# Frameshift and novel mutations in *FUS* in familial amyotrophic lateral sclerosis and ALS/dementia

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## ABSTRACT

**Objective:** Amyotrophic lateral sclerosis (ALS) is a progressive paralytic disorder caused by degeneration of motor neurons. Mutations in the *FUS* gene were identified in patients with familial ALS (FALS) and patients with sporadic ALS (SALS) from a variety of genetic backgrounds. This work further explores the spectrum of *FUS* mutations in patients with FALS and patients with FALS with features of frontotemporal dementia (FALS/FTD) or parkinsonism and dementia (FALS/PD/DE).

**Methods:** All exons of the *FUS* gene were sequenced in 476 FALS index cases negative for mutations in *SOD1* and *TARDBP*. A total of 561–726 controls were analyzed for genetic variants observed. Clinical data from patients with *FUS* mutations were compared to those of patients with known *SOD1* and *TARDBP* mutations.

**Results:** We identified 17 *FUS* mutations in 22 FALS families, 2 FALS/FTD families, and 1 FALS/PD/DE family from diverse genetic backgrounds; 11 mutations were novel. There were 4 frameshift, 1 nonsense, and 1 possible alternate splicing mutation. Patients with *FUS* mutations appeared to have earlier symptom onset, a higher rate of bulbar onset, and shorter duration of symptoms than those with *SOD1* mutations.

**Conclusions:** *FUS* gene mutations are not an uncommon cause in patients with FALS from diverse genetic backgrounds, and have a prevalence of 5.6% in non-*SOD1* and non-*TARDBP* FALS, and ~4.79% in all FALS. The pathogenicity of some of these novel mutations awaits further studies. Patients with *FUS* mutations manifest earlier symptom onset, a higher rate of bulbar onset, and shorter duration of symptoms. ***Neurology*® 2010;75:807–814**

## GLOSSARY

**ALS** = amyotrophic lateral sclerosis; **FALS** = familial amyotrophic lateral sclerosis; **FALS/FTD** = familial amyotrophic lateral sclerosis with features of frontotemporal dementia; **FALS/PD/DE** = familial amyotrophic lateral sclerosis with features of parkinsonism and dementia; **SALS** = sporadic amyotrophic lateral sclerosis.

Amyotrophic lateral sclerosis (ALS) is a degenerative disease of motor neurons.[1,2] Its etiologies are partially unknown. The most frequent known cause is mutations in the *SOD1* gene, which are responsible for ~20% of familial ALS (FALS) cases.[3] To date, 21 mutations in the *TARDBP* genes have been reported in 643 FALS cases with varied frequencies.[4-14] Mutations in *ALS2, SET, VAPB, DCTN1,* and *ANG* are very rare causes of ALS or ALS-like motor neuron diseases.[2,15-17]

Recently, *FUS* gene mutations were identified in a subset of patients with FALS and patients with sporadic ALS (SALS).[18-22] The largest FALS sample set studied was 293 cases; however, 209 of them were only screened for exon 15.[21] Most of the reported FALS cases with *FUS* mutations had no cognitive change.

ALS can overlap with frontotemporal dementia (FALS/FTD) or parkinsonism and dementia (FALS/PD/DE). FALS/FTD has been linked to chromosome 9q21-q22[23] and 9p21.2-

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9p13.3,[24-27] but no causative gene has been found. To further explore the spectrum of *FUS* mutations, we sequenced the *FUS* gene in a cohort of 476 FALS index cases and 41 SALS cases. Some of the FALS cases also had additional features like FTD or parkinsonism/dementia. We found 11 novel mutations including 4 frameshift, 1 nonsense, and 1 possible splicing site mutation in patients with FALS, FALS/FTD, and FALS/PD/DE from different ethnic backgrounds.

## METHODS

**Standard protocol approvals, registration, and patient consents.** Protocols were approved by the ethics committee on human experimentation of Northwestern University Feinberg School of Medicine. Blood samples were collected after patients gave written consent.

