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Recent advances in the molecular basis of frontotemporal dementia

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Abstract

Frontotemporal dementia (FTD) is a clinical syndrome with heterogeneous molecular basis. Until recently, our knowledge was limited to a minority of cases associated with abnormalities of the tau protein or gene (*MAPT*). However, in 2006, mutations in progranulin (*GRN*) were discovered as another important cause of familial FTD. That same year, TAR DNA binding protein 43 (TDP-43) was identified as the pathological protein in the most common subtypes of FTD and ALS. Since then, significant efforts have been made to understand the normal functions and regulation of GRN and TDP-43 and their roles in neurodegeneration. More recently, other DNA/RNA binding proteins (FUS, EWS and TAF15) were identified as pathological proteins in most of the remaining cases of FTD. And just six months ago, abnormal expansion of a hexanucleotide repeat in *C9ORF72* was found to be the most common genetic cause of both FTD and ALS. With this remarkable progress, it appears that all the common FTD-causing genes have now been discovered and the major pathological proteins identified. This review highlights recent advances in the molecular aspects of FTD, which will provide the basis for improved patient care through the future development of more targeted diagnostic tests and therapies.

Introduction

Frontotemporal dementia (FTD) accounts for 5–15% of all dementia and is the second commonest cause in the presenile age group.^{1,2} FTD is a clinical syndrome, characterized by progressive deterioration in behavior, personality and/or language, with relative preservation of memory.^{3–5} Clinical subtypes include the behavioral variant (bvFTD) and two forms of primary progressive aphasia; progressive non-fluent aphasia (PNFA) and semantic dementia (SD). In addition, FTD is often associated with an extrapyramidal movement disorder (parkinsonism or corticobasal syndrome) and/or motor neuron disease (MND).^{6,7} Given the variability in phenotype, it is not surprising that the molecular basis of FTD is also heterogeneous (Table 1).

A family history of FTD is present in 25–50% of cases, often with an autosomal dominant pattern of inheritance, indicating a strong genetic component.^{8,9} In 1998, mutations in the microtubule associated protein tau gene (*MAPT*) on chromosome 17 were identified in a number of families with FTD and parkinsonism.^{10–12} Since then, 44 different *MAPT*

mutations have been reported, accounting for 5–20% of familial FTD (www.molgen.ua.ac.be/ftdmutations).¹³ However, there remained a number of chromosome 17 linked FTD families that were not explained by *MAPT* mutations. A major breakthrough occurred in 2006 when progranulin (*GRN*) was identified as the second FTD-related gene on chromosome 17, with *GRN* mutations responsible for an even larger proportion of FTD families.^{14,15} Much less common are mutations in the valosin containing protein gene (*VCP*) which cause the rare familial syndrome of inclusion body myopathy with Paget disease of bone and FTD¹⁶ and a mutation in the gene for charged multivesicular body protein 2B (*CHMP2B*) found in a large Danish FTD pedigree.¹⁷ In addition, several families with a combination of FTD and amyotrophic lateral sclerosis (ALS) have been reported with genetic linkage to a locus on chromosome 9p.^{18–26} Despite years of intense effort by many research groups worldwide, the identity of the FTD/ALS gene on 9p remained elusive until just last year, when two independent studies identified the defect as being an expanded hexanucleotide repeat in a non-coding region of the chromosome 9 open reading frame 72 gene (*C9ORF72*).^{27,28} Discovery of the *C9ORF72* mutation has generated tremendous excitement in the FTD and ALS research communities, as it appears to be the most common genetic cause of both conditions (see below).

The neuropathology associated with clinical FTD is also heterogeneous.²⁹ A common feature is the relatively selective degeneration of the frontal and temporal lobes, and the term “frontotemporal lobar degeneration” (FTLD) is often used for those pathological conditions that predominantly or commonly present with FTD. In addition, most cases of FTLD are found to have abnormal intracellular accumulation of some disease-specific protein and it has become popular to classify FTLD into broad categories, based on the molecular defect thought to be most characteristic.^{30,31} Until quite recently, the only FTLD subgroup we knew much about were those conditions characterized by the aggregation of hyperphosphorylated tau protein in neurons and glia (FTLD-tau) (Table 1). However, most FTD is not associated with tau pathology, but is characterized by neuronal inclusions that were originally identified with ubiquitin immunohistochemistry (FTLD-U).^{32,33} Just months after publication of the *GRN* mutation discovery, another landmark paper reported identification of the transactive response DNA binding protein with molecular weight 43 kD (TDP-43) as the ubiquitinated pathological protein in most cases of FTLD-U (subsequently renamed FTLD-TDP), as well as the vast majority of ALS.^{34,35} This provided strong evidence that FTD and ALS are closely related conditions with overlapping molecular pathogenesis. This concept was further strengthened in 2009 when, following the discovery that mutations of the fused in sarcoma gene (*FUS*) cause autosomal dominant ALS,^{36,37} it was shown that most of the ~10% of FTLD that do not have either tau or TDP-43 based pathology are characterized by inclusions that are immunoreactive for FUS (FTLD-FUS).^{38–40} More recently, it has been shown that the FUS-positive inclusions in FTLD-FUS also label for the other members of the FET protein family (including Ewing’s sarcoma protein and TATA-binding protein-associated factor 15).⁴¹

The recent pace with which knowledge of the molecular genetics and neuropathology of FTD has advanced has been truly remarkable (Box 1). In just over five years, we have gone from knowing virtually nothing of the molecular basis of most cases of FTD, to now being able to determine the genetic cause in the majority of autosomal dominant families and being able to assign virtually all cases of FTLD to one of three major pathological subtypes (FTLD-tau, FTLD-TDP, FTLD-FUS).³¹ This insight is a crucial step towards improved FTD patient care, as it provides the basis for more informed counseling and the potential for more specific diagnostic tests and targeted therapies. In this review, we will highlight several recent advances in our understanding of molecular aspects of FTD, focusing on the recent discovery of the *C9ORF72* mutation and the roles of *GRN*, TDP-43, FUS and the other FET proteins in disease pathogenesis.

