Clinical feature difference between juvenile amyotrophic lateral sclerosis with *SPTLC1* and *FUS* mutations

Peishan Wang[1,2], Qiao Wei[1,2], Hongfu Li[1,2], Zhi-Ying Wu[1,2]

[1]Department of Neurology, Second Affiliated Hospital, Zhejiang University School of Medicine, and Key Laboratory of Medical Neurobiology of Zhejiang Province, Hangzhou, Zhejiang 310009, China;
[2]Department of Medical Genetics, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang 310009, China.

Abstract

Background: Juvenile amyotrophic lateral sclerosis (JALS) is an uncommon form of amyotrophic lateral sclerosis whose age at onset (AAO) is defined as prior to 25 years. *FUS* mutations are the most common cause of JALS. *SPTLC1* was recently identified as a disease-causative gene for JALS, which has rarely been reported in Asian populations. Little is known regarding the difference in clinical features between JALS patients carrying *FUS* and *SPTLC1* mutations. This study aimed to screen mutations in JALS patients and to compare the clinical features between JALS patients with *FUS* and *SPTLC1* mutations.

Methods: Sixteen JALS patients were enrolled, including three newly recruited patients between July 2015 and August 2018 from the Second Affiliated Hospital, Zhejiang University School of Medicine. Mutations were screened by whole-exome sequencing. In addition, clinical features such as AAO, onset site and disease duration were extracted and compared between JALS patients carrying *FUS* and *SPTLC1* mutations through a literature review.

Results: A novel and *de novo SPTLC1* mutation (c.58G>A, p.A20T) was identified in a sporadic patient. Among 16 JALS patients, 7/16 carried *FUS* mutations and 5/16 carried respective *SPTLC1*, *SETX*, *NEFH*, *DCTN1*, and *TARDBP* mutations. Compared with *FUS* mutation patients, those with *SPTLC1* mutations had an earlier AAO (7.9 ± 4.6 years *vs.* 18.1 ± 3.9 years, $P < 0.01$), much longer disease duration (512.0 [416.7–607.3] months *vs.* 33.4 [21.6–45.1] months, $P < 0.01$), and no onset of bulbar.

Conclusion: Our findings expand the genetic and phenotypic spectrum of JALS and help to better understand the genotype–phenotype correlation of JALS.

Keywords: *FUS*; Juvenile amyotrophic lateral sclerosis; Phenotype; *SPTLC1*

Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by aggressive degeneration of upper and lower motor neurons. Patients usually present with muscular weakness and atrophy, and they die from respiratory failure three to four years after the disease onset.[1] Juvenile amyotrophic lateral sclerosis (JALS) is an uncommon form of ALS whose age at onset (AAO) is defined as prior to 25 years with phenotypic variability.[2] It is universally known that genetics play significant roles in the pathogenesis of JALS. Over the last 30 years, more than ten causative genes have been identified in JALS.[3]

The *SPTLC1* gene encodes the long-chain base subunit one of serine palmitoyltransferase (SPT), which is the critical rate-limiting enzyme in the initial step of sphingolipid biosynthesis.[4] In 2001, *SPTLC1* was identified as the causative gene for hereditary sensory neuropathy type 1 (HSAN1),[5] and mutations identified in patients with HSAN1 reduced SPT activity, leading to the accumulation of pathogenic and neurotoxic sphingolipids.[6] Recently, *SPTLC1* was identified as a disease-causative gene for JALS, and its mutations promoted enzymic activity, resulting in an increase in standard products.[7,8] To date, a novel *SPTLC1* (c.113T>G, p.L38R) mutation has been identified in a Chinese JALS patient,[9] but other *SPTLC1* mutations have not been reported in Chinese patients with JALS.

The *FUS* gene contains 15 exons and encodes a protein consisting of 526 amino acids. Mutations in *FUS* were described as the most common cause of the autosomal

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Correspondence to: Prof. Zhi-Ying Wu, Department of Neurology and Department of Medical Genetics in Second Affiliated Hospital, Zhejiang University School of Medicine, and Key Laboratory of Medical Neurobiology of Zhejiang Province, 88 Jiefang Road, Hangzhou, Zhejiang 310009, China
E-Mail: zhiyingwu@zju.edu.cn

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dominant form in JALS, and the majority was *de novo*.[10,11] Notably, mutations in *SPTLC1* occurred *de novo* in ten out of 16 JALS patients carrying *SPTLC1* mutations,[7-9] indicating *de novo* mutagenesis as the underlying genetic mechanism. However, little is known regarding the difference in clinical features between JALS patients carrying *FUS* and *SPTLC1* mutations. Therefore, in this study, we screened *SPTLC1* and *FUS* mutations in JALS patients and compared the corresponding clinical features to better understand the genotype–phenotype correlation of JALS.

