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ORIGINAL ARTICLE

A novel S379A *TARDBP* mutation associated to late-onset sporadic ALS

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Abstract

Since 2008, several groups have reported a lot of dominant mutations in *TARDBP* gene as a primary cause of Amyotrophic lateral sclerosis (ALS). Mutations in *TARDBP* gene are responsible for 4–5% of familial ALS (fALS) and nearly 1% of sporadic ALS (sALS). To date, over 50 dominant mutations were found in TDP-43 in both familial and sporadic ALS patients, most of which were missense mutations in the C-terminal glycine-rich region. Herein, we describe the clinical and genetic analysis of an Italian non-familial ALS patient with a late onset and a rapid disease progression, which led to the discovery of a novel *TARDBP* mutation. After neurological evaluation, molecular investigation highlighted the heterozygous substitution in exon 6 of *TARDBP* gene (S379A), which has previously neither been described nor reported in the ALS database. Several evidences supported the S379A mutation as causative in our patient: (a) it was neither found in ExAC nor 1000G and it was absent in our database of control subjects; (b) the position of the mutation involves an evolutionarily highly conserved residue; (c) two different amino acid substitutions in the same 379 codon were already reported in Swedish and Italian fALS cases, supporting the critical role of this codon for the protein function. The identification of this novel mutation enlarges the number of *TARDBP* mutations in ALS patients.

Keywords ALS · TARDBP · TDP-43 · Mutation

Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal, neurodegenerative disease in which a progressive degeneration engaging both upper motor neurons in the motor cortex and lower motor neurons in the brain stem and spinal cord has been described. This condition leads to muscle wasting and weakness, bulbar palsy, and finally to death within 2–3 years after the onset of the first symptoms [1]. Several pathogenic mechanisms involved in altered signaling pathways, such as glutamate excitotoxicity, oxidative damage, apoptosis, mitochondrial dysfunction, neuroinflammation, protein aggregation, and aberrant axonal transport, have been associated with the disease [2]. Many reports have documented that 90–95% of ALS cases have no manifest genetic link (sporadic ALS, sALS), while the remaining 5–10% of cases are familial (familial ALS, fALS) [2]. Mutations in more than 30 genes have been recognized to cause familial ALS, including *C9orf72* [3, 4], *SOD1* [5], *FUS* [6], *TARDBP* [7], *OPTN* [8], *UBQLN2* [9], and *ERBB4* [10]. In particular, TAR DNA-binding protein 43 (TDP-43), a protein encoded by the *TARDBP* gene on chromosome 1, is a highly conserved component, ubiquitously expressed of the heterogeneous nuclear ribonucleoprotein family (hnRNP). TDP-43 interacting proteins widely cluster into two distinct pathways, a nuclear/splicing and a cytoplasmic/translation, thus suggesting that TDP-43 is involved in the RNA processing, including splicing, transport, and translation [11]. TDP-43 is the major constituent of ubiquitin-positive cytoplasmic inclusions that are the neuropathological hallmark of most cases of ALS, tau-negative

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frontotemporal lobar degeneration (FTLD), and inclusion body myopathy [12–16]. TDP-43 is part of the spliceosome localizing to sites of transcription and splicing [17]. The protein is made of 414 amino acid residues and comprises an N-terminal domain (NTD: 1–102) including a predicted nuclear localization signal (NLS: 82–98), two RNA recognition motifs (RRMs) composed of RRM1 (amino acids 106–177) and RRM2 (amino acids 192–259, with a nuclear export signal NES from residues 239–250), and a C-terminal domain (CTD: 274–414) [18] (Fig. 1). Mutations in *TARDBP* gene are responsible for 4–5% of fALS and nearly 1% of sALS [19]. To date, over 50 dominant mutations were found in TDP-43 in both familial and sporadic ALS patients, most of which were missense mutations in the C-terminal glycine-rich region (http://www.hgmd.cf.ac.uk) [20–23]. Herein, we report the clinical and genetic analysis of an Italian woman with ALS which led to the discovery of a novel *TARDBP* mutation.