Advances in the molecular genetics of FTD

GRN variants and its biological regulators in FTD

In less than six years, 69 different pathogenic *GRN* mutations have been reported in more than 230 families worldwide, accounting for 5–20% of familial FTD and 1–5% of sporadic cases (www.molgen.ua.ac.be/ftdmutations).⁴² Progranulin (GRN) is a multifunctional secreted growth factor, expressed by many cell types including neurons.⁴³ Pathogenic mutations are of various types and occur throughout the gene, but all cause disease via haploinsufficiency.^{14,15} As a result, significantly reduced levels of GRN are consistently observed in plasma, serum and CSF samples of symptomatic and asymptomatic *GRN* mutation carriers.^{44–46} Based on these findings, GRN enzyme-linked immunosorbent assays (ELISA) are now being developed as an inexpensive alternative to classical sequencing analyses for diagnostic testing of FTD patients.

Genetic modifiers and regulators of GRN expression—The clinical phenotype associated with *GRN* mutations is quite variable^{47–52} and penetrance is incomplete.⁵³ Understanding the factors that modify the expression of *GRN* mutations or regulate the normal *GRN* gene is of potential therapeutic importance. One such genetic factor is the uncharacterized transmembrane protein 106B (TMEM106B), which was recently identified in a genome-wide association study (GWAS) of cases with known FTLD-TDP pathology.⁵⁴ Genetic variants in and near *TMEM106B* appear to protect or delay the onset of FTD in individuals with pathogenic *GRN* mutations, possibly by increasing GRN levels.^{54–57} A number of microRNAs, including miR-29b and miR-107 have also been implicated in GRN regulation.^{58,59} In addition, the minor T-allele of genetic variant rs5848, located in the 3' untranslated region of *GRN*, increases the binding of miR-659 to *GRN*, thereby reducing GRN levels.⁶⁰ Genetic association studies have shown that carriers homozygous for the T-allele of rs5848 have a three-fold increased risk to develop FTLD-TDP compared with homozygous C-allele carriers⁶⁰, supporting a role for GRN in sporadic FTD and possibly other neurodegenerative diseases such as Alzheimer's disease.^{61–63} *GRN* expression may also be modified by certain exogenous factors. It was recently shown that *GRN* transcription can be enhanced by small molecules including suberoylanilide hydroxamic acid (SAHA),⁶⁴ while inhibitors of the vacuolar ATPase and some alkalizing drugs increase GRN production and secretion through a translational mechanism.⁶⁵

GRN cellular biology—Significant progress has also been made in recent years towards our understanding of GRN biology and its neuroprotective function. The addition of GRN to stressed or GRN-depleted neuronal cells promotes neurite outgrowth.^{66–69} The neuroprotective effects of GRN might be due, at least in part, to the activation of cell signaling pathways involved in cell survival.^{66,70–73} A role for GRN in excitotoxicity and synaptic transmission has also been suggested.^{68,74} Importantly, sortilin-1 (SORT1), a known receptor for other neurotrophic factors in the brain, was identified in two independent studies as the first known receptor for GRN.^{75,76} SORT1 has been shown to mediate GRN endocytosis and regulate the levels of GRN *in vivo* in mouse brain and in human plasma. More recently, tumor necrosis factor receptors were reported to directly interact with GRN.⁷⁷ The identification of GRN receptors is exciting as it opens new avenues in GRN cell biology research and another potential route to FTD therapy.

C9ORF72 mutation

Since 2006, increasing evidence has suggested the presence of a major locus for the combined phenotype of FTD and ALS on chromosome 9p21, but the disease mutation has remained elusive (Box 2).^{18–26} The key to the identification of the disease-causing mutation came from the apparent non-Mendelian inheritance of a GGGGCC hexanucleotide repeat

located in a non-coding region of *C9ORF72* (Figure 1a) in a large FTD-ALS family designated VSM-20 (Vancouver, San Francisco and Mayo family 20).²⁷ Using primers flanking the repeat region, all affected individuals appeared homozygous by fluorescent PCR, while affected children seemed not to inherit an allele from their affected parent. This finding suggested the presence of a repeat expansion that was too large to be amplified by the PCR method, which was confirmed using a repeat-primed PCR assay (Figure 1b) and southern blot analysis. The polymorphic nature of this GC-rich hexanucleotide repeat was independently recognized in a Welsh FTD-ALS family using next-generation sequencing, also implicating this genomic region in disease pathogenesis.²⁸

