CORRECTED 24 APRIL 2009; SEE LAST PAGE

23. C. D. Kaplan, K.-M. Larsson, R. D. Kornberg, *Mol. Cell* **30**, 547 (2008).
24. O. Pontes *et al.*, *Cell* **126**, 79 (2006).
25. R. J. Mroczek, R. K. Dawe, *Genetics* **165**, 809 (2003).
26. M. D. McMullen, B. Hunter, R. L. Phillips, I. Rubenstein, *Nucleic Acids Res.* **14**, 4953 (1986).
27. H. M. Sobell, *Proc. Natl. Acad. Sci. U.S.A.* **82**, 5328 (1985).
28. D. A. Bushnell, P. Cramer, R. D. Kornberg, *Proc. Natl. Acad. Sci. U.S.A.* **99**, 1218 (2002).
29. T. J. Lindell, F. Weinberg, P. W. Morris, R. G. Roeder, W. J. Rutter, *Science* **170**, 447 (1970).
30. R. Liu *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **104**, 114 (2007).
31. B. McClintock, *Cold Spring Harbor Symp. Quant. Biol.* **XVI**, 13 (1951).
32. T. S. Ream *et al.*, *Mol. Cell* **33**, 1 (2009).
33. Single-letter abbreviations for the amino acid residues are as follows: A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr.
34. We thank X. Parisky for technical assistance; N. Bolduc for providing nucleic acid samples; S. McCormick and D. Zilberman for comments; and the maize, *Sorghum bicolor*, and *Brachypodium* genome-sequencing projects for providing sequence information before publication. *Brachypodium* and *Sorghum bicolor* sequences were produced by the U.S. Department of Energy Joint Genome Institute (www.jgi.doe.gov/). cDNA sequences for *Rmr6-A619*, *rmr6-1*, *rmr6-7*, *rmr6-8*, and *rmr6-14* are archived under GenBank accession numbers FJ426107 to FJ426111, respectively. Germ plasm containing mutations in the *rmr6* gene is covered by U.S. patent 07264970 awarded to the Regents of the University of California. Supported by the National Research Initiative of the U.S. Department of Agriculture Cooperative State Research, Education and Extension Service (grants 99-35301-7753, 2001-35301-10641, and 2006-35304-17399) and NSF (grant MCB-0419909).

Supporting Online Material
www.sciencemag.org/cgi/content/full/323/5918/1201/DC1
Materials and Methods
Figs. S1 to S7
Tables S1 to S4
References

11 August 2008; accepted 16 December 2008
10.1126/science.1164508

Mutations in the *FUS/TLS* Gene on Chromosome 16 Cause Familial Amyotrophic Lateral Sclerosis

T. J. Kwiatkowski Jr.,[1]* D. A. Bosco,[1,2] A. L. LeClerc,[1,2] E. Tamrazian,[1] C. R. Vanderburg,[3] C. Russ,[1,4] A. Davis,[1] J. Gilchrist,[5] E. J. Kasarskis,[6] T. Munsat,[7]† P. Valdmanis,[8] G. A. Rouleau,[8] B. A. Hosler,[1] P. Cortelli,[9] P. J. de Jong,[10] Y. Yoshinaga,[10] J. L. Haines,[11] M. A. Pericak-Vance,[12] J. Yan,[13] N. Ticozzi,[1,2,14] T. Siddique,[13] D. McKenna-Yasek,[1] P. C. Sapp,[1,15] H. R. Horvitz,[15] J. E. Landers,[1,2] R. H. Brown Jr.[1,2]*

Amyotrophic lateral sclerosis (ALS) is a fatal degenerative motor neuron disorder. Ten percent of cases are inherited; most involve unidentified genes. We report here 13 mutations in the *fused in sarcoma/translated in liposarcoma* (*FUS/TLS*) gene on chromosome 16 that were specific for familial ALS. The FUS/TLS protein binds to RNA, functions in diverse processes, and is normally located predominantly in the nucleus. In contrast, the mutant forms of *FUS/TLS* accumulated in the cytoplasm of neurons, a pathology that is similar to that of the gene *TAR DNA-binding protein 43* (*TDP43*), whose mutations also cause ALS. Neuronal cytoplasmic protein aggregation and defective RNA metabolism thus appear to be common pathogenic mechanisms involved in ALS and possibly in other neurodegenerative disorders.