**Participants.** ALS was diagnosed according to the El Escorial criteria.[28] Some ALS cases had additional features of dementia and parkinsonism. The diagnosis of FTD was based on the revised criteria by Neary et al.[29] Pedigrees and clinical data were collected through specialists in neuromuscular diseases and were verified by medical records to establish diagnosis. A total of 476 FALS index cases without *SOD1* and *TARDBP* gene mutations and 41 SALS cases were sequenced for the *FUS* gene. Of the 476 FALS cases, 393 cases had only ALS, 76 cases had FALS/FTD, and 7 cases had FALS/PD/DE. Self-reporting ethnicity showed that 93.9% of the cases were white (European American), 2.5% were Asian, 1.9% were African American, and 1.3% were Latino. The ethnicity of 2 cases was unknown. Control DNA samples were primarily collected by our laboratory. A majority of the controls were white (97.6%), 0.56% were African American, 0.98% were Latino, and 0.84% were Asian. Less than 1% of the patients with FALS were on respiratory support. SPSS software (release 16.0.0) was used for statistical analysis. Differences in age at symptom onset were obtained with Kaplan-Meier analyses; percentage of site of symptom onset was analyzed with Pearson $\chi^2$ test. Mean duration of symptoms was obtained by the $t$ test.

**Sequencing analysis of the *FUS* gene.** Genomic DNA was extracted from transformed lymphoblastoid cell lines, whole blood, or brain tissues by standard methods (Qiagen, Valencia, CA). Intronic primers for PCR and sequencing covered the coding sequence as reported.[21] Genomic DNA was amplified with high-fidelity TaKaRa LA Taq™ polymerase (Takara, Japan). Unconsumed dNTPs and primers were digested with exonuclease I and shrimp alkaline phosphatase (ExoSAP-IT, USB, Cleveland, OH). Fluorescent dye–labeled single-strand DNA was amplified using Beckman Coulter sequencing reagents (GenomeLab DTCS Quick Start Kit) followed by bidirectional sequencing with a CEQ™ 8000 Genetic Analysis System (Beckman Coulter, CA). When a variant was identified, a large number of control DNA samples (561–726) were analyzed to exclude the possibility of a rare polymorphism. Splicing site changes were predicted with SpliceView (http://bioinfo.itb.cnr.it/oriel/splice-view.html).

## RESULTS

We sequenced the *FUS* gene for all 15 exons in a cohort of 476 non-*SOD1* and non-*TARDBP* FALS index cases and 41 SALS cases; cosegregation analysis was performed if DNA samples were available from additional family members. We found no *FUS* mutations in SALS cases, but 17 heterozygous nucleotide mutations were found in 25 index cases; 11 are novel mutations (table 1).

One nonsense and 4 frameshift mutations were found, all in exon 14 (table 1). One patient with G497AfsX527 mutation in F8726 developed left leg weakness at 12.5 years of age, and died in 18 months. Seven patients with nonsense and frameshift mutations also showed short duration of symptoms (table 2). Patients with *FUS* mutations showed remarkable variation at symptom onset. Obligate carriers in F1186 and F476 were symptom-free even after their offspring became affected (figure 1, table 2).

*FUS* mutations were also found in patients with ALS with parkinsonism or FTD. F8828 had the most frequent R521C mutation. The proband developed ALS with gait and speech difficulty at age 85. The proband's brother was diagnosed with Parkinson features and dementia, and her mother and sister had dementia. F7543 carried G206S, a novel mutation in exon 6. The index patient developed ALS at age 54; his 2 brothers had behavior problems in their 40s consistent with the diagnosis of FTD. The proband of F7390 was diagnosed with schizophrenia, and then developed ALS. No detailed medical records were available for the patient's diagnosis of schizophrenia, so the possibility of dementia could not be excluded. His sister had FTD with behavioral changes. The family had p.G174-G175del in exon 5 (table 1).