Mutation frequency—In the six months since the original discovery, numerous FTD and ALS patients have been screened for the presence of GGGGCC repeat expansions in *C9ORF72* using the repeat-primed PCR assay (Table 2).^{27,28,78–94} The mutation frequency has varied significantly among populations, with the highest being in genetically isolated populations from Finland and Sardinia, and in cohorts where all patients had a pathological diagnosis of FTLT-TDP (with or without ALS).^{27,28,81,85,88} The average mutation frequencies in North American and European populations reported are 37% for familial ALS, 6% for sporadic ALS, 21% for familial FTD and 6% for sporadic FTD patients. In all series, the *C9ORF72* mutation has been the most common genetic cause of familial ALS (more frequent than *SOD1* mutations) and at least similar in frequency to *GRN* mutations in FTD families. To date, most of the patients included in the mutation screenings have been Caucasian; however, *C9ORF72* repeat expansions have also been identified in patients of African American, Middle Eastern and Asian race.^{86,88,94} Interestingly, independent of the clinical presentation or ethnic origin, all *C9ORF72* mutation carriers inherit the expansion on the same genetic background, suggesting the presence of a common ancestor or, alternatively, the occurrence of multiple independent expansions on a fragile predisposing disease haplotype.^{88,95,96}

Clinical phenotypes—Several groups from North America and Europe have now published descriptions of the demographic, clinical and neuropathological features of their cohorts of patients with the *C9ORF72* mutation.^{27,28,78–94} The clinical presentation is heterogeneous and highly variable between and within families. Patients may present with FTD, ALS or features of both. The FTD subtype is most often bvFTD with PNFA less frequent. ALS usually has early involvement of both upper and lower motor neurons and bulbar presentation is particularly common.^{79,81,82,94} Several studies have found that ALS patients with the mutation have a slightly earlier onset and shorter disease duration than those without the mutation.^{79,81,82,84,91,94} In addition to FTD and ALS, other features may include memory disorder,^{78,85,87,90,92,93} psychosis,^{78,83,85,92,93} extrapyramidal movement disorder (usually an akinetic-rigid syndrome)^{78,82,83,85,90,92} and cerebellar signs.⁸⁵ Symptoms tend to accumulate and phenotypes converge with disease progression, so that most patients eventually develop at least some abnormalities of behavior, language and motor function.^{78,80,82,85,94} There is wide variation in the age at onset (27 – 83 years, mean = 50s) and disease duration (1 – 22 years) and several studies have noted earlier disease onset in subsequent generations, consistent with genetic anticipation.^{78,81,82,84,85,94} Structural neuroimaging tends to show symmetric bilateral atrophy, primarily affecting frontotemporal regions, but also involving other cerebral lobes and the cerebellum.^{78,85,87,92,97}

Neuropathology—The neuropathology associated with the *C9ORF72* mutation is a combination of FTLT-TDP and classical ALS.^{27,78,79,82,84,85,87,90,92–94,98,99} Regardless of the clinical phenotype, postmortem examination usually shows TDP-43 positive inclusions in a wide range of neuroanatomical regions including the extramotor cerebral cortex,

hippocampus, basal ganglia, substantia nigra and lower motor neurons of the brainstem and spinal cord. In addition, a unique and highly characteristic feature of cases with the mutation is the presence of neuronal inclusions in the cerebellar granule cell layer, hippocampal pyramidal neurons and other neuroanatomical sites, that label for proteins of the ubiquitin proteasome system (ubiquitin, ubiquilins and p62) but that are negative for TDP-43 (Figure 1c).^{27,78,79,82,84,85,87,90,92–94,98,99} This consistent finding supports the abnormal metabolism and accumulation of some, as yet unidentified molecule(s) that could include the mutant RNA, RNA-binding proteins or protein products of aberrant splicing. To date, immunohistochemical studies using commercial antibodies against C9ORF72 have failed to demonstrate any abnormal distribution or accumulation of the protein.^{27,79,82,85,87,93,94}

Repeat size—All *C9ORF72* mutation screenings performed to date have used the repeat-primed PCR method to detect the presence of a pathogenic GGGGCC repeat expansion. However, it is important to note that this method is only semi-quantitative and that the characteristic stutter pattern observed (Figure 1b) cannot be used to determine the exact number of repeats. In one family, southern blot analyses performed using DNA extracted from lymphoblast cell lines showed pathogenic repeat expansions of 700–1600 repeat units;²⁷ however, the minimal repeat size associated with disease may be considerably smaller. Similar to other non-coding repeat expansion disorders, there is evidence for somatic instability of the *C9ORF72* repeat.²⁷ This means that repeat lengths may vary among different tissues within the same individual, making it difficult to accurately size the repeat and determine genetic/clinical/pathological correlations.^{100–102} Our current lack of knowledge of the minimal pathogenic repeat-size combined with the technical challenges mentioned, raise important questions regarding genetic testing for this common mutation; particularly in the context of predictive genetic testing. Accurate sizing of the expanded repeat in larger FTD and ALS patient series will be crucial to establish reliable cut-off sizes needed to counsel individuals undergoing genetic testing. Future studies also need to determine whether the repeat-length contributes to the variability in onset age and clinical presentation or whether other genetic and/or environmental modifiers are involved.

Disease mechanism—C9ORF72 is a completely uncharacterized protein whose function is presently unknown. Two different C9ORF72 isoforms are predicted to be generated from a total of three different *C9ORF72* transcripts;²⁷ however, the relative expression of each of these transcripts in relevant brain regions has not yet been studied. Several groups have shown ~50% loss of at least one *C9ORF72* transcript in expanded repeat carriers, presumably resulting from the interference of the expanded GC-rich repeat with *C9ORF72* transcription regulation.^{27,28,84} Although these findings support a possible loss-of-function disease mechanism, the accumulation of GGGGCC repeat containing transcripts as nuclear RNA foci in frontal cortex and spinal cord of *C9ORF72* mutation carriers has also been demonstrated (Figure 1d), suggesting a possible toxic RNA gain-of function disease mechanism.²⁷ Based on commonalities with other non-coding repeat expansion disorders, these RNA foci may alter the function of one or more RNA-binding proteins resulting in downstream changes in gene expression and/or alternative splicing of a range of transcripts.¹⁰³ A number of cellular and animal models, either eliminating C9ORF72 expression or overexpressing human *C9ORF72* containing expanded GGGGCC repeats, are currently being generated to determine the relative contribution of each disease mechanism to neurodegeneration and TDP-43 aggregation.