Materials and methods

The patient involved in this study underwent psychological and genetic counseling. An 80-year-old woman, born from non-consanguineous parents, was referred to the ALS Clinical Research Center, Palermo (Italy), with a few-month history of progressive weakness and stiffness of the right leg, which caused frequent falls. Her family history was negative for ALS and other aging-related neurodegenerative disorders (i.e., dementia, Parkinson disease). The pedigree for the family is presented in Fig. 2a. The father was type 2 diabetic and he died of a myocardial infarction at the age of 70. The mother died of natural causes at the age of 90. The proband's sister died of colon cancer at the age of 78. The patient had two sons both healthy; they were unavailable for genetic testing. Her neuropsychological screening test showed no cognitive impairment with a Mini-Mental State Examination (MMSE) of 27/30. The Edinburgh Cognitive and Behavioral ALS Screen (ECAS) showed normal ALS-specific and ALS-nonspecific scores (i.e., 81,79 and 26,93, respectively) [24]. Both values suggested a normal frontal-lobe-related cognitive condition. The neurological examination revealed weakness and muscular atrophy in both upper and lower limbs, with fasciculations. Gait was spastic, only possible with a cane. Reflexes were brisk in both upper and lower limbs. She was dysarthric and dysphagic, but with normal tongue. After an extended diagnostic workup, a diagnosis of ALS with spinal onset was made according to the El Escorial revised criteria [25]. The rate of disease progression (ΔFS) [26], evaluated at diagnosis, gave a value of 4.2, indicating a rapidly progressing disease. Ten months after diagnosis, she died at the age of 81 because of a respiratory failure.

The patient gave a written informed consent and genomic DNA was extracted from peripheral blood leukocytes using salting out method. The four major ALS-related genes (*C9orf72*, *SOD1*, *FUS*, and *TARDBP*) were analyzed. In detail, the coding regions of these genes and their relative intron/exon boundaries were amplified by polymerase chain reaction (PCR) using specific primers. The amplified products were subsequently analyzed by direct sequencing on an ABI Prism 3130XL genetic analyzer (Applied Biosystems, Foster City, CA), using the BigDye Terminator Cycle Sequencing Ready Reaction Kit (Applied Biosystems, Foster City, CA).

Results

Molecular evaluation of the *TARDBP* gene showed the novel heterozygous missense mutation c.1135 T > G (NM_007375) in the exon 6 of our sporadic ALS patient (Fig. 2b). This TCT/GCT substitution, inducing an amino acid change from serine to alanine at position 379 (p.S379A), was not detected in a cohort of 943 unrelated ALS patients and 300 geographically matched healthy unrelated Italian individuals. However, recently, it was reported in gnomAD browser (rs80356738), but not found in ClinVar and never associated with a clinical phenotype. In silico analysis of this nucleotide variant with different software was performed. Both *PolyPhen2* and *SIFT* characterized p.S379A as benign, *Panther* classification system reported it with a substitution position-specific evolutionary conservation (subPSEC) score of − 1.00268, and p_0.11948 and *Mutation taster* predicted this variation as *disease causing* (Fig. 3).

Discussion and conclusion

Since 2008, several groups have reported a lot of dominant mutations in *TARDBP* gene as a primary cause of ALS. To