Unusual clinical features were also noted in patients with ALS with *FUS* mutations. A patient from F7432 with R524S developed right arm weakness at age 48, and MRI showed significant cortical and cerebellar atrophy (table 2). The R524S mutation due to c.1572G>C change has been previously reported, but R524S due to c.1572G>T in F7432 was novel. The proband of F9895 with S96del mutation in exon 4 had mental retardation (table 2). Individual IV-3 of F476 with R521L mutation had leukemia. II-2 also had leukemia, but his genotype was not known (figure 1). This is interesting as *FUS* was first identified as part of a fusion gene with DNA-damage-inducible transcript 3 (*CHOP)* from tissues of liposarcoma[30,31] and the transcription factor ERG-1 in human myeloid leukemias.[32]

Eight nucleotide mutations were located in exon 15 in 14 families. Four mutations involved residue R521 and were seen in 10 out of 25 FALS families. The R521C mutation was identified in 6 families of diverse ethnic background, including European American, Chinese, and African American. An A>T

**Table 1** *FUS* mutations in a cohort of 461 patients with FALS[a]

| Mutation type | Amino acid | Base pair | Exon | Families, n | Phenotype | Ethnicity | Pedigree | Controls |
|---|---|---|---|---|---|---|---|---|
| Deletion | p.S96del[b] | c.287291delCCTACinsAT | 4 | 1 | FALS | Caucasian | F9895 | 574 |
| Deletion | p.G174-G175del | delGAGGTG523 | 5 | 3 | FALS (2), ALS/FTD (1) | Caucasian (2), African American (1) | F7390, F9363, F9273 | 726 |
| Missense | p.G206S[b] | c.616G>A | 6 | 1 | ALS/FTD | South Korean | F7543 | 700 |
| Deletion | p.G223-G226del[b,c] | c.667-678delGGCGGCGGCGGC | 6 | 1 | FALS | Caucasian | F1090 | 700 |
| Deletion/frameshift | p.Y485AfsX514[b] | c.1449-1488delCTACCGGGGCCGCGGCGGGG ACCGTGGAGGCTTCCGAGGG | 14 | 1 | FALS | ? | F9455 | 622 |
| Nonsense | R495X[b,c] | c.1483C>T | 14 | 1 | FALS | Caucasian | F1186 | 622 |
| Deletion/frameshift | R495EfsX527[b] | c.1483delC | 14 | 1 | FALS | Caucasian | F7083 | 622 |
| Deletion/frameshift | p.G497AfsX527[b] | c.1485delA | 14 | 1 | FALS | Caucasian | F8726 | 622 |
| Insertion/frameshift | p.K510WfsX517[b] | c.1527insTGGC | 14 | 1 | FALS | Caucasian | F8957 | 622 |
| Missense | R521C | c.1561C>T | 15 | 6 | FALS (5), FALS/PD/DE (1) | Caucasian (4), African American (1), Chinese (1) | F8523, F8828, F9497, F9067, F6506, F7278 | 561 |
| Missense | R521G | c.1561C>G | 15 | 1 | FALS | Caucasian | F9656 | 561 |
| Missense | R521H | c.1562G>A | 15 | 2 | FALS (2) | Caucasian, Cambodian | F643,F7994 | 561 |
| Missense | R521L[b,c] | c.1562G>T | 15 | 1 | FALS | Caucasian | F476 | 561 |
| Missense | R524S | c.1572G>T[b]/C | 15 | 2 | FALS (2) | Caucasian, Hispanic | F7432,F9088 | 561 |
| Missense | P525L | c. 1574C>T | 15 | 1 | FALS | Caucasian | F7021 | 561 |
| Splicing | r.spl? | 5′-2A>T[b] | 15 | 1 | FALS | Caucasian | F9565 | 561 |
| Total | 16 | 17 | | 25 | | | | |

Abbreviations: ALS = amyotrophic lateral sclerosis; FALS = familial amyotrophic lateral sclerosis; FALS/PD/DE = familial amyotrophic lateral sclerosis with features of parkinsonism and dementia; FTD = frontotemporal dementia.

[a] Numbers of controls successfully sequenced for the specific mutation.

[b] Novel mutations.

[c] Segregation analysis was performed.