Other FTD genes and genetic risk factors

With the identification of the repeat expansion in *C9ORF72*, all previously published FTD families with genome-wide linkage have now been accounted for. While it is unlikely that any other common FTD-causing genes exist, rare mutations in other genes may each explain

a small number of the remaining families and combinations of genetic variants and environmental factors are likely to be responsible for disease in the majority of sporadic FTD patients. The use of exome and whole-genome sequencing will greatly facilitate the discovery of rare genetic defects in the future. This was recently demonstrated with the identification of the colony stimulating factor 1 receptor gene (*CSF1R*) as the cause of hereditary diffuse leukoencephalopathy with spheroids (HDLS),¹⁰⁴ a disorder with variable clinical presentation that includes features of FTD. Additional GWAS, such as the large collaborative study currently underway, which includes more than 2500 FTD patient samples, may identify additional genetic risk factors.

ALS-related genes in FTD—Other rare genetic causes of FTD that have been identified in recent years include *TARDBP* and *FUS*, although mutations in each of these genes usually cause a pure ALS phenotype.^{36,37,105,106} This past year, *UBQLN2*, which encodes a member of the ubiquilin family that is involved in the degradation of ubiquitinated proteins, was also added to the list of ALS-FTD genes.¹⁰⁷ In about 20% of *UBQLN2* mutation carriers, progressive dementia with abnormalities in both behavior and executive functions were reported; however, none of these patients presented with FTD alone.

Advances in the molecular pathology of FTD

TDP-43

TDP-43 is a highly conserved, predominantly nuclear protein, able to shuttle between the nucleus and cytoplasm. It has a number of well-described functions in RNA regulation such as control of splicing, mRNA transport and stability; however, the complexity of TDP-43 functions is just emerging.^{108–110}

FTLD-TDP—Abnormal accumulation of TDP-43 in neuronal and glial inclusions is the characteristic neuropathological feature in approximately 50% of FTD patients (FTLD-TDP) and the vast majority of ALS cases.^{30,34,35} Pathological modifications of TDP-43 in the disease state include a redistribution from the nucleus to the cytoplasm in cells with inclusions, hyperphosphorylation, ubiquitination and N-terminal truncation.³⁵ FTLD-TDP includes sporadic and genetic forms with mutations in *GRN*, *VCP*, *TARDBP* and the recently recognized *C9ORF72* repeat expansion (see above).^{27,28,111–114} Based on the morphology and anatomic distribution of TDP-43 pathology, four distinct FTLD-TDP subtypes are recognized.^{115–117} The relevance of this heterogeneity is supported by clinical and genetic correlations (Table 1), as well as emerging evidence for distinct biochemical properties of TDP-43 in the different subtypes.^{35,117,118}

Pathogenesis of TDP-43 proteinopathies—The neuropathological findings in FTLD-TDP implicate that both loss and gain-of-function mechanisms might be involved in TDP-43 associated cell death. Addressing these fundamental questions is the focus of numerous research activities worldwide and detailed discussions of TDP-43 pathogenesis are published elsewhere.^{119–121} Briefly, current *in vivo* models provide evidence for both scenarios by demonstrating that either reduced or increased expression levels of the physiologically tightly autoregulated TDP-43 are not well tolerated.^{119–121} However, no model has fully recapitulated the neuropathological and biochemical features of human TDP-43 related diseases. While the identification of *TARDBP* mutations is a clear indicator that dysfunction of TDP-43 is directly linked to neurodegeneration, the functional consequences of *TARDBP* mutations are still unresolved. There is no solid evidence that *TARDBP* mutations act through a toxic-gain-of function mechanism and no functional consequences of *TARDBP* mutations on processing of the few RNA targets studied to date have been reported. However, studies using crosslinking immunoprecipitation and high-

throughput sequencing have recently identified more than 6000 RNA targets of TDP-43, and a major challenge now is to dissect specific pathways regulated by TDP-43 and to identify possible disease-relevant RNA targets.^{109,110}

Another important but unresolved issue is the role of TDP-43 in the other genetic forms of FTLTDP. The fact that mutations in *GRN*, *VCP* and *C9ORF72* are all consistently characterized by TDP-43 pathology suggests that dysregulation of TDP-43 might be a crucial common downstream mechanism leading to cell death in all of them. However, the significance of TDP-43 accumulation in *C9ORF72* mutation carriers has recently been challenged by the identification of additional TDP-43 negative, ubiquitin-positive pathology that is more abundant than TDP-43 pathology in distinct brain regions (Figure 1c), raising the possibility that another unidentified protein(s) might be more important in the pathogenesis in these cases (see above).^{27,78,79,82,84,85,87,90,92–94,98,99}

FUS and other FET proteins

FUS belongs to the FET protein family that also includes Ewing's sarcoma (EWS), TATA-binding protein-associated factor 15 (TAF15) and the drosophila orthologue cabeza. They are highly conserved, ubiquitously expressed, predominantly nuclear (Figure 2a), multifunctional DNA/RNA binding proteins,¹²² that can bind to a large number of partially overlapping RNA targets.¹²³

