

A de novo nonsense mutation of the *FUS* gene in an apparently familial amyotrophic lateral sclerosis case

Andrea Calvo^{a,*}, Cristina Moglia^a, Antonio Canosa^a, Maura Brunetti^b, Marco Barberis^b, Bryan J. Traynor^c, Giovanna Carrara^d, Consuelo Valentini^d, Gabriella Restagno^b, Adriano Chiò^{a,e}

^a “Rita Levi Montalcini” Department of Neuroscience, ALS Center, University of Torino, Torino, Italy

^b Laboratory of Molecular Genetics, Azienda Ospedaliera Città della Salute e della Scienza, Torino, Italy

^c Neuromuscular Diseases Research Unit, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA

^d Department of Neuroradiology, Azienda Ospedaliera Città della Salute e della Scienza, Torino, Italy

^e Neuroscience Institute of Torino, Torino, Italy

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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) with an apparently familial ALS. This mutation causes 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.

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1. Introduction

Amyotrophic lateral sclerosis (ALS) is a 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 (FALS), the most common in Caucasian populations being *C9ORF72* (DeJesus-Hernandez, 2011; Renton et al., 2011), *SOD1* (Rosen et al., 1993), *TARDBP* (Sreedharan et al., 2008), and *FUS* (Kwiatkowski et al., 2009; Vance et al., 2009), accounting for ~60% of familial cases and 5% of apparently sporadic patients (Chiò et al., 2012; Kenna et al., 2013; van Blitterswijk et al., 2012). 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, nonpaternity, or de novo mutations (Chiò et al., 2013).

Here, we present a case of an apparently FALS 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 FALS patient carrying the p.R495X nonsense mutation (c.1483c>t) in exon 14 of *FUS* that 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. Because 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 1–15 of *FUS* were sequenced as previously described (Chiò et al., 2009; Lai et al., 2010; Vance et al., 2009). To exclude that a single-nucleotide polymorphism under the primers could lead to selective amplification of only normal allele, a second polymerase chain reaction (PCR) sequence was performed using a second set of primers with a different binding site. PCR products were sequenced using the Big-Dye Terminator version 3.1 sequencing kit (Applied Biosystem) and run on an ABIPrism

* Corresponding author at: “Rita Levi Montalcini” Department of Neuroscience, ALS Centre, University of Turin, Via Cherasco 15, Torino 10126, Italy. Tel.: +39 0116335439; fax +39 0116963487.

E-mail address: achio@usa.net (A. Chiò).

3100Avant genetic analyzer. Exon 14 was also sequenced in 368 control Italian individuals (Chiò et al., 2009; Lai et al., 2010). Quantitative fluorescence PCR was performed to assess paternity and maternity of the proband, with a multiplex analysis of short tandem repeats located on 5 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 Fig. 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 neurologic examination, the tongue was 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 magnetic resonance imaging showed a cortical atrophy at the precentral gyri; brain spectroscopy revealed a reduction of the N-acetyl-aspartate to creatine ratio (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 because of worsening of dysphagia and weight loss and noninvasive ventilation because of 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), mother (III-2), and maternal grandmother (II-2) are 75, 70, and 91 years, respectively, and are healthy. Her maternal great grandmother (I-1) died at 87 years from heart failure.

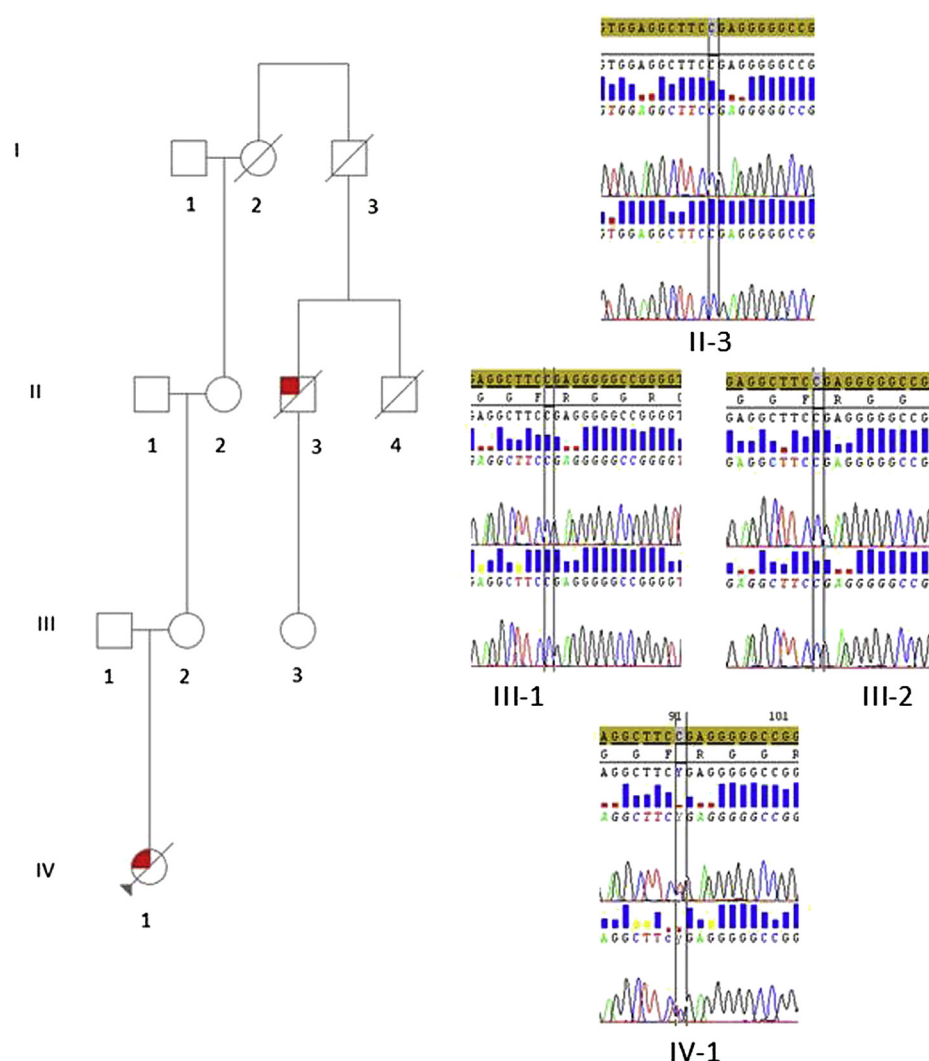


Fig. 1. Family pedigree with chromatograms of part of exon 14 of *FUS* gene. Square indicates male; circle, female; slash, deceased; solid symbol, affected; and arrow, index patient. Chromatograms of part of exon 14 of *FUS* gene of the proband (IV-1), her parent (III-1 and III-2), and her grandmother's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

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