Published in final edited form as:

Neurobiol Aging. 2014 June ; 35(6): 1513.e7–1513.e11. doi:10.1016/j.neurobiolaging.2013.12.028.

A *de novo* nonsense mutation of the *FUS* gene in an apparently familial ALS case

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Abstract

Mutations in *C9ORF72*, *SOD1*, *TARDBP* and *FUS* genes account for approximately two third of familial cases and 5% of sporadic amyotrophic lateral sclerosis (ALS) cases. We present the first case of an ALS patient carrying a *de novo* nonsense mutation in exon 14 of the *FUS* gene (c.1483c>t; p.R495X) in a young patient with an apparently familial ALS. This mutation cause a phenotype characterized by a young age at onset, a rapid course (<24 months) and a bulbar onset with early respiratory involvement with a predominant lower motor neuron disease. *De novo* mutations could account for a sizable number of apparently sporadic ALS patients carrying mutations of ALS-related genes.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is neurodegenerative disorder of the adult life, characterized by a progressive loss of cortical, bulbar and spinal motor neurons. Approximately 5.10% of patients have a family history of disease, whereas the remaining 85–90% of cases appear to occur sporadically in the community. To date, mutations of at least 15 genes have been described to be related to familial ALS, the most common in Caucasian populations being *C9ORF72* (Renton et al, 2011; DeJesus-Hernandez 2011), *SOD1* (Rosen et al, 1993), *TARDBP* (Sreedharan et al, 2008) and *FUS* (Kwiatkowski et al,

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Financial Disclosure: None reported.

Data contained in the manuscript being submitted have not been previously published, have not been submitted elsewhere and will not be submitted elsewhere while under consideration at Neurobiology of Aging.

2009; Vance et al, 2009), accounting for about 60% of familial cases and 5% of apparently sporadic patients (Chiò et al, 2012; van Blitterswijk et al, 2012; Kenna et al, 2013). The detection of genetic mutations in apparently sporadic ALS cases has been variously explained as reduced gene penetrance, misdiagnosis of ALS or early death in preceding generations, non-paternity, or *de novo* mutations (Chio et al, 2013).

Here, we present a case of an apparently familial ALS patient carrying a *de novo* missense mutation of the *FUS* gene.

2. Methods

While performing mutational screening of large series of ALS cases in Piemonte region, Italy, we detected a young onset apparently familial ALS patient carrying the p.R495X nonsense mutation (c.1483c>t) in exon 14 of *FUS* which causes the truncation of the final 32 amino acids of the protein from the C-terminus of FUS, abrogating a putative nuclear localization signal (Bosco et al, 2010). A first cousin of her maternal grandmother also had ALS, and was negative for this mutation. Since both her parents were still alive and not affected by ALS, we searched for the mutation in the parents.

2.1 Genetic analysis

Genomic DNA was extracted using a Biorobot MDX DSP (Qiagen Inc.). Exons 1 to 15 of *FUS* were sequenced as previously described (Vance et al, 2009; Lai et al, 2010, Chiò et al, 2009). In order to exclude that a SNP under the primers could lead to selective amplification of only normal allele, a second PCR and sequence was performed using a second set of primers with different binding site. PCR products were sequenced using the Big-Dye Terminator v3.1 sequencing kit (Applied Biosystem) and run on an ABIPrism 3100Avant genetic analyzer. Exon 14 was also sequenced in 368 control Italian individuals (Chiò et al, 2009; Lai et al, 2010). Quantitative fluorescence polymerase chain reaction (QF-PCR) was performed to assess paternity and maternity of the proband, with a multiplex analysis of short tandem repeats (STRs) located on five chromosomes (Devys Resolution kit, Devyser). The electropherograms in all 5 chromosomes confirmed the paternity and the maternity of the proband.

2.2 Standard Protocol Approvals and Patient Consents

The study was approved by the Ethical committee of our institution. The patient and her family members signed a written informed consent.