Methods

Ethical approval

This study was approved by the Ethics Committee of the Second Affiliated Hospital, Zhejiang University School of Medicine (No. 2015-048). Written informed consent was signed by participants or their legal guardians.

Patients and sample collection

A total of 16 JALS patients were included in this study. Three of them were newly recruited between July 2015 and August 2018 from the Second Affiliated Hospital, Zhejiang University School of Medicine, and the other 13 were reported in our previous studies.[11,12] All patients were evaluated by two experienced neurologists, underwent electromyography (EMG), and fulfilled the revised El Escorial criteria.[13] Blood samples from available family members were also obtained.

DNA extraction, sequencing, and analysis

Genomic DNA was extracted from peripheral white blood cells using QIAamp Blood Genomic Extraction Kits (Qiagen, Hilden, Germany) following the standard instructions. Whole-exome sequencing (WES) was performed using an Agilent SureSelect Human All Exome V6 kit (Agilent Technologies Inc., Santa Clara, CA, USA). Then, the captured 150-bp library fragments were sequenced on an Illumina HiSeq X Analyzer (XY Biotechnology Co. Ltd., Hangzhou, China) and annotated. Public databases, including the Genome Aggregation Database (gnomAD), Exome Aggregation Consortium (ExAC) database, National Heart, Lung, and Blood Institute Grand Opportunity (NHLBI GO) Exome Sequencing Project (ESP6500), and 1000 Genomes Project (1000G) database, were used to estimate the frequency of the identified variants in the general population. *In silico* prediction of functional effects was evaluated using Sorting Intolerant from Tolerant (SIFT, https://sift.bii.a-star.edu.sg/), PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/), Combined Annotation Dependent Depletion (CADD, https://cadd.gs.washington.edu/), and Mutation Taster (http://www.mutationtaster.org/). The National Center for Biotechnology Information Web (NCBI, https://www.ncbi.nlm.nih.gov) was used to evaluate the evolutionary conservation of mutant amino acids. Sanger sequencing was carried out to validate the variant and co-segregation in each proband and available familial members. Haplotype analysis was performed with GlobalFiler PCR amplification kits according to the manufacturer's instructions (Thermo Fisher Scientific, Waltham, MA, USA).

Literature review

We reviewed all of the research considering JALS patients carrying *SPTLC1* and *FUS* mutations through PubMed based on the following terms: JALS and specific genes (*SPTLC1* and *FUS*). After screening all articles or case reports in English, 32 articles were retrieved (including a preprint of a novel *SPTLC1* mutation identified in a Chinese JALS patient). Inclusion criteria were defined as having both genetic information (*FUS* or *SPTLC1* mutation) and phenotypic descriptions (including AAO, onset site, and disease duration). Cases met the inclusion criteria were included for further analyses.

Statistical analyses

Statistical analyses were performed using SPSS version 26.0 (IBM, Armonk, NY, USA). Categorical variables were displayed as numbers of cases (%). Continuous variables with normal distribution were shown as mean ± standard deviation; non-normally distributed variables were presented as median (interquartile range). Clinical features were compared between the two groups using Student's *t* test for AAO and the χ^2 test for gender and onset site. Clinical features were compared among the three groups using one-way analysis of variance (ANOVA) followed by the Scheffe *post hoc* test with different sample sizes for AAO and the χ^2 test followed by a Bonferroni *post hoc* test for gender and onset site. Fisher's exact test was used when the expected frequency in one or more cells was less than five. Kaplan–Meier analysis was performed to compare survival between groups. Statistical significance was defined as a P value <0.05.