Amyotrophic lateral sclerosis (ALS) is a progressive, uniformly fatal, age-dependent degenerative disorder of motor neurons. Its incidence (0.6 to 2.6 per 100,000 humans) peaks in the sixth decade of life (*1*). Death from ALS is typically 2 to 5 years after onset and is usually a consequence of respiratory paralysis. Familial cases account for about 10% of ALS. Of these, about 20% are caused by mutations in the *superoxide dismutase 1* (*SOD1*) gene (*2*). A small number of both familial and apparently sporadic cases are caused by mutations in various other genes, including *TAR DNA-binding protein 43* (*TDP43*) (*3*–*5*), although in the majority of familial ALS (FALS) cases the causative gene is unknown.

In a family of Cape Verdean origin (F577) (fig. S1A), four members developed distinctive ALS with onset in the proximal upper extremities and spreading to the lower extremities, but not the bulbar region. The maternal grandparents of the proband were first cousins; the family originates from a small island of roughly 6000 inhabitants, raising the possibility that the inheritance pattern is recessive. To pursue this, we conducted loss-of-heterozygosity (LOH) mapping and identified a major LOH cluster within a previously reported chromosome 16 ALS locus. Five smaller regions of homozygosity were observed in other chromosomal regions (table S1).

The major LOH cluster spanned approximately 4 Mb and contained 56 candidate ALS genes. Genomic sequencing of these genes revealed a sequence variant in the index ALS cases in exon 15 of the *fused in sarcoma/translated in liposarcoma* (*FUS/TLS*) gene (*6*). This variant, a base pair C1551G missense mutation (*7*), substituting glutamine for histidine at amino acid residue 517 (Table 1), was heterozygously present in asymptomatic individuals and homozygously present in four individuals with FALS and three individuals who were asymptomatic; one was just entering the age of risk for ALS, whereas the other two were below that age. The variant was not detected in 1446 control DNA samples from North America; a single heterozygote was observed in 66 DNA samples (132 chromosomes) from Cape Verde.

We next fully sequenced all of the 15 *FUS/TLS* exons in two families genetically linked to chromosome 16 (F55, fig. S1B, and NUFMS9900, fig. S1C), (*8*). In family 55 (F55), we detected a missense mutation (C1561G) that substituted glycine for arginine at residue 521; this was coinherited with ALS (in five of five affected members for whom DNA was available but in no unaffected individuals). Incomplete penetrance is evident in F55: two mutation carriers lived past the average age of onset without developing ALS. In family NUFMS9900, a G1553A mutation substituting lysine for arginine at residue 518 was present in 10 of 10 available affected members. These variants were not detected in 1446 control subjects. Haplotype analysis of six single-nucleotide polymorphisms (SNPs) across the *FUS/TLS* locus does not exclude a common founder among apparently unrelated R521G pedigrees (*9*).

We sequenced all 15 exons in 81 other unrelated FALS cases and 293 sporadic ALS (SALS) DNA samples, and an additional 209 ALS families were screened for mutations in exon 15. Overall, in 17 different FALS families, 13 different mutations were detected, including 10 in exon

[1]Department of Neurology, Massachusetts General Hospital, 114 16th Street, Charlestown, MA 02129, USA. [2]Department of Neurology, University of Massachusetts School of Medicine, Worcester, MA 01655, USA. [3]Massachusetts General Institute for Neurodegeneration, Massachusetts General Hospital, 114 16th Street, Charlestown, MA 02129, USA. [4]Broad Institute, Massachusetts Institute of Technology (MIT), Cambridge, MA 02141, USA. [5]Department of Neurology, Rhode Island Hospital, Providence, RI 02192, USA. [6]Department of Neurology, Veterans Affairs Medical Center, University of Kentucky, Lexington, KY 40511, USA. [7]Department of Neurology, Tufts New England Medical Center, Tufts University, Boston, MA 02111, USA. [8]Department of Neurology, Centre de Recherche du Centre Hospitalier de l'Université de Montreal, University of Montreal, Quebec H2L 4M1, Canada. [9]Clinica Neurologica, Departimento di Scienze Neurologiche, University de Bologna, Via Ugo Foscola, 7,40123 Bologna, Italy. [10]Childrens' Hospital Oakland Research Institute, Oakland, CA 94609, USA. [11]Center for Human Genetics Research, Molecular Physiology and Biophyscis, Vanderbilt University, Nashville, TN 37240, USA. [12]Miami Institute of Human Genetics, Miami, FL 33136, USA [13]Departments of Neurology and Molecular and Cellular Biology, Northwestern Feinberg School of Medicine, Chicago, IL 60611, USA. [14]Department of Neurology, University of Milan Medical School, Dino Ferrari Center, Istituto Auxologico Italiano, Milan 20149, Italy. [15]Department of Biology, Howard Hughes Medical Institute, MIT, Cambridge, MA 02139, USA.