3. Case history

The patient's family pedigree is shown in Figure 1. The patient (III-5) was a 30 year-old woman who developed mild dysphagia and dysarthria at the age of 28 years. One year later she was referred to our ALS center because of a rapid worsening of bulbar symptoms and the onset of generalized asthenia. At neurological examination, the tongue with atrophic with fasciculation. Diffuse fasciculation were seen at upper and lower limbs, but muscle strength was normal. Deep tendon reflexes were hyperactive. Babinski and Hoffman signs were not present. She was cognitively normal. Neurophysiological examination demonstrated chronic and active denervation of tongue (genioglossus) and chronic denervation of proximal muscles of upper limbs, with normal repetitive nerve stimulation test. Cerebrospinal fluid examination was normal. Creatine kinase serum levels were raised. Head MRI showed a cortical atrophy at the precentral gyri; brain spectroscopy revealed a reduction of the NAA/Cr ratio in the motor cortex, more pronounced at left. She was diagnosed as possible ALS. In the following months, she underwent percutaneous

radiological gastrostomy due to worsening of dysphagia and weight loss, and non-invasive ventilation due to a rapidly evolving respiratory failure. She refused tracheostomy and deceased from respiratory failure 24 months after the onset of symptoms.

She had no mutation in *SMN1*, *SOD1*, *TARDBP* and *C9ORF72*. She carried a c.1483c>t (p.R495X) truncating mutation of the *FUS* gene.

Her father (III-1) is 75 years of age and is healthy. Her mother (III-2) is 70 years old and healthy. Her maternal grandmother (II-2) is 91 and healthy. Her maternal great-grandmother (I-1) died at 87 from heart failure.

A 82 year-old first cousin of the proband's maternal grandmother (II-3) developed right foot drop, subsequently progressing to proximal muscles and to the left lower limb. He was referred to our ALS clinic 6 months after the onset of symptoms. Brisk reflex with clonus at lower limbs and bilateral Babinski sign were found. Wasting at the right hand was also observed, with diffuse fasciculations at all limbs. Creatine kinase serum levels were raised. Neurophysiological examination demonstrated chronic and active denervation at upper and lower limbs. He could not undergo MRI due to claustrophobia. He was diagnosed as probable ALS. One year after the onset of symptoms he developed respiratory failure and underwent noninvasive ventilation. He died 31 months after the onset of ALS. He was cognitively normal. He had no mutation in *FUS*, *SOD1*, *TARDBP* and *C9ORF72* genes. His brother (II-4) died at 60 due to renal failure. His daughter (III-3) is 65 years-old and healthy. His father (I-2) died at 54 from hepatic cirrhosis.

Neither the father nor the mother or the first cousin of the maternal grandmother carry the *FUS* mutation identified in the proband, nor any other mutation of genes related to ALS.

4. Discussion

Here we report a proven case of *de novo* *FUS* mutation presenting as a familial ALS. The parents as well the ALS affected first cousin of her maternal grandmother did not carry the mutation, and highly informative polymorphic markers confirmed paternity and maternity. This truncating mutation has been previously described both in familial (Bosco et al, 2010; Yang et al, 2010; Waibel et al, 2013) and apparently sporadic ALS patients (Kwon et al, 2012; van Blitterswijk et al, 2012; Zou et al, 2013). This particular mutation has not been detected in a large number of neurologically normal controls (Kwiatkowski et al, 2009; Vance et al, 2009; van Blitterswijk et al, 2012).

De novo mutations account for at least a part of patients affected by genetic diseases, as well known for familial adenomatous polyposis (Bisgaard et al, 1994) and Duchenne muscular dystrophy (Grimm et al, 2012). Recently, the detection of *de novo* mutations in patients with unaffected parents has led to the discovering of novel genes of autism (O'Roak et al, 2012; Neale et al, 2012; Sanders et al, 2012) and schizophrenia (Xu et al, 2011; Girard et al, 2011). In ALS, whole exome sequencing in young onset sporadic patients with unaffected relatives (so-called trios) represents a good resource for the discovery of new ALS genes, as recently demonstrated by a proof-of-concept study on 47 trios which identified several possible genetic mutations (Chesi et al, 2013).

The analysis of our pedigree raises some considerations. First, according to the proposed classification of familial ALS (FALS) (Byrne et al, 2011), our patient was initially classified as possible FALS, since a first cousin of her grand-mother also was diagnosed with ALS. The identification of the *de novo* mutation in the proband demonstrated that the two ALS cases in the same family were indeed phenocopies. The co-occurrence of two ALS cases in

the same pedigree by chance is not negligible, since the risk of developing ALS in the Italian population is 1 out of 300 male and 1 out of 450 female (Chiò et al, 2009).

Second, the proband carried a truncating mutation of *FUS*. Three different truncating *FUS* mutations have been described, one in exon 15 in a French case (c.1555 C>T p.Q519X) (Belzil et al, 2011) and two in exon 14, i.e. a large heterozygous deletion of 47 nucleotides (p.G478LfsX23) in a German patient (Waibel et al, 2013) and the single nucleotide nonsense mutation found in our patients (c.1483c>t, p.R495X), which had been already described in familial and sporadic ALS patients (Table 1). Truncating mutations of *FUS* are characterized by an age at onset between the 2nd and 4th decade, a rapid course (usually <24 months) and a predominant bulbar phenotype. Interestingly, the p.R495X mutations has been detected both in Caucasian and in Asian patients.