Results

Genetic findings and mutation spectrum in our JALS patients

WES was performed on the three newly recruited JALS patients. A novel variant (NM_006415.4: c.58G>A, p.A20T) within *SPTLC1* was identified in a sporadic JALS patient (patient 1, II-1 in Figure 1A) after WES analysis and Sanger sequencing, which was absent in his parents. Then, we performed haplotype analysis and confirmed that the variant was *de novo* [Figures 1A and 1B]. This variant was not observed in gnomAD, ExAC, ESP6500 and the 1000G database, nor in our in-house dataset comprising 1000 unrelated Chinese individuals. *In silico* prediction of this variant revealed an extremely deleterious possibility (Polyphen-2=0.999, REVEL=0.529, ClinPred=0.946, and CADD=25.3) and high evolutionary conservation among multiple species [Figure 1C]. The location of this variant was in exon 2, which differed from those mutations detected in HSAN1 patients [Figure 1D]. By using University of California, San Francisco Chimera version 1.15 (University of California, San Francisco, CA, USA), we found that the position of the 20th amino acid in SPTLC1 was close to ORMDL3 in the 3D protein

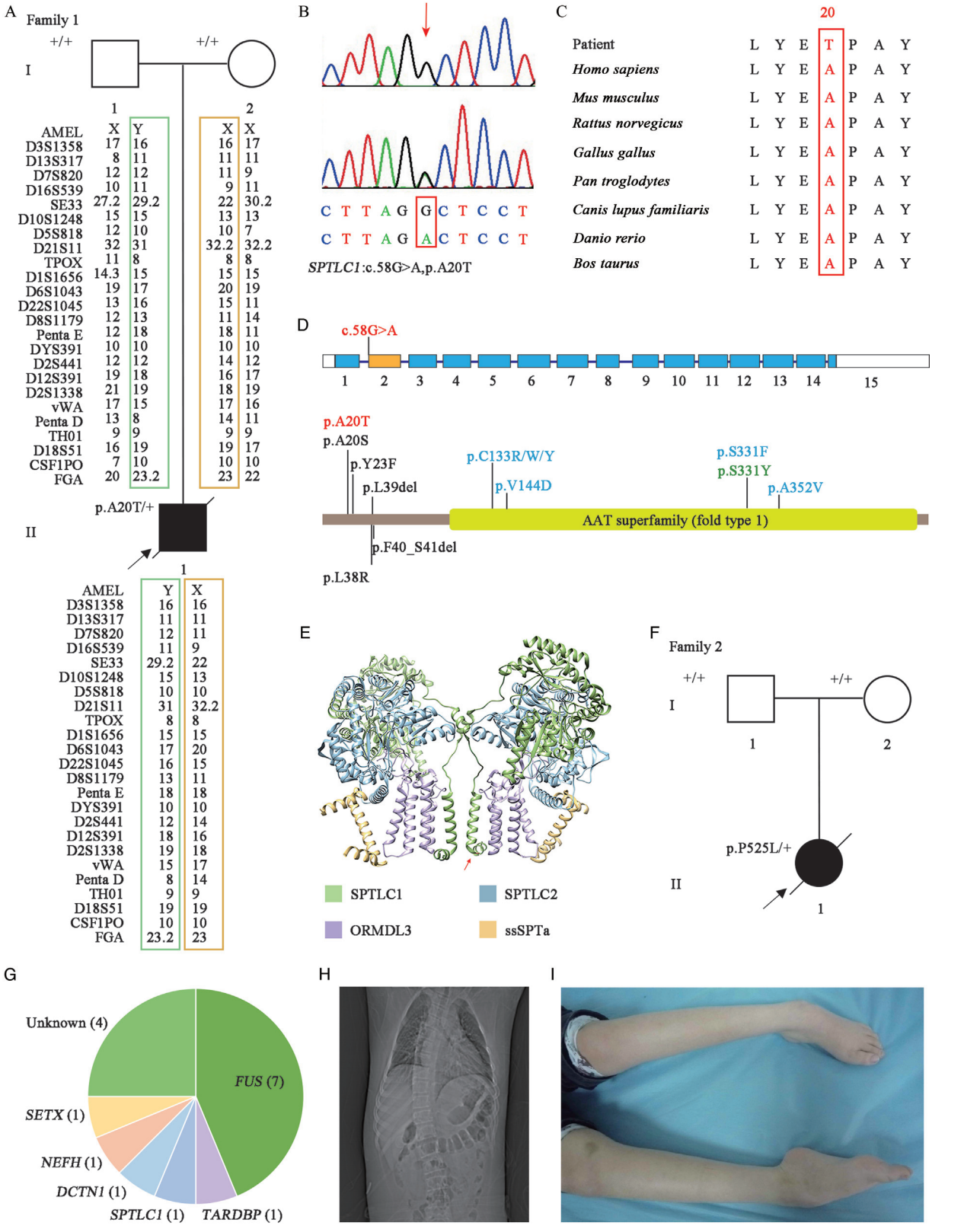

Figure 1: Genetic analysis in JALS patients and their clinical features. (A) Pedigree of Family 1 and haplotype analysis. Square indicates male; circle indicates female; solid symbol indicates affected individual, and arrow indicates the proband. (B) Sequence chromatograms of *SPTLC*1 mutation. The red arrow and red frame indicate the mutation site. (C) Amino acid conservation of the *SPTLC1* mutation in multiple species. The red frame indicates the 20th amino acid in *SPTLC1*. (D) Distribution of *SPTLC1* mutations (NM_006415.4) in JALS and HSAN1 patients. Mutations in HSAN1 are shown in blue; those in JALS are shown in black; and those in both HSAN1 and JALS are shown in green. The novel one is in red. (E) Three-dimensional structure of the human SPT complex: SPTLC1/SPLTC2/ssSPTa/ORMDL3. The red arrow indicates the position of the 20th amino acid in SPTLC1, which is close to ORMDL3. (F) Pedigree of Family 2. Square indicates male; circle indicates female; solid symbol indicates affected individual; and arrow indicates the proband. (G) Genetic spectrum in our JALS cohort. *FUS* mutations were identified in seven patients (43.8%), and mutations in *SPTLC1*, *SETX*, *NEFH*, *DCTN1*, and *TARDBP* were identified in one patient each. (H) X-ray film of the chest showed severe scoliosis in patient 1. (I) Photograph of the lower extremities from patient 1. The photo was taken at the age of 13 years in the last review and showed atrophy of the lower extremities and pes cavus. HSAN1: Hereditary sensory neuropathy type 1; JALS: Juvenile amyotrophic lateral sclerosis; SPT: Serine palmitoyltransferase.