*To whom correspondence should be addressed. E-mail: tkwiatkowski@partners.org (T.J.K.); robert.brown@umassmed.edu (R.H.B.)
†Retired.

15, two in exon 5, and one in exon 6 (Table 1 and Fig. 1). The most common mutations were R521C and R521G, each present in 3 of the 17 families. No mutations were found in the SALS DNA set. None of the exon 15 variants was observed in 1446 control individuals sequenced. All of the mutated residues in exon 15 of *FUS/TLS* were highly conserved (fig. S1D); each of the 5 arginines in exon 15 is mutated (Fig. 1).

Autopsy tissue from a single patient from F55 (R521G mutation) showed loss of motor neurons in the anterior horn of the spinal cord and the hypoglossal nucleus. Myelin pallor in the anterior corticospinal tracts, macrophages surrounding shrunken Betz cells in the motor cortex (neuronophagia), and increased lipofuscin staining in neurons were also noted. The distribution of FUS/TLS was assessed using immunostaining of frozen brain and spinal cord sections from this affected individual. Both control and patient sections revealed immunostaining of FUS/TLS within the nuclei (of neurons and of nonneuronal cells). However, in F55 patient sections there was additional prominent cytoplasmic staining (Fig. 2). Further immunostaining revealed diffuse ubiquitin positivity in nuclei in the patient's tissue but not control tissue (fig. S2), suggesting that one or more nuclear proteins are misfolded.

Thus, the R521G missense mutation in FUS/TLS led to aberrant trafficking with subsequent cytoplasmic retention of the mutant protein. To evaluate this, we analyzed the subcellular distribution of wild type (WT), R521G (F55), or H517Q (F577) FUS/TLS fused to green fluorescent protein (GFP) 24 hours after transient transfection in N2A and SKNAS cells. With immunofluorescence, the R521G (F55) mutant *FUS/TLS*–GFP transfections showed dense cytoplasmic staining (Fig. 3A). The ratio of the fraction of cells with exclusively nuclear staining versus cells with combined cytoplasmic and nuclear staining was approximately 0.80/0.20 for the WT protein. In contrast, the ratio for R521G was roughly 0.50/0.50. These ratios were similar in the N2A and SKNAS cells. Immunofluorescence did not detect cytoplasmic retention in cells transfected with the H517Q-GFP (F577)