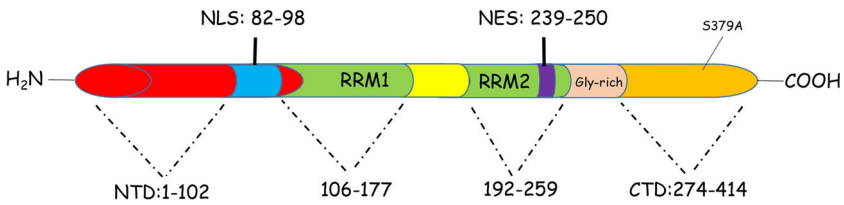

Fig. 1 Schematic structure of TDP-43 protein

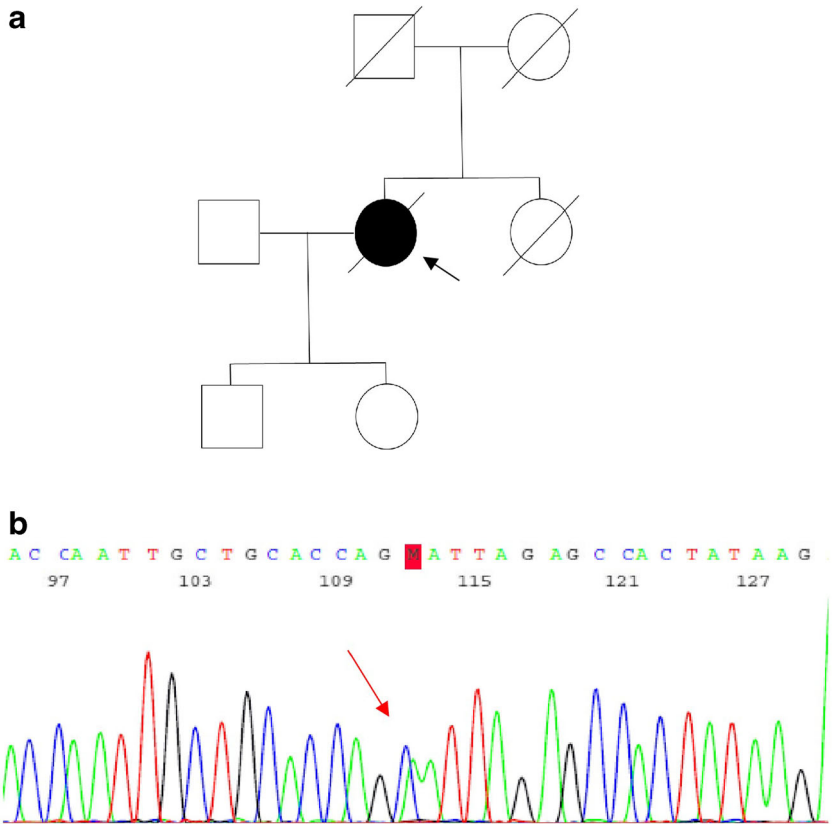

Fig. 2 Family pedigree (**a**) and electropherogram of the *TARDBP* gene exon 6 showing the missense mutation S379A (**b**)

date, over 50 mutations of *TARDBP* have been described in both familial and sporadic ALS cases (Table 1). Herein, we describe a non-familial ALS patient with a late onset and a rapid disease progression, carrying a new heterozygous *TARDBP* mutation in the codon 379 of exon 6. This variant has previously neither described nor reported both in our