**Table 2** Phenotype of selected ALS families with additional features

| Pedigree | Mutation | ID | Sex | Age at onset | Site onset | Symptom duration, mo | Notes |
|---|---|---|---|---|---|---|---|
| **F8726** | p.G497AfsX527 | 1 | M | 29 | Left arm | 12 | "Drug baby," undersized, slow in school |
| | | 104 | M | 13 | Left leg | 18 | Pyloric stenosis, hyperactive, learning disabilities |
| | | 1001 | F | 29 | Left arm | 13 | Drug use, pyloric stenosis, hyperactivity, dyslexia, learning difficulties |
| **F8957** | K510WfsX517 | 1 | F | 23 | Bulbar | 13 | |
| | | 1001 | F | 46 | Bulbar | 12 | |
| **F7083** | R495EfsX527 | 1 | M | 23 | Bulbar | 48 | |
| | | 2002 | M | 72 | | 12 | |
| **F1186** | R495X | I-2 | F | 24 | | 12 | |
| | | II-1 | F | 44 | Bulbar | 20 | |
| | | II-3 | F | 39 | Left leg | 9 | |
| | | II-2 | F | | | | Unaffected at 61 years old |
| | | II-5 | F | | | | Unaffected at 57 years old |
| | | III-2 | M | 14 | | 98 | Autopsy consistent with Fazio Londe syndrome |
| | | III-1 | M | 27 | | 14 | |
| **F476** | R521L | I-1 | F | 71 | Legs | 12 | |
| | | I-3 | F | 40 | | | |
| | | II-1 | F | | | | Unaffected at 76 years old |
| | | II-2 | M | | | | Leukemia, genotype unknown |
| | | II-3 | M | | | | Unaffected at 76 years old |
| | | II-4 | F | 36 | Right arm | 30 | |
| | | IV-3 | M | | | | Leukemia |
| **F7432** | R524S | 1 | F | 48 | Right arm | 10 | MRI: Cortical and cerebellar atrophy |
| | | 1000 | M | 39 | | 11 | |
| **F9895** | S96del | 1 | M | Early 20s | | 216 | Mental retardation |
| **F7390** | p.G174-G175del | 1 | F | | | | Schizophrenia |
| | | 105 | F | | | | FTD |

Abbreviation: ALS = amyotrophic lateral sclerosis.

change in intron 14, 2 base pairs away from the acceptor site, was found in F9565 of Italian origin. This changes the typical acceptor site sequence from AG to TG, which was expected to eliminate the splicing site between intron 14 and exon 15. This possibility was also supported by an analysis in silico with SpliceView.

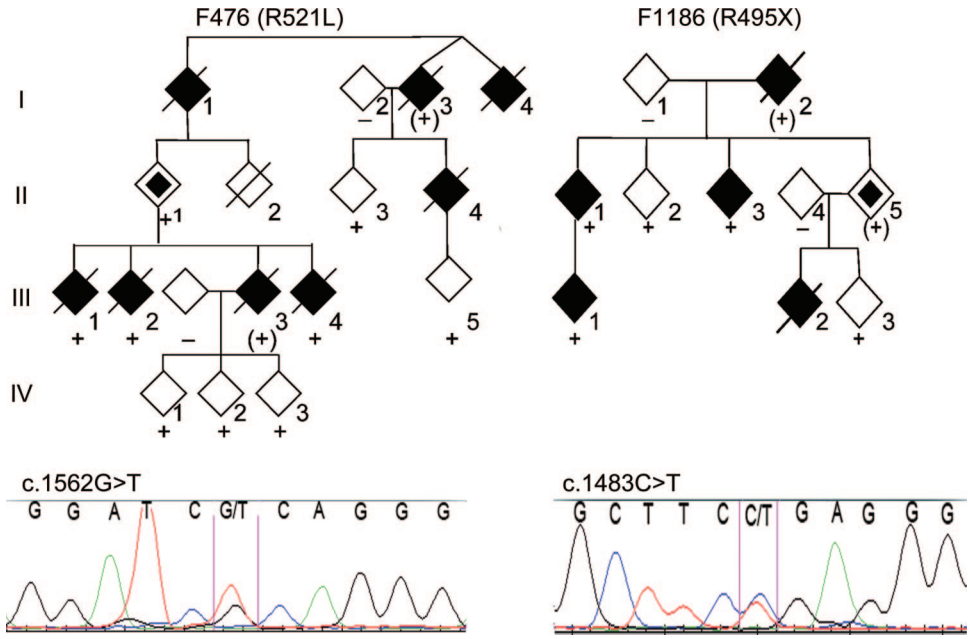
We obtained clinical data of 101 patients from these 25 families with *FUS* gene mutations. Fifty-five of the 101 cases were male (54.5%). The average age at symptom onset was 43.6 ± 15.8 years (n = 54) for *FUS* mutations, 47.7 ± 13.0 (n = 164) for *SOD1*, and 54.7 ± 15.3 (n = 34) for *TARDBP* mutations. The average age at symptom onset in patients with *FUS* gene mutations was remarkably earlier than patients with *TARDBP* mutations and the distribution of age at symptom onset was significantly different among the patients with *FUS*, *SOD1*, or *TARDBP* mutations (figure 2).