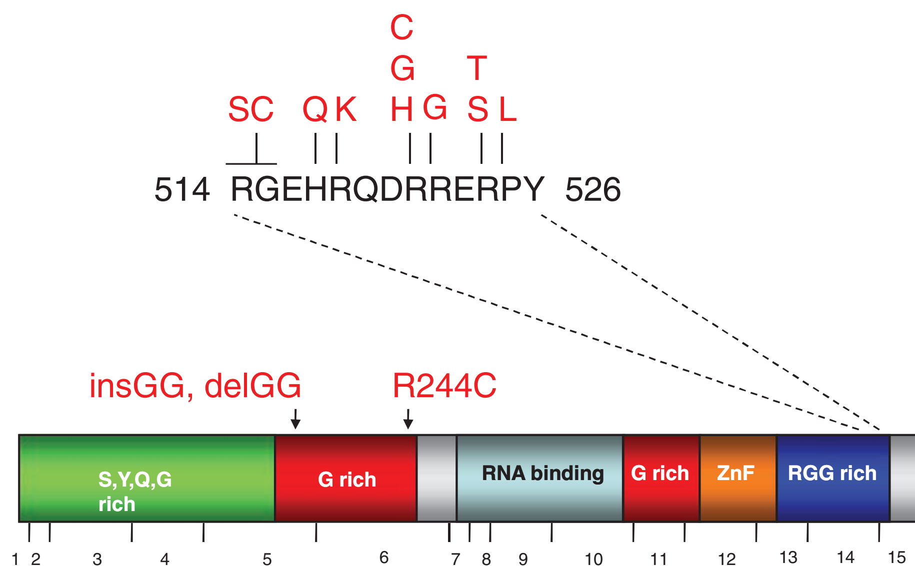

Fig. 1. Positions of the FUS/TLS mutations superimposed on the exon and domain organization of the gene. FUS/TLS is encoded by 15 exons that span a genomic region of 11.6 kb. S,Y,Q,G–rich denotes a region rich in the amino acids serine, tyrosine, glutamine, and glycine; G-rich and RGG-rich regions are enriched in either glycine or the arginine-glycine-glycine motif, respectively (*11*). Further details for each mutation are in Table 1.

Table 1. *FUS/TLS* mutations in ALS cases, with onset and disease duration data. Base numbering begins with the start codon; amino acid numbering begins with the methionine start codon.

ID	Mutation		Exon	Controls	Pattern	Age onset (years)		Duration (months)	
	Amino acid	Base pair				Mean ± SD	Patients	Mean ± SD	Patients
Index cases									
F577	H517Q	C1551G*	15	1446	AR	45.0 ± 3.6	4	168.0	1
F55	R521G	C1561G	15	1446	AD	39.6 ± 13.3	13	26.6 ± 16.5	13
Other cases									
F213	insGG	insGAGGTG523	5	176	AD	65	1	31	1
MTL 10	delGG	delGAGGTG523	5	176	AD	43.3 ± 6.4	3	147.0 ± 55.2	2
MTL 7	R244C	C730T	6	231	AD	54.0 ± 8.5	2	28.5 ± 10.6	2
F360	R514S, G515C	G1542T, G1543T†	15	1446	AD	32.5 ± 3.5	2	36.0	1
NUFMS9900	R518K	G1553A	15	1446	AD	40.3 ± 6.6	12	26.7 ± 14.4	9
F072	R521C	C1561T	15	1446	AD	35.0 ± 14.8	3	26.0 ± 8.2	3
F080	R521C	C1561T	15	1446	AD	54.0 ± 2.8	2	14.0 ± 2.8	2
F085	R521C	C1561T	15	1446	AD	39.7 ± 10.8	6	31.2 ± 17.7	5
F002	R521G	C1561G	15	1446	AD	60.7 ± 10.7	3	28.3 ± 17.9	3
F136	R521G	C1561G	15	1446	AD	37.5 ± 5.0	2	24.0	1
F067	R521H	G1562A	15	1446	AD	57.7 ± 9.0	3	54.1 ± 26.2	3
F287	R522G	A1564G	15	1446	AD	28.5 ± 14.8	2	25.1 ± 15.6	2
F597	R524T	G1571C	15	1446	AD	61.6 ± 4.8	2	32.9 ± 18.2	2
F346	R524S	G1572C	15	1446	AD	34.0	1	39.0	1
F568	P525L	C1574T	15	1446	AD	22.0	1	6.0	1
Average					All	46.3 ± 14.7	62	33.1 ± 25.3	52
					AD	46.4 ± 15.1	58	30.6 ± 17.3	51

*1 heterozygote C1551G (and no homozygotes) was detected in 66 Cape Verdean controls (132 chromosomes). †These mutations are in cis.