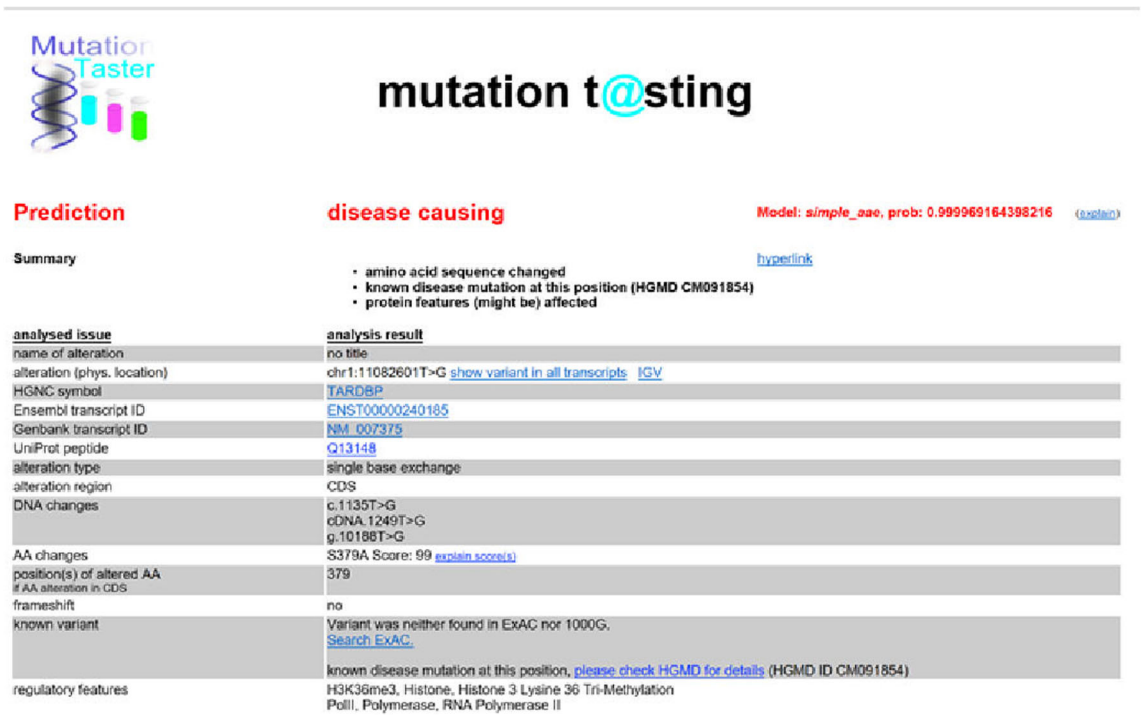

Fig. 3 In silico protein prediction by Mutation taster software

Table 1 Currently known missense mutations in *TARDBP* gene linked to ALS

Variant ID	Mutation	Exon	Amino acid change	References
rs80356715	c.269C>G	3	p.A90V	Winton et al. (2008) [27]
rs1475736511	c.269C>T	3	p.A90V	Sreedharan et al. (2008) [7]
rs80356717	c.506A>G	4	p.D169G	Kabashi et al. (2008) [28]
rs80356718	c.800A>G	6	p.N267S	Corrado et al. (2009) [29]
rs80356719	c.859G>A	6	p.G287S	Kabashi et al. (2008) [28]
rs121908395	c.869G>C	6	p.G290A	Van Deerlin et al. (2008) [30]
CM100585	c. 875G>A	6	p.S292 N	Xiong et al. (2010) [22]
rs80356721	c.881G>T	6	p.G294 V	Corrado et al. (2009) [29]
rs80356721	c.881G>C	6	p.G294A	Sreedharan et al. (2008) [7]
rs80356723	c.883G>A	6	p.G295S	Corrado et al. (2009) [29]
rs80356723	c.883G>C	6	p.G295R	Corrado et al. (2009) [29]
CM125899	c.883G>C	6	p.G295C	van Blitterswijk et al. (2012) [32]
rs4884357	c.892G>A	6	p.G298S	Van Deerlin et al. (2008) [30]
rs1375684772	c.909A>C	6	p.Q303H	Lattante et al. (2012) [33]
rs80356725	c.931A>G	6	p.M311 V	Lemmens et al. (2009) [34]
CM118507	c.943C>A	6	p.A315E	Fujita et al. (2011) [35]
rs80356726	c.943G>A	6	p.A315T	Gitcho et al. (2008) [36]
CM104429	c.962C>T	6	p.A321V	Kirby et al. (2010) [37]
CM097288	c.962G>C	6	p.A321G	Bäumer et al. (2009) [38]
rs80356727	c.991C>A	6	p.Q331K	Sreedharan et al. (2008) [7]
rs80356728	c.995G>A	6	p.S332 N	Corrado et al. (2009) [29]
rs80356729	c.1004G>A	6	p.G335D	Corrado et al. (2009) [29]
rs80356730	c.1009A>G	6	p.M337 V	Sreedharan et al. (2008) [7]
rs80356731	c.1028A>G	6	p.Q343R	Yokoseki et al. (2008) [39]
rs80356732	c.1035C>A	6	p.N345K	Rutherford et al. (2008) [40]
rs80356733	c.1042G>T	6	p.G348C	Kabashi et al. (2008) [28]
CM104428	c.1043G>T	6	p.G348 V	Kirby et al. (2010) [37]
rs80356734	c.1055A>G	6	p.N352S	Kühnlein et al. (2008) [41]
CM121241	c.1069G>A	6	p.G357S	Iida et al. (2012) [42]
CM121241	c.1069G>C	6	p.G357R	Chiang et al. (2012) [31]
rs80356735	c.1083G>T	6	p.R361S	Kabashi et al. (2008) [28]
CM124055	c.1082G>C	6	p.R361T	Chiang et al. (2012) [31]
CM091312	c.1086G>C	6	p.P363A	Daoud et al. (2009) [43]
rs755393183	c.1102G>A	6	p.G368S	De Marco et al. (2011) [44]
rs766196255	c.1123A>G	6	p.S375G	Cady et al. (2015) [45]
CM106963	c.1127G/A	6	p.G376D	Conforti et al. (2011) [46]
CM112270	c.1132>G	6	p.N378D	Ticozzi, et al. (2011) [47]
CM122356	c.1133>G	6	p.N378S	Huang et al. (2012) [48]
rs80356739	c.1136C>G	6	p.S379C	Corrado et al. (2009) [29]
rs80356738	c.1135T>C	6	p.S379P	Corrado et al. (2009) [29]
rs367543041	c.1144G>A	6	p.A382T	Kabashi et al. (2008) [28]
rs367543041	c.1144G>C	6	p.A382P	Daoud et al. (2009) [43]
rs80356740	c.1147A>G	6	p.I383V	Rutherford et al. (2008) [40]
rs797044594	c.1150G>C	6	p.G384R	Millecamps et al. (2010) [19]

Table 1 (continued)