Third, several *de novo* mutations involving the *FUS* gene have been described, including two missense mutations (c.1561C>T [p.R521C], one case, and c.1574 C>T [p. P525L], two cases) (Chiò et al, 2011; Conte et al, 2012, Zhou et al, 2013), a heterozygous 2-base pair deletion (c.1509_1510delAG [p.G504Wfs*12]) (Zhou et al, 2013), and a heterozygous splice-site mutation in *FUS* intron 13 (IVS13-2A>G) (Dejesus-Hernandez et al, 2010). Currently, only one *de novo* mutation in the *SOD1* gene has been reported (Alexander et al, 2002). The relatively high frequency of *de novo* mutations in the *FUS* gene could be related to the younger age at onset usually associated with mutations in this gene compared to other ALS-related genes (Millecamps et al, 2010; Yan et al, 2010; Chiò et al, 2012), so that it is more likely that both patient's parents are still available for DNA analysis. Another possibility is that *FUS* gene is particularly susceptible to mutations (i.e. "mutational hotspots"), presumably because of the characteristics of the surrounding sequence (Chiò et al, 2011).

We have identified a proven *de novo* mutation in the *FUS* gene in a patient with an apparently familial ALS. This finding, together with previous identifications of other *de novo* mutations in ALS-related genes, indicates that at least a part of apparently sporadic patients are in fact characterized by *de novo* mutations that cannot be demonstrated due to the unavailability of the DNA of patients' parents. The relative frequency of proven *de novo* mutations in the *FUS* is therefore likely to be due to the young age at onset of subjects carrying these mutations.

Acknowledgments

Adriano Chiò had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. We thank the patient and her family for having collaborated to this study.

Funding/Support: This work was funded by grants of Fondazione Vialli e Mauro for ALS Research Onlus, Federazione Italiana Giuoco Calcio (FIGC), Ministero della Salute (Ricerca Sanitaria Finalizzata 2007, grant RF-PIE-2007-635695, and 2010, grant RF-2010-2309849), and Joint Programme - Neurodegenerative Disease Research (Strenght Project). The research leading to these results has received funding from the European Community's Health Seventh Framework Programme (FP7/2007–2013) (grant agreement no. 259867). This work was supported in part by the Intramural Research Program of the NIH, and the National Institute on Aging (project Z01 AG000949-02). Funding organizations had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

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Figure 1.

Family pedigree with chromatograms of part of exon 14 of *FUS* gene. Square indicates male; circle, female; slash, deceased; solid symbol, affected; and arrow, index patient. Chromatograms of part of exon 14 of *FUS* gene of the proband (IV-1), her parent (III-1 and III-2) and her grandmother's cousin (II-3) are shown.

Table 1

Summary of *FUS* gene nonsense mutations identified in ALS patients

Mutation	Transmission	Gender	Age at onset (years)	Onset	Duration (months)	Ancestry	Reference
p.G478LfsX23	Familial	1 M, 1 F	21–26	2 B	23–24	Caucasian	Waibel et al, 2013
c.1483c>t (p.R495X)	Familial	2 M, 3 F	14–39	1 B, 1 S*	9–98	Caucasian	Yan et al, 2010
c.1483c>t (p.R495X)	Familial	5 M, 3 F	16–59	4 B, 4 S	11–36	Caucasian	Bosco et al, 2010
c.1483c>t (p.R495X)	Sporadic	F	29	B	NR	Korean	Kwon et al, 2012
c.1483c>t (p.R495X)	Sporadic	F	19	B	24	Caucasian	van Blitterswijk et al, 2012
c.1483c>t (p.R495X)	Sporadic	M	22	S	>5	Chinese	Zou et al, 2013
c.1483c>t (p.R495X)	Familial	1 M, 2 F	31–36	3 B	12–18	Caucasian	Waibel et al, 2013
c.1483c>t (p.R495X)	<i>De novo</i>	F	28	B	24	Caucasian	Present paper
c.1555 C>T (p.Q519X)	Familial	NR	NR	NR	NR	NR	Belzil et al, 2011

* the site of onset of 3 cases is not reported. F, female; M, male; B, bulbar; S, spinal; NR, not reported.