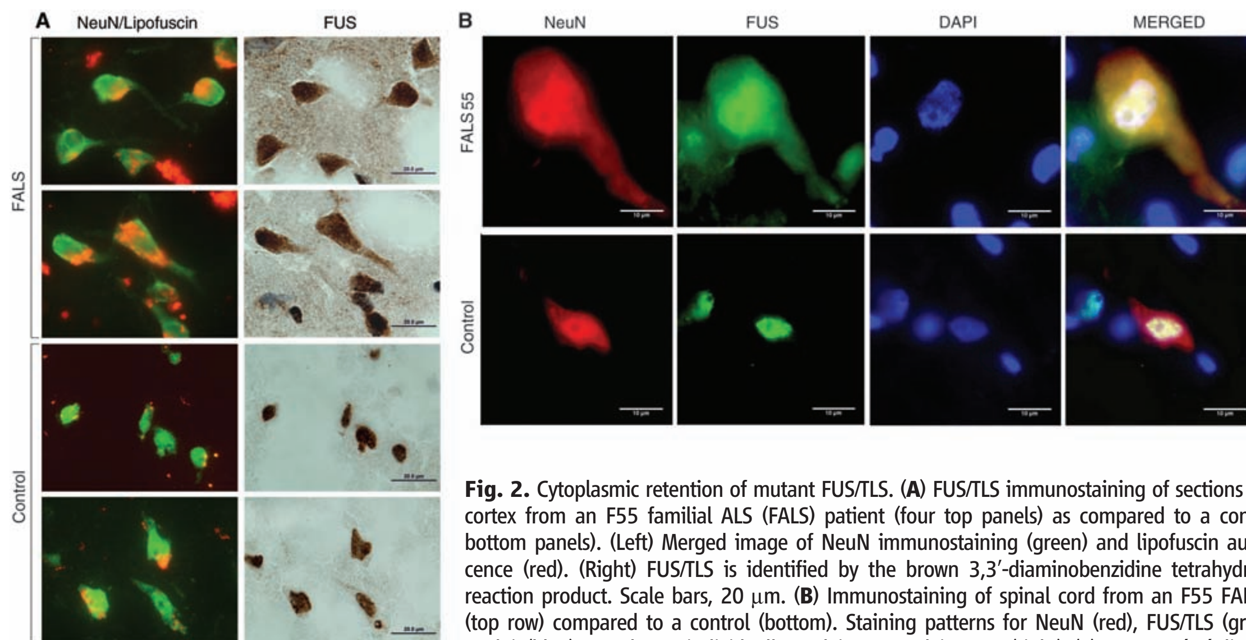

Fig. 2. Cytoplasmic retention of mutant FUS/TLS. (**A**) FUS/TLS immunostaining of sections of frontal cortex from an F55 familial ALS (FALS) patient (four top panels) as compared to a control (four bottom panels). (Left) Merged image of NeuN immunostaining (green) and lipofuscin autofluorescence (red). (Right) FUS/TLS is identified by the brown 3,3′-diaminobenzidine tetrahydrochloride reaction product. Scale bars, 20 μm. (**B**) Immunostaining of spinal cord from an F55 FALS patient (top row) compared to a control (bottom). Staining patterns for NeuN (red), FUS/TLS (green), and nuclei (blue) are shown individually and in merged images (right) (*9*). DAPI, 4′,6′-diamidino-2-phenylindole. Scale bars, 10 μm.