FTLD-FUS / FTLD-FET—In early 2009, *FUS* mutations were reported to be the cause of ~3 % of familial ALS cases, in which the associated pathology is characterized by inclusions that are FUS positive but TDP-43 negative (ALS-*FUS*).^{36,37} Subsequently, FUS was found to be the most characteristic marker for the pathology in most of the remaining tau/TDP-negative FTLD cases, which include three closely related but distinct clinicopathological entities; atypical FTLD-U (aFTLD-U), neuronal intermediate filament inclusion disease (NIFID) and basophilic inclusion body disease (BIBD).^{38–40,124} The identification of FTLD-FUS as a new molecular subgroup³¹ provided further evidence that FTD and ALS are closely related conditions and emphasized the pathogenic role of RNA binding proteins. However, despite there being some overlap in the phenotype and pathological features of FTLD-FUS and ALS-*FUS*, significant differences were also observed.^{125,126} Moreover, the publication of additional cases made it evident that ALS with FUS pathology is almost always caused by a *FUS* mutation; whereas, cases of FTLD-FUS tend to be sporadic and none has yet been associated with any genetic abnormality of *FUS*.^{38–40,124} Further evidence for different pathomechanisms has been provided by a recent study that investigated the other FET protein members in a series of ALS-*FUS* and FTLD-FUS cases.⁴¹ In cases of ALS-*FUS* with a range of different mutations, there was no co-accumulation of other FET proteins into FUS-positive inclusions and cells retained the physiological nuclear staining of TAF15 and EWS (Figure 2b). In striking contrast, in all FTLD-FUS subtypes TAF15 and EWS were also found to co-accumulate in FUS-positive inclusions and inclusion-bearing cells showed a reduction in the normal nuclear staining of all three FET proteins, particularly TAF15 (Figure 2c). The addition of TAF15 and EWS to the growing list of RNA binding proteins involved in neurodegeneration is further supported by studies in which TAF15 was predicted as a potential candidate through an independent approach using a yeast functional screen aimed to identify RNA binding proteins with similar function to TDP-43 and FUS¹²⁷ and descriptions of genetic variants (of undetermined pathogenic significance) in *TAF15* and *EWSR1* in a small number of ALS cases.^{128,129} Although the respective roles of FUS, TAF15 and EWS in FTLD-FUS remains to be elucidated, the term FTLD-FET now seems more appropriate for this molecular FTLD subgroup.

Pathogenesis of FUS-proteinopathies—The above described differences in the molecular pathology of ALS-*FUS* and FTL-D-FUS imply different pathological processes underlying inclusion formation and cell death, with ALS-*FUS* being restricted to dysfunction of FUS, while FTL-D-FUS might involve dysfunction of all FET proteins (Figure 2).

In ALS-*FUS*, mutations in the C-terminus of the protein disrupt a region characterized as non-classical nuclear localization sequence. This results in an impaired transportin-mediated nuclear import with redistribution of FUS to the cytoplasm (Figure 2b).^{130,131} Importantly, no alteration of other FET proteins is seen under these conditions.⁴¹ The degree of FUS nuclear transport impairment varies between different *FUS* mutations, but correlates with the observed variability in disease course associated with different mutations and with distinct pathological patterns of ALS-*FUS* pathology,¹²⁵ thereby providing strong evidence that impaired nuclear import of FUS is a key event in disease pathogenesis of ALS-*FUS*.

In FTL-D-FUS, a more general defect of transportin-mediated nuclear import is postulated that affects the distribution of all FET proteins, with two broad scenarios plausible (Figure 2c). First, a primary defect of transportin itself, either resulting from genetic variations in *TNPO1*, posttranslational modifications, or altered expression levels of transportin, could result in reduced efficiency of nuclear import of all FET proteins. However, in this scenario one might also expect alterations in the subcellular distribution of other transportin cargos, such as hnRNPA1, which is not supported by preliminary data.⁴¹ Second, the proper nuclear import of FET proteins might be affected by abnormal posttranslational modifications of FET proteins, such as arginine methylation or phosphorylation, that have been shown to modulate nucleocytoplasmic transport, protein-protein interaction and protein stability.^{122,132–138} So far, biochemical analysis of protein extracted from FTL-D-FUS brains has revealed only increased insolubility of all FET proteins, without other obvious disease-associated changes, such as truncation or abnormal phosphorylation;^{39,41,139} however, more detailed analysis is required.

The downstream effects of redistributed FUS or all FET proteins in the pathogenesis of ALS-*FUS* and FTL-D-FUS, respectively, have not yet been determined. Similar to TDP-43, both a gain of toxic properties and a loss of functions via their sequestration in aggregates are plausible. Results from initial *in vivo* models of ALS-*FUS* have been inconsistent and the mechanisms remain unresolved.^{121,140}

Molecular correlates of FTD phenotypes

Table 1 lists the molecular subtypes of FTL-D pathology with the associated genetic defects and common clinical features. Each genetic cause is associated with a specific neuropathology. However, predicting the underlying molecular pathology or genetics, based on the pattern of inheritance and clinical features, is often imprecise.^{141,142} SD is usually sporadic and associated with FTL-D-TDP type C with fewer cases having the pathology of classical PiD. Cases of sporadic PNFA are somewhat more likely to have FTL-D-tau than FTL-D-TDP, but bvFTD may be associated with any of the major pathologies. Early-onset bvFTD with severe psychobehavioral abnormality but minimal motor features or aphasia is characteristic of the aFTL-D-U subtype of FTL-D-FUS. When FTD is combined with ALS, the pathology is usually FTL-D-TDP; whereas, FTD with prominent parkinsonism is more often FTL-D-tau (PSP or CBD). In families with autosomal dominant inheritance of bvFTD or PNFA without significant motor dysfunction, the underlying gene defect may be a mutation in *C9ORF72*, *GRN* or *MAPT*. When parkinsonism or primary lateral sclerosis (PLS) are also prominent features, a *MAPT* mutation is more likely; whereas, coexistence of classical ALS in a family strongly suggests a *C9ORF72* mutation.