Variant ID	Mutation	Exon	Amino acid change	References
rs797044595	c.1153T>G	6	p.W385G	Millecamps et al. (2010) [19]
rs80356741	c.1168A>G	6	p.N390D	Kabashi et al. (2008) [28]
rs80356742	c.1169A>G	6	p.N390S	Kabashi et al. (2008) [28]
rs80356743	c.1178C>T	6	p.S393 L	Corrado et al. (2009) [29]
rs80356738	c.1135T>G	6	p.S379A	This report

and in ALS database (http://www.alsod.org). In addition, several evidences supported the S379A mutation as causative in our patient: (a) it was neither found in ExAC nor 1000G (Frequency: G = 0.0000; 1/30966, GnomAD), and it was absent in our database of control subjects; (b) the position of the mutation involving the codon 379, an evolutionarily highly conserved residue serine 379 (Fig. 4), is located within C-terminal Gly-rich domain, where the *TARDBP* ALS-related mutations in both fALS and sALS patients have been clustered; (c) interestingly, two different amino acid substitutions (serine to proline and serine to cysteine) in the same codon (c.379) were already reported in Swedish and Italian fALS cases [29, 31], supporting the critical role of this codon for the protein function. In particular, the p.S379P was first described by Corrado et al. in a 40-year-old-man with a positive familial ALS history. Later, it was described by Chiang et al. in a 62-year-old patient who developed muscle weakness and muscular atrophy also included his lower extremities. This patient had a family history of ALS and died 3 years after disease onset. The effect of the detected *TARDBP* missense mutations was investigated with two prediction programs: *PolyPhen* and *SNAP*. Although the programs predicted the S379P variation as benign or neutral, due to that the mutation is located in a conserved residue and was not reported in 771 healthy individuals, the authors considered the mutation as likely pathogenic. In our case, we were not able to validate the pathogenicity of the p.S379P variation in a segregation analysis because the patient died shortly after diagnosis.

The identification of this novel mutation enlarges the number of *TARDBP* mutations in ALS patients. Although genetic mutations are clearly responsible for the disease, it remains ambiguous how much other factors such as environmental factors, aging or lifestyle choices might play a critical role in its pathogenesis. Since environmental and genetic risk factors on TDP-43 further confirmed that this protein is involved in the pathogenesis of ALS, the identification of the potential drugs targeting on modulating the TDP-43 degradation pathway might be a potential therapeutic strategy for ALS patients with TDP-43 proteinopathies. Further, in vitro functional analyses and studies using transgenic animal models are needed to confirm the pathogenicity and to elucidate the exact role of novel mutations and potentially pathogenic variants in ALS neurodegeneration.

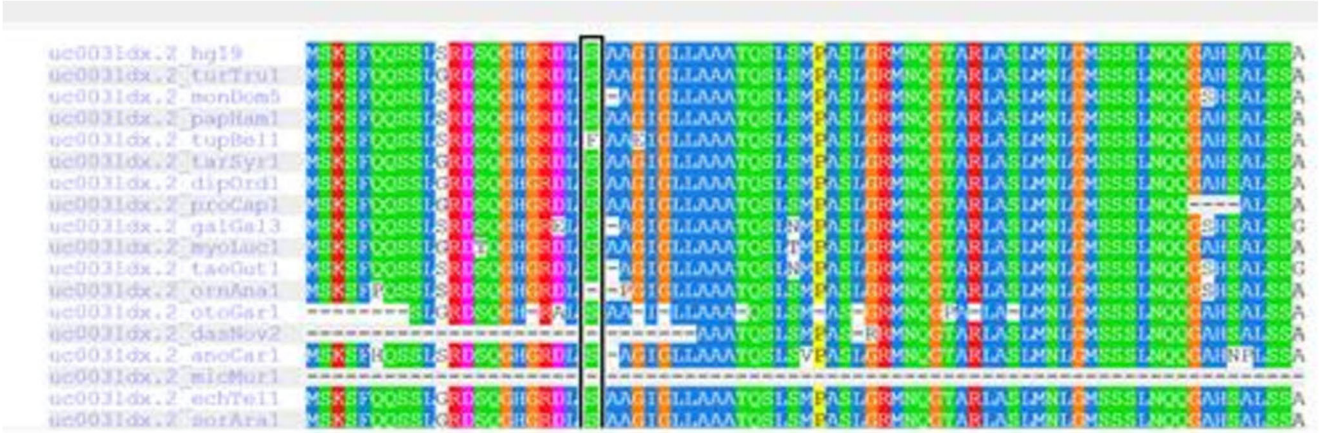

Fig. 4 Multi-species alignment of amino acides of TARDBP gene from different species

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Authors' contributions Analysis, acquisition, and interpretation of data: CU, TS, BP, and GDN. Provision of patient samples and collection of clinical data: RS and VLB. Drafting and revising of manuscript: FLC, CU, TS, SB, VLB. Study conception and design: FLC.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all patients.

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