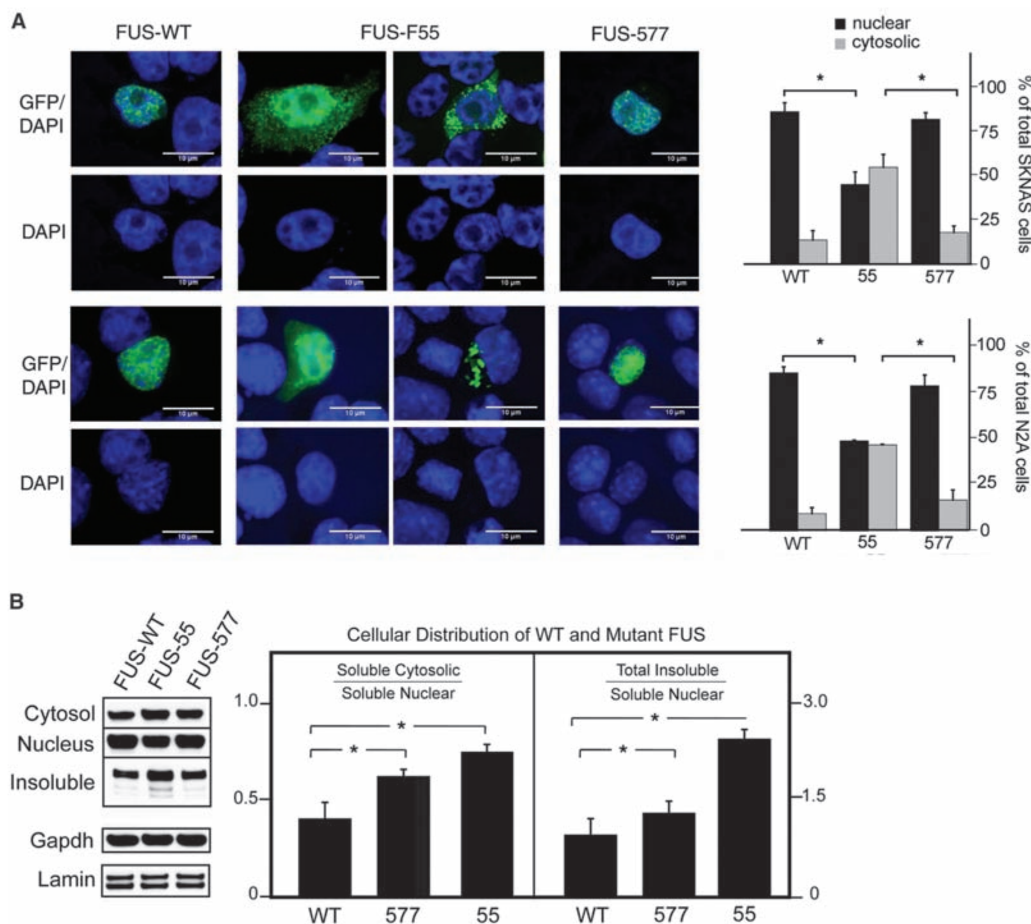

Fig. 3. Mislocalization of mutant FUS/TLS. (**A**) SKNAS (top) or N2A (bottom) cells transfected with WT or mutant (F55 = R521G or F577 = H517Q) recombinant FUS/TLS–GFP fusion protein, counterstained with DAPI. Top row, merged images; lower row, DAPI only. The percentage of cells observed with nuclear-only (dark bars) and any cytosolic (light bars) FUS/TLS staining is indicated in the bar graphs at right. The error bars indicate SD (from total number of cells counted on three coverslips). Asterisks indicate statistically significant differences between FUS constructs [$P < 0.0001$; analysis of variance (ANOVA) followed by Holms test for multiple comparisons]. Scale bars, 10 μm. (**B**) Cell fractionation studies. SKNAS cells transfected with WT or mutant (F55 = R521G or F577 = H517Q) recombinant FUS/TLS–GFP fusion protein were harvested and fractionated at 24 hours for analysis by immunoblotting using an antibody to GFP, with binding quantified by chemiluminescence. Lamin and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) loading controls are shown below. Densitometric ratios are at right. The error bars indicate SD from three triplicate immunoblot measurements. Asterisks indicate statistically significant differences between WT and mutant FUS constructs ($P < 0.0001$, ANOVA followed by Holms test for multiple comparisons).

mutant. Subcellular localization of FUS/TLS was additionally studied by compartmental fractionation of SKNAS cells transfected with WT, R521G, or H517Q FUS/TLS–GFP fusion proteins. Immunoblotting of fractions followed by immunostaining with an antibody to GFP demonstrated a substantially higher ratio of soluble cytosolic to soluble nuclear FUS/TLS for both mutants (Fig. 3B). Additionally, a higher ratio of total insoluble to soluble nuclear FUS/TLS protein was also seen for both mutants, although it is more pronounced for the R521G mutant; this reflected both an increase in total insoluble FUS and a decrease in soluble nuclear FUS (fig S3).

The major defined RNA-interacting domains of FUS/TLS are located in the mid-region of the protein, from amino acids 280 to 370, encoded by exons 9 to 11 (*10*, *11*); sequences of target RNA domains recognized by FUS/TLS have been reported. To show that the FALS-associated FUS/TLS mutations detected here do not alter the RNA-binding domain of FUS, we performed in vitro RNA-binding experiments with recombinant histidine (His)–tagged mutant and WT FUS/TLS proteins and RNA 24-nucleotide oligomer containing GGUG motifs and known to bind FUS/TLS (*10*). Binding of the RNA oligomers was similar for mutant and WT FUS/TLS protein (fig. S4).