structure [Figure 1E]. Based on the American College of Medical Genetics and Genomics Guideline (ACMG), the variant was classified as "pathogenic" (PS2 + PM1 + PM2 + PM5 + PP3). Moreover, we identified one known *FUS* mutation (NM_004960.4: c.1574C>T, p.P525L) in patient 2 [II-1 in Figure 1F], which was genetically confirmed as a *de novo* mutation by Sanger sequencing and haplotype analysis of parental DNA [Supplementary Table 1, http://links.lww.com/CM9/B339]. Therefore, as shown in Figure 1G, in our 16 JALS patients, 7/16 patients carried *FUS* mutations, including three with p.P525L mutation and four with different frameshift mutations. No pathogenic mutation in known ALS-related genes was detected in another 4/16 patients.

Clinical features of patients

Patient 1 carried the novel and *de novo* mutation within *SPTLC1* (c.58G>A, p.A20T) and was a boy with lower limb onset. When he was 7 years old, his parents noticed that he experienced toe walking. He could not run as fast as other children of the same age and was prone to falling down. Soon after, he developed walking difficulty and muscle weakness in his lower limbs. Three years later, the weakness gradually progressed to the bulbar muscles, and he had some trouble in drinking water and swallowing food. Neither sensory nor cognitive impairment was observed. Neurological examinations at the age of 10 years showed marked atrophy of the tongue as well as weakness of neck muscle (Muscle Strength Grading Scale 2/5). His muscle strength decreased remarkably in distal areas of the lower limbs (0/5) compared with other parts (4/5). The extremities' deep tendon reflexes were brisk. Hoffman's sign, ankle clonus, and Babinski sign were positive. EMG at that time revealed a reduced compound muscle action potential (CMAP) of the right median (2.8 mV) and peroneal motor nerves (0.8 mV). Nerve conduction velocities and sensory nerve action potential (SNAP) were normal [Supplementary Table 2, http://links.lww.com/CM9/B339]. Fibrillation potential, sharp waves, and prolonged polyphasic motor unit potentials were observed in the right first dorsal interosseous muscle, rectus abdominis, and tibialis anterior muscle. During a 9-year follow-up period, weakness and atrophy progressively worsened and spread to his whole body. He could not walk and became wheelchair-dependent five years after onset. He presented with severe scoliosis and pes cavus at the age of 13 years [Figures 1H and 1I]. When he was 15 years old, he became bedridden and was treated with non-invasive ventilation due to resting dyspnea. He died of cardiac arrest with a disease duration of 12 years and 4 months.