Conclusions and future directions

The past six years have seen remarkable progress in our understanding of the molecular basis of FTD. It appears that all the common FTD-causing genes have now been discovered and the major pathological proteins identified. Although many aspects of the specific pathogenic mechanisms still need to be resolved, we are already in position to begin translating this newly acquired knowledge into improved FTD patient care. The recent discoveries of *GRN* and *C9ORF72* mutations allow for more informed genetic counseling. Knowledge of the signature pathological proteins is prompting attempts to develop more disease-specific, molecular-based diagnostic tests, such as the quantification of total or pathological protein species in biofluids.^{143,144} Recognition of GRN insufficiency as an important mechanism in familial and some sporadic forms of FTD, combined with improved understanding of GRN regulation and cell biology, has already led to initial plans for GRN-based clinical trials (<http://www.alzforum.org/new/pdf/FTLDSeries.pdf>). The identification of TDP-43, FET proteins and *C9ORF72* has opened up new avenues of research related to RNA regulation. Finally, a greater appreciation of the overlap between FTD and ALS is now bringing these two areas of research and patient care closer together. Hopefully, patients with FTD will soon experience real benefits from these and future advances.

Box 1

Important events in the molecular pathogenesis of FTD

- 1892: Arnold Pick describes lobar atrophy in a patient with presenile dementia and aphasia.¹⁴⁵
- 1911: Alois Alzheimer characterizes Pick bodies using silver stains.¹⁴⁶
- 1960's: descriptions of PSP and CBD clinicopathological syndromes.^{147,148}
- 1974: different pathological subtypes of PiD disease described.¹⁴⁹
- mid 1980's - early 1990's: identification of tau as major component of pathological lesions in AD, PiD, PSP and CBD (reviewed in Lee *et al.*).¹⁵⁰
- 1990: description of FTD cases without specific histopathology (DLDH).¹⁵¹
- mid 1990's: identification of subset of FTD with FTLN-U pathology.¹⁵²
- 1998: *MAPT* mutations identified in some families with FTD and parkinsonism genetically linked to chromosome 17.¹⁰⁻¹²
- 2004-06: recognition that most cases of DLDH are really FTLN-U and that FTLN-U is the most common FTD-associated pathology.³³
- 2006: description of different patterns of FTLN-U that correlate with clinical phenotypes, genetic abnormalities and biochemical properties of inclusions.^{115,117}
- 2006: discovery that *GRN* mutations cause autosomal dominant FTD and explain all remaining chromosome 17 linked families.^{14,15}
- 2006: TDP-43 identified as pathological protein in most cases of FTLN-U and ALS.^{34,35}
- 2008: identification of a subset of FTLN-U cases that lack TDP-43-immunoreactive pathology (aFTLN-U).^{153,154}
- 2009: discovery that most cases of tau/TDP-43-negative FTLN have FUS-immunoreactive pathology (FTLN-FUS).³⁸⁻⁴⁰

- 2011: discovery that FTL-D-FUS shows accumulation of other FET protein members TAF15 and EWS.⁴¹
- 2011: FTD/ALS associated gene defect on chromosome 9p identified as repeat expansion in *C9ORF72*.^{27,28}

Abbreviations: AD, Alzheimer's disease; aFTLD-U, atypical FTL-D-U; C9ORF72, chromosome 9 open reading frame 72; CBD, corticobasal degeneration; DLDH, dementia lacking distinctive histopathology; EWS, Ewing's sarcoma; FTD, frontotemporal dementia; FTL-D, frontotemporal lobar degeneration; FTL-D-U, FTL-D with ubiquitin immunoreactive inclusions; FUS, fused in sarcoma protein; PSP, progressive supranuclear palsy; PiD, Pick's disease; TAF15, TATA-binding protein-associated factor 15; TDP-43, transactive response DNA binding protein with molecular weight 43 kD.

Box 2

History of the chromosome 9p FTD-ALS locus

Since 2006, at least 10 autosomal dominant families in which patients were affected with FTD, ALS, or both were published with conclusive or suggestive linkage to chromosome 9p.^{18–26} The minimal candidate region shared by all families was a 3.7Mb region containing only 10 known or predicted genes. In 2010, three genome-wide association studies (GWAS) in sporadic ALS populations identified a novel susceptibility locus on chromosome 9p which completely overlapped with the candidate region for familial FTD-ALS.^{155–157} Strongest association was identified in a ~80kb haplotype block containing only three genes; *MOBK2B*, *IFNK* and *C9ORF72*. An independent GWAS study in patients with pathologically confirmed FTL-D-TDP nominated the same chromosomal region, implicating the chromosome 9p gene defect in sporadic forms of both FTD and ALS.⁵⁴ However, despite concentrated efforts by the FTD and ALS research communities, in-depth candidate-gene sequencing and targeted next-generation sequencing of the minimal candidate region failed to identify the causative mutation, suggesting that a complex mutational mechanism may be involved. In 2011, an expanded hexanucleotide repeat in the non-coding region of *C9ORF72* was found to be the long sought-after cause of FTD and ALS on chromosome 9p.^{27,28}

