molgen.vib-ua.be/FTDMutations>). The majority of the mutations are missense and are located in exon 6 of the gene, encoding the C-terminal glycine-rich domain, which is thought to be important for protein–protein interactions.

Mutations in *TARDBP* are usually associated with classic adult onset ALS. They account for 3%–4% of familial and around 1% of sporadic ALS. The site of onset varies, and some patients presented with a predominantly lower motor neuron disorder. In 74 index patients carrying 31 different *TARDBP* mutations, the disease age of onset varied from 30 to 74 years, with an average of 55 years (ALSOD database, <http://alsod.iop.kcl.ac.uk/>). Several *TARDBP* families showed evidence for incomplete penetrance. For example, in an Italian founder family segregating the p.A382T mutation, the penetrance was estimated at 60% by the age of 70 years (140).

TARDBP mutations may also be a rare but notable cause of FTLN-ALS and FTLN. Evidence is relatively strong in the case of FTLN-ALS. Several reports have been published of *TARDBP* mutations in FTLN-ALS patients (141–144). For example, one study that included a large number (*n* = 149) of FTLN-ALS patients found that two (1%) of those patients carried a *TARDBP* mutation (144). *TARDBP* missense mutations have to date been described in two pure FTLN patients with sporadic onset (145,146). One of these mutations has also been found in one ALS patient, adding evidence for its pathogenic character. Further, one *TARDBP* mutation has been described in a FTLN patient with additional features of supranuclear palsy and chorea, who showed TDP-43 pathology at autopsy (147). On the other hand, negative findings from other large cohorts of FTLN patients (together, *n* = 674) indicated that *TARDBP* mutations in pure FTLN are very rare (148–151).

ALS patients with a *TARDBP* mutation that come to autopsy show ALS-TDP pathology that is indistinguishable from the TDP-43 pathology observed in sporadic ALS (152–156). Although

reports are limited, TDP-43 inclusions are found more widespread than the actual motor neuron degeneration (152,153).

FUS

Shortly following the identification of mutations in *TARDBP* in ALS patients, pathogenic mutations in *FUS* were detected in autosomal dominant ALS families linked to chromosome 16 (65,66). Over 40 *FUS* mutations have now been reported in ALS and 3 mutations in FTLN-ALS or FTLN (<http://www.molgen.vib-ua.be/FTDMutations>). Most were found in the C-terminal end of *FUS* encoded by exons 14 and 15. These may be missense or nonsense mutations, splice site or frameshift mutations that result in the production of a C-terminal truncated protein. Interestingly, the C-terminal part of the *FUS* protein holds a nuclear localization signal (NLS), a sequence necessary for transport of the protein into the nucleus of the cell (157–159). A second cluster of mutations is observed in the Gly-rich region of *FUS*, encoded by exons 4 to 6, which are mostly found in sporadic patients.

Mutations in *FUS* are also mostly associated with a classic ALS phenotype. In several *FUS* mutation carriers, the signs of the disease were restricted to LMN damage, with little or no evidence for UMN disease (160–162). An unusual presentation affecting predominantly the axial musculature has been described in a number of ALS patients with the p.R521C mutation (163–165). The frequency of *FUS* mutations is estimated at 4% in familial ALS and 1% in sporadic ALS.

FUS mutation carriers have been reported with a disease onset for ALS from as early as 13 years old to over 70 years of age. A correlation was observed between onset age and the degree in which the mutation affects the NLS of *FUS*. Truncating mutations, which completely remove the NLS or missense mutations strongly affecting the NLS, such as the p.P525L mutation, occur in patients with earlier disease onset (before the age of 30 years) and more rapid decline (158,166–168). However, even within families segregating the same *FUS* mutation a broad spread in onset age has been observed, indicating that other genetic and/or environmental factors also influence the disease manifestation (160,169).

Few *FUS* mutations have been identified in patients with an FTLN or FTLN-ALS phenotype. We have described a missense mutation in a bvFTD patient without signs of motor neuron dysfunction (170). The mutation affects a highly conserved amino-acid residue and was absent in a large group of control individuals, suggesting a pathogenic role. However, family history was negative for FTLN or ALS, and there was no autopsied brain material available to investigate the associated brain pathology. Other investigators have described *FUS* mutations in FTLN-ALS patients (143,165,171). Some reports also mentioned the presence of FTLN or dementia in relatives of *FUS* mutation carriers

(160,168). However, two further studies of *FUS* in large FTLN cohorts (together, $n = 465$) observed no mutations (72,171), suggesting that *FUS* has only a limited role in the genetic etiology of FTLN.