Patient 2 carried the reported *de novo* mutation within *FUS* (c.1574C>T, p.P525L) and was an 18-year-old girl who initially exhibited left arm weakness. Three months after onset, she had dysphonia and progressive weight loss. Four months after onset, she had difficulties in swallowing and drinking. Her sensation and cognition were not impaired. Neurological examinations revealed extensive muscle atrophy across her body. The thenar muscle, forearm muscle group, and gastrocnemius muscle on the left side showed moderate to severe atrophy, while those on the right side showed mild atrophy. The strength was 4/5 in the right limbs, 2/5 in the left upper limb, and 3/5 in the left lower limb. The deep tendon reflexes were depressed in the left limbs. EMG revealed a reduced CMAP of the right median (2.1 mV) and slightly reduced motor nerve conduction velocity. SNAP and sensory nerve conduction velocity were normal [Supplementary Table 2, http://links.lww.com/CM9/B339]. Fibrillation potential and sharp waves and prolonged polyphasic motor unit potentials were observed in the bulbar region, and acute denervation was observed in the cervical and lumbar regions. Five months after onset, she received gastrostomy and non-invasive ventilation. The patient died 13 months after onset.

Comparison of clinical features between JALS with SPTLC1 and FUS mutations

In total, 58 patients from 29 out of 32 articles met our inclusion criteria, including 16 JALS patients with *SPTLC1* mutations [Table 1] and 42 with *FUS* mutations [Supplementary Table 3, http://links.lww.com/CM9/B339]. Most *FUS* mutations tended to cluster in exons 14 and 15 of *FUS*, while *SPTLC1* mutations tended to cluster in exon 2 of *SPTLC1*. *De novo* mutagenesis is common in both genes. Clinical features such as AAO, onset site, respiratory failure, cognitive impairment, and disease duration were extracted manually for further analysis. The patients with *SPTLC1* mutations tended to have an earlier AAO and the initial symptoms of lower limb spasticity and toe walking with longer disease duration (512.0 [416.7–607.3] months). Instead, most JALS patients with *FUS* mutations first presented with limb onset and had a rapidly deteriorating course (33.4 [21.6–45.1] months) [Table 2]. Both groups of patients suffered respiratory failure at the end of disease duration. Patients with *FUS* mutations also had a large proportion of bulbar onset (37.2%, 16/43), while those with *SPTLC1* mutations only presented spinal onset. Sensory symptoms were presented in two JALS with *SPTLC1* mutations (11.8%, 2/17) manifested as numbness and glove-stocking pain loss. However, sensory symptoms were not presented in JALS patients with *FUS* mutations, but other features, such as mental retardation and developmental delay, appeared more commonly. We found that the majority of JALS patients with *SPTLC1* (88.2%, 15/17) and *FUS* (86.7%, 26/30) mutations presented with denervation on EMG. A small portion of JALS with *FUS* mutations (10.0%, 3/30) had prolonged central conducting times in motor-evoked potentials. Sensory involvement in EMG was presented in two patients with *SPTLC1* mutations (11.8%, 2/17), consistent with their sensory symptoms. Three cranial magnetic resonance imaging abnormalities were presented in patients with *FUS* mutations (15.0%, 3/20), while there were none presented in those with *SPTLC1* mutations.

To date, the majority of JALS patients with *SPTLC1* mutations was Caucasian, and some of them have a positive family history; by contrast, most JALS patients with *FUS* mutations are Asian and have a negative family history. Therefore, to exclude the influence of different genetic backgrounds, we compared the clinical features

Table 1: Clinical features of 17 JALS patients with *SPTLC1* mutations (including one patient reported in this study and 16 patients collected from 29 articles met our inclusion criteria).