The average duration of symptoms was 3.4 ± 5.7 years (n = 44) for patients with *FUS* mutations, 4.1 ± 4.9 years (n = 144) with *SOD1* mutations, and 3.3 ± 2.3 years (n = 30) with *TARDBP* mutations. The duration of symptoms varied widely: 1 patient with the *FUS* p.S96del mutation survived for 18 years. However, 88.6% of *FUS* mutated patients died in less than 4 years, significantly higher than patients with *SOD1* (70.1%) and *TARDBP* (70.0%) mutations.

Patients with *FUS, SOD1,* and *TARDBP* gene mutations showed increased incidence of spinal onset vs bulbar onset, but the percentage of bulbar onset of patients with *FUS* (33.3%) and *TARDBP* (32.1%) was significantly higher than that of patients with *SOD1* mutations (7.6%) (appendix e-1 on the *Neurology*® Web site at www.neurology.org).

**DISCUSSION** The genetic causes of FALS are partly known. In this study, we found that 22 out of 393

**Figure 1** Cosegregation of *FUS* mutations in representative familial amyotrophic lateral sclerosis pedigrees

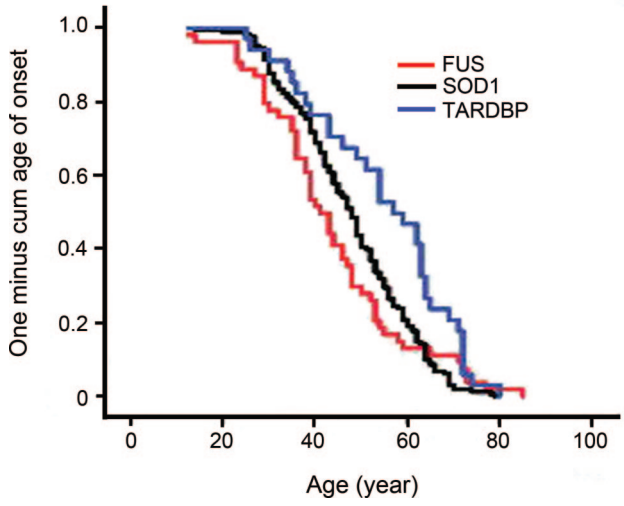



Affected patients are marked by a black symbol, unaffected with an open symbol. A slashed symbol indicates a deceased patient. + = With the mutation; − = without the mutation; (+) = genotype inferred. Gender and birth order have been omitted for reasons of confidentiality.

FALS index cases without FTD or PD, 2 out of 76 patients with FALS/FTD, and 1 out of 7 FALS/PD/DE index cases had *FUS* gene mutations. The *FUS* gene mutation frequency of non-*SOD1* and non-*TARDBP* cases of FALS was 5.6%, and of all cases of FALS was about 4.79%. It was reported that 4.5% of 198 index cases without *SOD1, VAPB, ANG, DYNACTIN, CHMP2B,* or *TARDBP* mutations[22] and 5.3% of 94 cases of FALS without *SOD1, TARDBP,* and *ANG* mutations had *FUS* mutations.[20] Both reports estimated the *FUS* mutational frequency of the general FALS population to be ~4%. FUS mutation frequency was found to be 5.8% in 293 FALS, but it was unclear which gene mutations were excluded, and 209 cases of the 293 cases of FALS were screened only for exon 15.[21] *FUS* and *TARDBP* are both DNA/RNA binding proteins.[33] The prevalence of mutations of *TARDBP* in ALS varied from 0.65% to 4.85% in studies with 80 to 154 patients with FALS examined and 0% to 5% in studies with 86 to 541 patients with SALS screened[4-14]; the variation might be related to clinical heterogeneity of patients. To date, 21 mutations in the *TARDBP* genes were found in 643 cases of FALS with a mutational frequency of 3.27%. *FUS* mutations are more frequent than *TARDBP* mutations, and appear to be the second most frequent cause of disease after *SOD1* mutations in FALS. For SALS, we found no *FUS* gene mutations in 41 cases; however, the sample size was very small. One report found no *FUS* mutation in 293 patients with SALS,[21] but another found 3 out of 405 SALS cases had *FUS* gene mutation.[18]