FUS/TLS is a nucleoprotein that functions in DNA and RNA metabolism (*12*–*15*). It has also been implicated in tumorigenesis (*6*, *16*, *17*) and RNA metabolism. *FUS/TLS* knockout mice show perinatal mortality (*18*) or male sterility and radiation sensitivity (*19*). FUS/TLS–deficient neurons show decreased spine arborization with abnormal morphology. In hippocampal neuronal slice cultures, the protein is found in RNA granules that are transported to dendritic spines for local RNA translation in response to metabotropic glutamate receptor (mGluR5) stimulation (*20*).

We detected 13 FUS/TLS mutations in patients with FALS but none in patients with SALS. We estimate that FUS/TLS mutations are detected in about 5% of FALS; this is comparable to the frequency of *TDP43* gene mutations in ALS but less than that for *SOD1* (mutated in ~20% of FALS cases). The FUS/TLS mutations described here led to cytoplasmic retention and apparent aggregation of FUS/TLS. This is reminiscent of several models of the pathogenesis of FALS that are mediated by the aggregation of mutant superoxide dismutase (*21*) and the mislocalization in ALS of both mutant and WT TDP43 (*4*, *22*). FUS/TLS has also been reported to be a major nuclear aggregate–interacting protein in a model of Huntington's disease (*23*). Genes implicated in other motor neuron diseases also involve aspects of DNA and RNA metabolism [table S5 in (*24*)]; understanding the convergent pathophysiologies of these genetic variants will provide insights into new targets for therapies for the motor neuron diseases.

References and Notes

1. L. M. Nelson, *Clin. Neurosci.* **3**, 327 (1995).
2. D. R. Rosen, *Nature* **364**, 362 (1993).
3. E. Kabashi *et al.*, *Nat. Genet.* **40**, 572 (2008).
4. J. Sreedharan *et al.*, *Science* **319**, 1668 (2008).
5. V. M. Van Deerlin *et al.*, *Lancet Neurol.* **7**, 409 (2008).
6. A. Crozat, P. Aman, N. Mandahl, D. Ron, *Nature* **363**, 640 (1993).
7. In the mutants, other amino acids were substituted at certain locations; for example, R182Q indicates that arginine at position 182 was replaced by glutamine. Single-letter abbreviations for the amino acid residues are as follows: A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr.
8. P. Sapp *et al.*, *Am. J. Hum. Genet.* **73**, 397 (2003).
9. Materials and methods are available as supporting material on *Science* Online.
10. A. Lerga *et al.*, *J. Biol. Chem.* **276**, 6807 (2001).
11. F. Morohoshi *et al.*, *Gene* **221**, 191 (1998).
12. H. Baechtold *et al.*, *J. Biol. Chem.* **274**, 34337 (1999).
13. P. Bertrand, A. T. Akhmedov, F. Delacote, A. Durrbach, B. S. Lopez, *Oncogene* **18**, 4515 (1999).
14. L. Yang, L. J. Embree, S. Tsai, D. D. Hickstein, *J. Biol. Chem.* **273**, 27761 (1998).
15. X. Wang *et al.*, *Nature* **454**, 126 (2008).
16. T. H. Rabbitts, A. Forster, R. Larson, P. Nathan, *Nat. Genet.* **4**, 175 (1993).
17. W. J. Law, K. L. Cann, G. G. Hicks, *Brief. Funct. Genomics Proteomics* **5**, 8 (2006).
18. G. G. Hicks *et al.*, *Nat. Genet.* **24**, 175 (2000).
19. M. Kuroda *et al.*, *EMBO J.* **19**, 453 (2000).
20. R. Fujii *et al.*, *Curr. Biol.* **15**, 587 (2005).
21. S. Boillee, C. Vande Velde, D. W. Cleveland, *Neuron* **52**, 39 (2006).
22. M. J. Winton *et al.*, *J. Biol. Chem.* **283**, 13302 (2008).
23. H. Doi *et al.*, *J. Biol. Chem.* **283**, 6489 (2008).
24. C. Simpson *et al.*, *Hum. Mol. Genet.* **18** (no. 3), 472 (2008).

