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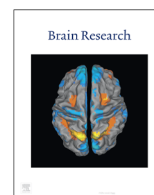

# Mechanisms of FUS mutations in familial amyotrophic lateral sclerosis

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## ABSTRACT

Recent advances in the genetics of amyotrophic lateral sclerosis (ALS) have provided key mechanistic insights to the pathogenesis of this devastating neurodegenerative disease. Among many etiologies for ALS, the identification of mutations and proteinopathies in two RNA binding proteins, TDP-43 (TARDBP or TAR DNA binding protein 43) and its closely related RNA/DNA binding protein FUS (fused in sarcoma), raises the intriguing possibility that perturbations to the RNA homeostasis and metabolism in neurons may contribute to the pathogenesis of these diseases. Although the similarities between TDP-43 and FUS suggest that mutations and proteinopathy involving these two proteins may converge on the same mechanisms leading to neurodegeneration, there is increasing evidence that FUS mutations target distinct mechanisms to cause early disease onset and aggressive progression of disease. This review focuses on the recent advances on the molecular, cellular and genetic approaches to uncover the mechanisms of wild type and mutant FUS proteins during development and in neurodegeneration. These findings provide important insights to understand how FUS mutations may perturb the maintenance of dendrites through fundamental processes in RNA splicing, RNA transport and DNA damage response/repair. These results contribute to the understanding of phenotypic manifestations in neurodegeneration related to FUS mutations, and to identify important directions for future investigations.

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## 1. Introduction

### 1.1. *The expanding genetic landscape of amyotrophic lateral sclerosis*

Amyotrophic lateral sclerosis (ALS) is an adult-onset neurodegenerative disease that affects upper and lower motor neurons. As initially described by Jean-Martin Charcot more than 140 years ago, the key clinical features in ALS patients include muscle wasting, and progressive loss of spinal motor neurons and upper motor neurons and their axons in the lateral columns of the spinal cord. Recent advances in human genetics have identified many genetic loci that are mutated in patients with familial ALS (FALS). Among a growing number of genes involved in FALS, mutations in four genes account for the majority of cases. These mutations include missense mutations in superoxide dismutase 1 (*SOD1*), two genes encoding RNA/DNA binding proteins, *TDP-43* (*TARDBP* or TAR-DNA-binding protein-43) and *FUS/TLS* (*fused in sarcoma/translocation in liposarcoma* or *FUS*), and the GGGGCC hexanucleotide expansions in *C9ORF72* gene (Cirulli et al., 2015; Lee et al., 2012; Ling et al., 2013). The discovery of TDP-43 as a major component in the ubiquitin-positive, tau-negative insoluble protein aggregates in neurons and glia represents a major breakthrough in FTD (frontotemporal dementia) and ALS research (Arai et al., 2006; Neumann et al., 2006). Moreover, the impact of this discovery goes beyond the identification of a single disease gene and essentially ushers in a new era of research that focuses on the potential contributions of transcription, RNA splicing and RNA metabolism on neurodegenerative diseases.

TDP-43 is originally identified to bind to the TAR DNA sequence in HIV-1 genome to regulate viral gene expression (Ou et al., 1995). Under physiological conditions, TDP-43 is a ubiquitous nuclear protein, however, in FTD patients, TDP-43 aggregates are present predominantly in neuronal cytoplasm and dystrophic neuronal processes (Arai et al., 2006; Neumann et al., 2006). This distinct feature, defined as TDP-43 proteinopathy, constitutes a major neuropathological diagnosis entity in sporadic ALS (ALS-TDP). Several subsequent studies show that dominant mutations in the *TARDBP* gene can also be identified in FALS patients (Lattante et al., 2013). The identification of autosomal dominant mutations in the *FUS* gene in a large kindred of familial ALS (FALS) further expanded the genetic and neuropathological landscape of ALS (Kwiatkowski et al., 2009; Vance et al., 2009). Similar to TDP-43, FUS proteins reside primarily in the neuronal nuclei, but in ALS-FUS patients FUS proteins form large aggregates in the cytoplasm. The morphology of FUS proteinopathy in FALS ranges from diffuse and dense cytoplasmic aggregate present in late onset cases, to basophilic inclusions commonly found in juvenile FALS with FUS-P525L mutation. Finally, in 2011 two groups independently reported the GGGGCC hexanucleotide repeat expansions in the noncoding region of the *C9ORF72* gene as causal links to ALS and FTD (DeJesus-Hernandez et al., 2011; Renton et al., 2011). Although TDP-43 proteinopathy can be detected in FTD and ALS patients with *C9ORF72* mutations, the neuropathological features in these cases are quite heterogeneous and also include prominent ubiquitin and p62 positive, but TDP-43 negative intracytoplasmic and intranuclear inclusions (Bigio, 2012; Mackenzie et al., 2014).