FUS mutation carriers typically show inclusions of *FUS* but not of TDP-43 in affected motor neurons (66,160,163,172). Some reports indicate that the degeneration can be limited to the LMN, with minimal damage of the UMN (163,173). *FUS* staining is, however, more widespread and shows pathological inclusions in glial cells and neurons outside the motor system, including the striatum, basal ganglia, and frontal and temporal cortex. Some researchers also noticed basophilic inclusions in the degenerating motor neurons (160,163).

FUS has also been established as a major inclusion protein in three rare pathological phenotypes related to FTLN, being BIBD, NIFID, and aFTLN-U (75). BIBD can present clinically as ALS, FTLN-ALS, or FTLN (73). In patients with BIBD pathology and juvenile onset ALS, *FUS* mutations have been identified (166,167). The *FUS* mutations in these patients result in a strong disruption of the NLS of *FUS*, which reflects the early onset age of the disease. Intriguingly, not all patients with juvenile or adult onset ALS and *FUS*-positive BIBD can be explained by a *FUS* mutation (167). Further, no reports exist to date of *FUS* mutation carriers with BIBD and an FTLN-ALS or FTLN phenotype. *FUS* pathology was also demonstrated in NIFID (74). NIFID is a rare disorder and is seen in patients with bvFTD with or without ALS. Mutation screening of *FUS* in a small number of NIFID patients was negative. Finally, *FUS* pathology also characterizes the rare FTLN pathology subtype aFTLN-U, in which the ubiquitinated inclusions are *FUS*-positive but TDP-43-negative (69–72). Patients with aFTLN-U have typical clinical characteristics in common such as early disease onset (around 40 years), negative family history, bvFTD, little motor dysfunction, and pronounced atrophy of the caudate nucleus of the brain (67,68). Atrophy of the caudate nucleus on MRI has been proposed as a useful marker to predict aFTLN-U pathology (70,174). Also, in this subgroup with *FUS* pathology no mutations were found in the *FUS* gene (69,71,72).

VCP

The gene *VCP* has also been linked to different phenotypes of the FTLN-ALS disease spectrum. To date, about 20 different *VCP* mutations have been identified in 50 unrelated families (<http://www.molgen.vib-ua.be/FTLMutations>). All are missense mutations, and in about 75% of *VCP*-linked families the mutation is located in exon 5 of the gene.

VCP mutations were known to cause a rare autosomal dominant disorder with inclusion body myopathy (IBM) associated with Paget's disease of the bone (PDB) and FTLN, denoted as IBMPFD (105). The clinical presentation of IBMPFD is markedly variable. In a review of 20 IBMPFD families, approximately 90% of affected persons had IBM, 45% had PDB, and FTLN was seen in 38% of patients (175). We have described two unrelated families segregating the same p.R159H mutation in which pure FTLN was the most frequent clinical manifestation (176). Onset age of FTLN in these two families was on average 55 years (range 44–63 years) (176).

The clinical spectrum associated with *VCP* mutations has recently been extended to include also ALS (177). Through a whole-exome sequencing approach a p.R191Q mutation in *VCP* was identified in a family with autosomal dominant ALS (177). Screening of additional 210 familial and 78 autopsy-confirmed ALS patients revealed 4 more *VCP* missense mutation carriers (1%–2% of familial ALS). The identified *VCP* mutation carriers had been diagnosed with clinical definite ALS (mean age at onset

of 49 years, range 37–53 years), supported by the typical findings of ALS on EMG testing, and one *VCP* mutation carrier had a pathologically confirmed diagnosis of ALS-TDP. Of note, four patients of the described *VCP* families had been diagnosed with FTLN-ALS. The autopsy-confirmed ALS patient was part of a family with documented IBMPFD, but otherwise signs of PDB or IBM were mild or absent in the majority of these *VCP* families. In FTLN, *VCP* mutations lead to a signature TDP-43 pathology with numerous intranuclear inclusions, referred to as FTLN-TDP type D (Figure 2) (135,178). Since then, other studies have confirmed a contribution of *VCP* to the etiology of ALS (179,180).