25. We gratefully acknowledge I. Carr (University of Leeds, UK) for support with AutoSNPa and IBDfinder software, A. Storey for assistance with sequencing, C. LeClerc for genealogical investigations, and D. Crowe for administrative assistance. This work was supported by NIH grants NS050557 (R.H.B. and T.K.) and NS050641 (T.S., R.H.B., J.L. H., and M.P.-V.). R.H.B. also receives support from the Angel Fund, the ALS Therapy Alliance, the ALS Association Project ALS, the Al-Athel ALS Research Foundation, and the Pierre L. de Bourgknecht ALS Research Foundation. T.S. also receives support from The Les Turner ALS Foundation, Vena E. Schaff ALS Research Fund, Harold Post Research Professorship, Herbert and Florence C. Wenske Foundation, Ralph and Marian Falk Medical Research Trust, The David C. Asselin M.D. Memorial Fund, Les Turner ALS Foundation/Herbert C. Wenske Foundation Professorship, Help America Foundation and the ALS Therapy Alliance, Inc. H.R.H. is an investigator of and was supported by the Howard Hughes Medical Institute. R.H.B. is a cofounder of AviTx Inc., which targets development of ALS therapies. R.H.B. and T.J.K. have applied for a patent covering FUS mutations in ALS. We dedicate this report to the memories of Jimmy and Christopher Kennedy, Sharon Timlin, and Ginny Delvecchio.

Supporting Online Material

www.sciencemag.org/cgi/content/full/323/5918/1205/DC1
Materials and Methods
Figs. S1 to S4
Table S1
References

17 September 2008; accepted 6 January 2009
10.1126/science.1166066

Mutations in FUS, an RNA Processing Protein, Cause Familial Amyotrophic Lateral Sclerosis Type 6

Caroline Vance,[1]* Boris Rogelj,[1]* Tibor Hortobágyi,[1]* Kurt J. De Vos,[2]* Agnes Lumi Nishimura,[1] Jemeen Sreedharan,[1] Xun Hu,[1] Bradley Smith,[1] Deborah Ruddy,[1] Paul Wright,[1] Jeban Ganesalingam,[1] Kelly L. Williams,[3] Vineeta Tripathi,[1] Safa Al-Saraj,[1] Ammar Al-Chalabi,[1] P. Nigel Leigh,[1] Ian P. Blair,[3,5] Garth Nicholson,[3,4,5] Jackie de Belleroche,[6] Jean-Marc Gallo,[1] Christopher C. Miller,[1,2] Christopher E. Shaw[1]†

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease that is familial in 10% of cases. We have identified a missense mutation in the gene encoding fused in sarcoma (FUS) in a British kindred, linked to ALS6. In a survey of 197 familial ALS index cases, we identified two further missense mutations in eight families. Postmortem analysis of three cases with FUS mutations showed FUS-immunoreactive cytoplasmic inclusions and predominantly lower motor neuron degeneration. Cellular expression studies revealed aberrant localization of mutant FUS protein. FUS is involved in the regulation of transcription and RNA splicing and transport, and it has functional homology to another ALS gene, *TARDBP*, which suggests that a common mechanism may underlie motor neuron degeneration.

Amyotrophic lateral sclerosis (ALS) causes progressive muscular weakness due to the degeneration of motor neurons in the brain and spinal cord. The average age at onset is 60 years, and annual incidence is 1 to 2 per 100,000. Death due to respiratory failure occurs on average 3 years after symptom onset (*1*). Autosomal dominant familial ALS (FALS) is clinically and pathologically indistinguishable from sporadic disease (SALS) and accounts for ~10% of cases (*2*). Three genes have been confidently linked to classical FALS: *SOD1*, encoding CuZn superoxide dismutase (SOD1) (*ALS1* OMIM 105400) (*3*); *ANG*, encoding angiogenin (*4*–*6*); and *TARDP*, encoding TAR DNA binding protein TDP-43 (*ALS10* OMIM 612069) (*7*). SOD1 mutations are detected in 20% of FALS and 5% of SALS cases (*3*, *8*). Mice transgenic for mutant human SOD1 develop selective motor neuron degeneration due to a toxic gain of function (*9*) that is not cell autonomous

ERRATUM

Post date 24 April 2009

Reports: "Mutations in the *FUS/TLS* gene on chromosome 16 cause familial amyotrophic lateral sclerosis" by T. J. Kwiatkowski Jr. *et al.* (27 February, p. 1205). The fifth author should have been listed as Charles R. Vanderburg. His affiliation also was incorrect; it should be Harvard NeuroDiscovery Center, Harvard University, Boston, MA 02115, USA.