### 1.2. *Early disease onset in FALS caused by FUS mutations*

It is estimated that mutations in *TARDBP* and *FUS* each account for ~5% of FALS, whereas the GGGGCC expansion mutations in *C9ORF72* account for 20–40% of ALS and FTD-ALS cases, depending on the population studied (Cirulli et al., 2015). One important feature noted in a recent study indicates that the age of disease onset for FALS caused by *FUS*, *TARDBP* and *C9ORF72* mutations differ quite drastically. Mutations in *FUS* account for ~35% of FALS in patients younger than 40 years old, whereas mutations in *C9ORF72* are much more common in patients older than 50 years of age (Millecamps et al., 2012). Indeed, meta-analyses of 154 ALS cases with *FUS* mutations (including FALS and SALS with *de novo FUS* mutations) show an average disease onset of $43.8 \pm 17.4$ years (Fig. 1) (Deng et al., 2014a; Lattante et al., 2013). More than 60% of cases with *FUS* mutations show disease onset before 45 years of age, with many juvenile ALS cases presenting with disease onset in late teens and early 20's (Fig. 1) (Baumer et al., 2010; Huang et al., 2010). These findings are similar to those from another study using smaller sample size, and show that the average disease onset for *FUS*, *SOD1* or *TARDBP* mutations is $43.6 \pm 15.8$, $47.7 \pm 13.0$ and $54.7 \pm 15.3$, respectively (Yan et al., 2010). Kaplan–Meier survival analysis shows statistically significant differences in the age of onset among these three mutations. This distinctive feature of *FUS* mutations raises the intriguing hypothesis that mutations in FUS may target divergent mechanisms that perturb the development, maintenance and homeostasis of the nervous system in early postnatal life and in the aging process.

This review focuses on the recent progress on the molecular, cellular and genetic approaches to uncover the mechanisms of wild type and mutant FUS proteins. These findings provide important insights to understand how FUS mutations may perturb the fundamental processes in DNA damage response/repair, RNA splicing, and RNA transport, to interpret the phenotypic manifestations in neurodegeneration related to FUS mutations, and to identify important directions for future investigations.

## 2. Physical properties of FUS and their implications in RNA metabolism

### 2.1. *RNA binding properties of FUS*

FUS is identified as an oncogene that undergoes chromosomal translocation in myxoid liposarcoma, in which the N-terminal transcriptional activation domain of FUS is fused to CHOP (CAAT enhancer-binding homologous protein), a growth arrest and DNA-damage inducible member of the C/EBP family of transcription factors (Crozat et al., 1993; Rabbitts et al., 1993). Subsequent studies further reveal that chromosomal translocations involving FUS can be identified in several other human cancers, including acute myeloid leukemia, where the N-terminus of *FUS* gene is translocated to the *ERG* gene, a member of the ETS transcription factor family (Ichikawa et al., 1994; Prasad et al., 1994). Structurally, FUS belongs to a family of FET RNA binding proteins, including FUS, Ewing's sarcoma RNA binding protein 1 (EWSR1) and Tata-binding protein-associated factor 2N (TAF-15), that are known to interact with the C-terminal domain of RNA polymerase II (RNAP II) and

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