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Key points

- All common FTD-causing genes and signature proteins have now been discovered
- Regulation of GRN is one potential therapeutic strategy for FTD
- Expansion of a GGGGCC hexanucleotide repeat in a non-coding region of *C9ORF72* is the most common genetic cause of FTD and ALS
- The pathomechanism of *C9ORF72* mutation may include haploinsufficiency and/or toxic RNA foci
- Most cases of tau/TDP-negative FTLD are characterized by inclusions that are immunoreactive for FUS (FTLD-FUS) and the other FET proteins (EWS and TAF15)
- Differential involvement of the FET proteins implies different pathomechanisms in ALS with *FUS* mutations versus FTLD-FUS

Figure 1.

Expanded GGGGCC hexanucleotide repeat in non-coding region of *C9ORF72* causes FTD and ALS linked to chromosome 9p. **a** Overview of the genomic structure of *C9ORF72*. Numbered boxes represent coding (white) and non-coding (gray) exons and the position of the start codon (ATG) and stop codon (TAA) are indicated. The position of the (GGGGCC)_n repeat in the intronic region between exons 1a and 1b is indicated with a red star. **b** PCR products of repeat-primed PCR reactions separated on an ABI3730 DNA Analyzer and visualized by GENEMAPPER software. Electropherograms are zoomed to 2,000 relative fluorescence units to show stutter amplification. One FTD patient with a pathogenic expanded *C9ORF72* repeat (top) and one FTD patient with a *C9ORF72* normal repeat length (bottom) are shown. **c** In addition to FTLD-TDP and ALS pathology, all patients with the *C9ORF72* mutation show a unique pattern of ubiquitin-positive (brown), TDP-43-negative neuronal inclusions in the cerebellar granule layer and other specific neuroanatomical regions. This disease-specific finding implies the mis-metabolism and accumulation of some yet unidentified protein(s). **d** RNA foci, visualized using a Cy3-labeled (GGCCCC)₄ oligonucleotide probe (red), in the nuclei of two lower motor neurons from an FTD-ALS patient carrying the expanded GGGGCC repeat in *C9ORF72*.

Figure 2.

Distinct pathomechanisms of ALS-*FUS* and FTLD-FUS. **a** The FET protein members, FUS, EWS and TAF15 contain a proline-tyrosine nuclear localization signal (PY-NLS, triangle) which is bound by the receptor protein Transportin (Trp). This mediates the transport of these proteins across the nuclear pore complex into the nucleus, resulting in a predominant nuclear localization of all three proteins under physiological conditions. **b** In ALS with *FUS* mutations, the PY-NLS of FUS is disrupted due to mutations (rectangle) leading to an impaired interaction with Trp and nuclear import of FUS, while TAF15 and EWS are normally transported to the nucleus. This results in a selective accumulation of FUS into cytoplasmic inclusion in ALS-*FUS* patients, with retained nuclear localization of TAF15 and EWS. **c** In contrast, FTLD-FUS patients show co-accumulation of all FET proteins into cytoplasmic inclusions accompanied with their nuclear depletion. This complex dysregulation of all FET proteins in FTLD-FUS might be explained by either of two broad scenarios: **c-1** alterations of Trp itself, e. g. by genetic variations, reduced expression levels or posttranslational modifications; or **c-2** posttranslational modifications of FET proteins, which interfere with proper Trp binding. Each photomicrograph shows a single neuron with

a cytoplasmic inclusion (arrow) and the nucleus indicated by the asterisk (*), immunostained for the FET protein indicated (brown stain).

Table 1

Molecular classification of FTL D with genetic and clinical correlations

major molecular class	pathological subtype*	associated genes†	associated clinical phenotypes				
			bvFTD	PNEA	SD	park	MND
FTLD-tau	• PiD	• MAPT	+	(+)	(+)	+	ALS, PLS
	• CBD		+	+	(+)	+	PLS
	• PSP		+	+		+	PLS
	• AGD		+				
	• NFT-dementia		+				
	• MSTD		+			+	PLS
FTLD-TDP	• WMT-GGI		+			+	PLS
		• (TARDBP)	(+)			+	ALS
	• type A	• GRN	+	+		+	
	• type B	• C9ORF72	+	+	(+)	+	ALS
	• type C		+		+		
	• type D	• VCP	+			(+)	ALS
FTLD-FUS		• (FUS)	(+)				ALS
	• aFTLD-U		+				
	• NIFID		+			+	PLS
	• BIBD		+			+	ALS

major molecular class	pathological subtype*	associated genes†	associated clinical phenotypes				
			bvFTD	PNFA	SD	park	MND
FTLD-UPS	• FTD-3	• CHMP2B	+				(ALS)
FTLD-ni						(+)	