Risk factors for TDP-43 proteinopathy

The inherent molecular heterogeneity of FTLN and the relative infrequency of the disease initially hampered the set-up of a successful GWA study on FTLN. With the recognition of TDP-43 pathology in FTLN an international GWA study was undertaken which focused on a homogeneous population of autopsy-confirmed FTLN-TDP patients. Significant association was identified with DNA variants located within the *TMEM106B* gene on chromosome 7p21 (131). Results of a number of follow-up studies seem to indicate that *TMEM106B* is a true risk factor for FTLN (181–184), but further confirmation is needed (185).

Because of the similar TDP-43 pathology, the disease-modifying effect of *TMEM106B* was evaluated in a cohort of ALS patients (186). No association between *TMEM106B* and ALS was observed, which was in line with results from previous ALS GWA studies that did not detect an association with the *TMEM106B* locus (128,130). However, the *TMEM106B* risk allele did appear to be associated with cognitive dysfunction in the ALS patients. Correlation with cognitive performance was strong as measured by the phonemic verbal fluency test but could not be confirmed by other cognitive tests. These findings are interesting but need to be replicated in other and larger ALS cohorts with more thorough neuropsychological evaluation. If confirmed, this would indicate that genetic risk factors for FTLN act as modifiers of the clinical presentation in ALS and underlie the risk for associated cognitive impairment.

Conclusions

Substantial overlap exists between FTLN and ALS at the clinical level. In a small group of patients, the concurrence of both disorders is obvious. However, there exists also a large group of patients in which signs of co-morbidity are more subtle, e.g. the ALS patients with mild cognitive impairment or behavior changes. Recent advances in the pathology and genetics of FTLN and ALS have demonstrated that these disorders are also tightly connected at the molecular level. Whilst on the one hand providing evidence for overlap, these discoveries have also highlighted that FTLN and ALS are etiologically diverse. TDP-43 and *FUS* pathology seems to be largely mutually exclusive, which suggests the involvement of different pathways that lead to neurodegeneration. The relevance of this heterogeneity is supported by the strong genetic–pathological correlations and, to a lesser degree, also by correlations with clinical sub-phenotypes. While some of the identified genes contribute to only one extreme of the clinical continuum, others have been implicated in different phenotypes of the FTLN-ALS spectrum. The exciting recent identification of pathological repeat expansions in *C9orf72* in FTLN-ALS spectrum diseases, in particular, provided firm evidence for a biological link between these diseases. Future studies might provide insights into why some carriers have FTLN whereas others develop ALS and

what the biological mechanisms could be by which the expanded repeat in *C9orf72* contributes to neurodegeneration. *TARDBP* and *FUS* mutations have most often been associated with a classical ALS phenotype. Recent findings have suggested that these genes also have a limited role in FTLN pathogenesis. *VCP* mutations occur in the setting of a rare and heterogeneous multi-systemic syndrome that includes both FTLN and ALS as well as a bone (PDB) and a peripheral muscle disease (IBM). Genetic variants at the *TMEM106B* gene have been associated with increased risk for the more common sporadic forms of FTLN. An interesting hypothesis is that the susceptibility genes for FTLN-TDP, e.g. *TMEM106B*, could act as modifiers of cognitive performance in ALS. Finding relationships at the molecular level between two seemingly separate disorders has not been unique to FTLN and ALS. In fact, modern high-throughput genomic and proteomic analyses have discovered links between many diseases, which has culminated in the concept of a human diseasome that maps relationships between diseases and genes associated with them (187). The recognition that FTLN and ALS are closely related could have important implications not only for research but also for the management of FTLN-ALS patients. With the identification of new genes within the spectrum, screening of all FTLN-ALS phenotypes is justified. And in the event of emerging therapeutic techniques, approaches aimed at preventing or removing TDP-43 or FUS aggregations should be investigated in the different phenotypes associated with TDP-43 or FUS proteinopathy, as they will likely benefit patients on both ends of the FTLN-ALS spectrum.

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