We found that 1 FALS/PD/DE index case out of 7 and 2 ALS/FTD index cases out of 76 had *FUS* gene mutations. The R521C mutation in the index case of F8828 with FALS/PD/DE was the most frequent mutation documented in FALS.[21,22] The G206S mutation in F7543 with ALS/FTD has not

**Figure 2** Comparison of age at symptom onset




Kaplan-Meier analysis. Y-axis: proportion of patients with symptom onset. X-axis: age. Trend difference was analyzed with log rank ($p = 0.012$), Breslow ($p = 0.02$), and Tarone-Ware ($p = 0.02$) tests. *FUS*, n = 54; *SOD1*, n = 164; *TARDBP*, n = 34.

been reported. G174-G175 mutation in exon 5 was first reported in a FALS pedigree (F213) with a screening of 176 controls.[21] We found it in 1 ALS/FTD and 2 FALS index cases, and it was not present in the sequencing of 726 controls. No patients with FALS with cognitive deficiency were reported in the first 2 *FUS* mutation reports,[21,22] but *FUS* immunoreactive neuronal inclusions have been reported in FTD.[34] However, a G156E mutation was found in an Italian FALS index case who developed FTD in his fourth decade.[20] The proband with S96del had mental retardation, the proband with G174-G175 del in F7390 had the diagnosis of schizophrenia, and the proband with R524S had cerebellar atrophy on MRI, but no additional clinical records were available for further characterization. All the affected individuals in F8726 with G497AfsX527 mutation had learning disabilities; 1 died at age 14; the 2 adults were drug users. It was suggested that *FUS* mutations might result in cognitive dysfunction, which merits further study.

The deletion of 4 glycine residues (G223–G226del) in exon 6 occurred in a 10-glycine stretch from amino acid residue 222 to 231. Six out of the 10 glycine residues were coded by 6 GGC repeats. A loss of 3 glycine residues was found in a SALS case and in 1 out of 190 controls. A glycine insertion in the same region was found in a patient with schizophrenia and autism.[18] The 4-glycine residue deletion in F1090 segregated with the patients and was not present in 700 controls (appendix e-1). In this study, the controls were mainly European Americans, and we had no autopsy tissue for pathologic evaluation; the glycine stretch changes could be polymorphism, and pathogenicity of some of the novel mutations awaits further verification.

Identification of 4 novel frameshift mutations and 1 nonsense mutation in exon 14 suggests that the c-terminal amino acid residues may be of key biologic relevance if the pathogenesis of *FUS* mutation was due to loss of function. It may also imply that a shorter N-terminal peptide of 494 amino acids is sufficient to cause neuronal toxicity via a gain of function mechanism (figure e-1). Such a phenomenon was previously observed in truncated *SOD1*-mediated ALS in humans and transgenic mice.[35] A nonsense change at Y374X in the *TARDBP* gene resulting in a truncated C-terminal has also been reported in SALS.[5] The nonsense R495X and frameshift mutations in *FUS* may suggest that haploinsufficiency rather than a gain of function of *FUS* could cause ALS. Truncated transcript and protein would be degraded or functionless, nevertheless, *FUS* knockout mice had perinatal mortality, sterility, and radiation sensitivity, but had no obvious neurologic manifestation.[36,37]

The distribution of *FUS* mutations reported to date (figure e-1) may delineate 2 major mutation clusters in the *FUS* gene: 1 in exon 4 to 6 and the other in exon 14 to 15. The apparent grouping of mutations in these 2 clusters may imply the functional importance of these regions in triggering motor neuron degeneration. It may also indicate regions of interest for genetic screening of *FUS* mutations in patients with ALS.