aFTLD-U, atypical frontotemporal lobar degeneration with ubiquitinated inclusions; AGD, argyrophilic grain disease; ALS, amyotrophic lateral sclerosis; BIBD, basophilic inclusion body disease; bvFTD, behavioral variant FTD; *C9ORF72*, chromosome 9 open reading frame 72 gene; CBD, corticobasal degeneration; *CHMP2B*, charged multivesicular body protein 2B gene; FTD, frontotemporal dementia; FTD-3, FTD linked to chromosome 3; FTLD, frontotemporal lobar degeneration; FUS, fused in sarcoma; *GRN*, granulin gene; *MAPT*, microtubule associated protein tau gene; MND, motor neuron disease; MSTD, multiple system tauopathy with dementia; NFT-dementia, neurofibrillary tangle predominant dementia; ni, no inclusions; NIFID, neuronal intermediate filament inclusion disease; park, parkinsonism; PiD, Pick's disease; PLS, primary lateral sclerosis; PNFA, progressive non-fluent aphasia; PSP, progressive supranuclear palsy; SD, semantic dementia; *TARDBP*, transactive response DNA binding protein gene; TDP, TDP-43; UPS, ubiquitin proteasome system; *VCP*, valosin containing protein gene; WMT-GGI, white matter tauopathy with globular glial inclusions.

* indicates the characteristic pattern of pathology, not the clinical syndrome.

† genes in which variation may cause or increase the risk of FTD with the corresponding FTLD pathological subtype.

(+) rare cause or unusual phenotype.

Table 2

Frequency of the *C9ORF72* repeat expansion in FTD and ALS patient populations

Study region ^a	Ref.	Familial FTD		Sporadic FTD		Familial ALS		Sporadic ALS		Cases excluded ^h
		N	<i>C9ORF72</i> mutation	N	<i>C9ORF72</i> mutation	N	<i>C9ORF72</i> mutation	N	<i>C9ORF72</i> mutation	
Europe										
Finland	28,88	27	13 (48.1%)	48	9 (18.8%)	112	52 (46.4%)	289	61 (21.1%)	Yes
Ireland	80	-	-	-	-	47	18 (38.3%)	386	19 (4.9%)	NS
UK ^b	82	-	-	-	-	63	27 (42.9%)	500	35 (7.0%)	No
UK ^b	87	93	12 (12.9%)	163	6 (3.7%)	-	-	-	-	No
UK ^b	93	161	20 (12.4%)	209	16 (7.7%)	-	-	-	-	No
Netherlands	88,92	129	37 (28.7%)	224	5 (2.2%)	-	-	-	-	Yes
Belgium ^c	84	75	12 (16.0%)	230	9 (3.9%)	15	7 (46.7%)	122	6 (4.9%)	Yes
France	88	50	22 (44.0%)	150	14 (9.3%)	-	-	-	-	-
Germany	28,81,88	29	4 (13.8%)	-	-	69	15 (21.7%)	421	22 (5.2%)	Yes
Italy (mainland)	28,81,88,91	-	-	-	-	120	45 (37.5%)	1523	55 (3.6%)	Yes
Italy (Sardinia)	81,88,91	-	-	-	-	21	12 (57.1%)	133	9 (6.8%)	Yes
Italy (Sicily)	91	-	-	-	-	-	-	101	5 (4.9%)	Yes
Greece	89	-	-	-	-	10	5 (50.0%)	136	11 (8.1%)	NS
North America										
US	27,78	171	20 (11.7%)	203	6 (3.0%)	34	8 (23.5%)	195	8 (4.1%)	No
US ^d	28,88	-	-	-	-	163	59 (36.2%)	1014	56 (5.5%)	NS
Canada	94	-	-	-	-	62	17 (27.4%)	169	6 (3.6%)	No
Canada ^e	27,85	26	16 (61.5%)	3	0 (0.0%)	-	-	-	-	No
US ^e	27	40	9 (22.5%)	53 ^f	8 (15.1%)	-	-	-	-	No
US ^e	79	18	6 (33.3%)	6	0 (0.0%)	14	6 (42.9%)	43 ^f	5 (11.6%)	NS
Other regions										
Israel	88	-	-	-	-	14	3 (21.4%)	-	-	NS
India	88	-	-	31	0 (0.0%)	-	-	31	0 (0.0%)	NS

Study region ^a	Ref.	Familial FTD		Sporadic FTD		Familial ALS		Sporadic ALS		Cases excluded ^h
		N	C9ORF72 mutation	N	C9ORF72 mutation	N	C9ORF72 mutation	N	C9ORF72 mutation	
Asia ^g	88	3	2 (66.7%)	10	0 (0.0%)	20	1 (5.0%)	238	0 (0.0%)	NS
Guam	88	-	-	-	-	-	-	90	0 (0.0%)	NS
Australia	88	-	-	-	-	-	-	263	14 (5.3%)	NS

ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; C9ORF72, chromosome 9 open reading frame 72; UK, United Kingdom; US, United States.

^a Only geographical regions with at least 10 FTD or ALS patients are listed.

^b Cohorts are part of a larger series of UK patients which are grouped in Majounie et al. with highly comparable mutation frequencies.⁵⁶

^c Numbers do not include 23 patients with both FTD and ALS of which 85.7% of familial and 6.3% of sporadic patients were C9ORF72 mutation carriers.

^d In the sporadic ALS cohort, 5.4% (48 of 890) of white and 4.1% (2 of 49) of African American patients carried a C9ORF72 repeat expansion.

^e Only included patients with a pathological diagnosis of FTLD-TDP.

^f Includes individuals for which no information on family history was available.

^g The geographical origin of the Asian patients was not reported in detail; however, the familial ALS patient carrying the C9ORF72 repeat expansion was Japanese.

^h In studies where cases known to carry mutations in other genes were excluded, the frequency of C9ORF72 repeat expansions are overestimated (NS, not stated).