In previous studies, *FUS* mutations were found in ALS cases of European American and Cape Verdean Island origins.[21,22] We identified *FUS* mutations in additional ethnic groups, including European American, African American, Asian (Chinese, Korean, and Cambodian), and Latino. Most *FUS* mutations identified in European Americans were also identified in patients from other ethnicity except G206S, which was found in a family of South Korean origin. Although this study is not a population study, it suggests that *FUS* mutations may be a globally distributed genetic cause of FALS in patients of different genetic backgrounds.

When comparing patients with ALS with *SOD1* and *TARDBP* mutations, patients with *FUS* mutations had earlier symptom onset, a higher rate of bulbar onset, and a shorter duration of symptoms in general. No report has compared the phenotype of *FUS, SOD1,* or *TARDBP* mutations, but the average age at symptom onset and duration of symptoms of patients with *FUS* mutations from previous studies were close to those of this study.[21,22] The reported average age at symptom onset of patients with TARDBP mutations was 55.6 years ($n = 8$),[6] close to the 54.7 years observed in the 34 cases in this study. The variability in survival noted in *FUS* families may pose difficulties in assessing response to treatment. We found a patient with the p.S96del mutation who survived for 18 years, suggesting that patients with certain specific *FUS* mutations may have a better prognosis than others. This variation in survival has also been observed in some mutant *SOD1*-mediated ALS cases. Patients with the H46R mutation have a much longer survival (>17 years) than those with the A4V mutation (1 year) in *SOD1*.[38,39] We also noted that patients in the same pedigree may have significant differences in age and site of symptom onset. Some individuals with *FUS* mutations had no symptoms even as their children were getting affected. This phenomenon suggests that other factors, including genetic background and environmental exposure, may modulate the clinical course. Differences in age at onset between *FUS* and *TARDBP* mutations are interesting as these 2 molecules share similar domains, and both are RNA/DNA binding proteins.[33] Our study has enlarged the spec-

trum of neurodegenerative phenotype associated with mutations in *FUS*.

## AUTHOR CONTRIBUTIONS

Patients with FALS were identified and their clinical findings verified by Teepu Siddique or Benjamin Brooks and W. King Engel. Clinical data were complied by Nailah Siddique and Sandra Donkervoort. DNA samples were prepared by Jian Guo Zheng. Sequencing was done by Jianhua Yan, Faisal Fecto, Wenjie Chen, Erdong Liu, Yi Yang, and Yong Shi, and verified by Teepu Siddique and Han-Xiang Deng. Statistical analysis was done by Kreshnik Ahmeti and Jianhua Yan. Drafting the manuscript, including responding to reviewers' comments, editing, copyediting, and word processing, was done by Teepu Siddique, Han-Xiang Deng, and Jianhua Yan. All authors participated in the review of the manuscript at each of these stages and approved the final draft.

## DISCLOSURE

Dr. Yan and Dr. Deng report no disclosures. N. Siddique receives salary support from the NIH (NINDS NS050641 [research nurse]) and the Les Turner ALS Foundation. Dr. Fecto, Dr. Chen, Y. Yang, and Dr. Liu report no disclosures. S. Donkervoort receives research support from the NIH (NINDS NS050641). Dr. Zheng, Dr. Shi, and K.B. Ahmeti report no disclosures. Dr. Brooks serves/has served on scientific advisory boards for Avanir Pharmaceuticals and Sanofi-Aventis and receives research support from Avanir Pharmaceuticals, Carolinas ALS Research Fund, and Harris Research Fund–Carolinas Healthcare Foundation. Dr. Engel reports no disclosures. Dr. Siddique serves on the scientific advisory board of NIH: Skeletal Muscle and Exercise Physiology (SMEP) Study Section; serves on the editorial boards of *Neurogenetics* and *Amyotrophic Lateral Sclerosis*; holds a patent re: Human alpha-tocopherol transport protein: compositions and methods; and receives research support from the NIH (NINDS RO1 NS046535 [PI], NINDS RO1 NS050641 [PI], NIEHS-RO1 ES014469 [PI], NIEHS PO1 ES016742 [PI]), the Harold Post ALS Research Fund, the Les Turner ALS Foundation/Herbert C. Wenske Foundation, Vena Schaaf, Frank White ALS Research Fund, the Spastic Paraplegia Foundation, Inc., the Amyotrophic Lateral Sclerosis Association, the CVS/ALS Therapy Alliance, and the Blazeman Foundation for ALS.

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