Patient	Country	*SPTLC1* mutation	Exon	Inheritance pattern	Gender	AAO (years)	Onset site	Onset symptom	Respiratory failure	Sensory involvement	Cognitive impairment	Disease duration (years)	EMG (Motor)	EMG (Sensory)	Cranial and spinal MRI	Reference
1	China	p.A20T	2	*de novo*	M	7	Spinal	Toe walking	+	–	–	12.3	Axonal loss, denervation	Normal	NA	Our study
2	US	p.A20S	2	*de novo*	F	5	Spinal	LL spasticity	+	–	+	>15	Axonal loss, denervation	Normal	NA	Johnson *et al*[8]
3	US	p.A20S	2	*de novo*	F	<10	Spinal	LL weakness	NA	–	+	~10	Axonal loss, denervation	Normal	Normal	Johnson *et al*[8]
4	US	p.S331Y	11	*de novo*	F	4	Spinal	Toe walking	+	+	–	>7	Axonal loss, denervation	Axonal loss	Normal	Johnson *et al*[8]
5	Turkey	p.L39del	2	NA	F	15	Spinal	UL + LL weakness	–	–	NA	>19	Denervation	Normal	NA	Johnson *et al*[8]
6	US and CA	p.Y23F	2	*de novo*	F	4	Spinal	LL spasticity	+	–	–	>12	Axonal loss, denervation	Normal	NA	Mohassel *et al*[7]
7	US and CA	p.Y23F	2	*de novo*	F	3	Spinal	LL spasticity	–	–	–	>5	Axonal loss	Normal	NA	Mohassel *et al*[7]
8	US and CA	p.F40_S41del	2	*de novo*	F	4	Spinal	LL spasticity	+	–	–	>24	Axonal loss, denervation	Normal	NA	Mohassel *et al*[7]
9	US and CA	p.L39del	2	*de novo*	M	8	Spinal	Toe walking	+	–	–	>20	Axonal loss, denervation	Normal	NA	Mohassel *et al*[7]
10	US and CA	p.L39del	2	*de novo*	M	3	Spinal	Falls	–	–	–	>10	Axonal loss, denervation	Normal	NA	Mohassel *et al*[7]
11	US and CA	p.A20S	2	*de novo*	M	3	Spinal	Not able to run	+	–	–	>18	Axonal loss	Normal	NA	Mohassel *et al*[7]
12	US and CA	p.L39del	2	AD	M	15	Spinal	Ankle sprains	–	+	–	>47	Axonal loss, denervation	Axonal loss	NA	Mohassel *et al*[7]
13	US and CA	p.L39del	2	AD	F	16	Spinal	UL discoordination	–	–	–	>9	Axonal loss, denervation	Normal	NA	Mohassel *et al*[7]
14	US and CA	p.L39del	2	AD	F	14	Spinal	Abnormal gait	–	–	–	>11	Axonal loss, denervation	Normal	NA	Mohassel *et al*[7]
15	US and CA	p.L39del	2	AD	M	10	Spinal	Abnormal gait	–	–	–	>11	Axonal loss, denervation	Normal	NA	Mohassel *et al*[7]
16	US and CA	p.L39del	2	AD	F	6	Spinal	Abnormal gait	–	–	–	>13	Axonal loss, denervation	Normal	NA	Mohassel *et al*[7]
17	China	p.L38R	2	*de novo*	F	<10	Spinal	LL weakness and falls	+	–	NA	>0.2	Axonal loss, denervation	Normal	NA	Lone *et al*[9]

–: Absent; +: Present; AAO: Age at onset; AD: Autosomal dominant inheritance; CA: Canada; EMG: Electromyography; F: Female; JALS: Juvenile amyotrophic lateral sclerosis; LL: Lower limb; M: Male; MRI: Magnetic resonance imaging; NA: Not available; UL: Upper limb; USA: United States.

Table 2: Clinical features differ between JALS patients with *SPTLC1* and *FUS* mutations (including two patients reported in this study and 58 patients collected from 29 articles met our inclusion criteria).

Variables	JALS patients with *SPTLC1* mutations ($n = 17$)	JALS patients with *FUS* mutations ($n = 43$)	Statistics	*P* values
Gender ratio (male/female)	0.6 (6/11)	0.8 (19/24)	0.40*	0.53
AAO (years, mean ± SD)	7.9 ± 4.6	18.1 ± 3.9	8.64†	<0.01
Onset site, *n* (%)			8.40*	0.01
Bulbar	0	10 (23.3)		
Bulbar and spinal	0	6 (13.9)		
Spinal	17 (100)	27 (62.8)		
Disease duration (months, mean [95% CI])	512.0 (416.7–607.3)	33.4 (21.6–45.1)	26.32‡	<0.01

*χ^2 test. †Student's *t* test. ‡Kaplan–Meier analysis. AAO: Age at onset; CI: Confidence interval; JALS: Juvenile amyotrophic lateral sclerosis; SD: Standard deviation.

among different races of JALS patients with *SPTLC1* and *FUS* mutations and clinical features between JALS patients with *de novo SPTLC1* and *FUS* mutations. The results were similar to the above results [Supplementary Tables 4 and 5, http://links.lww.com/CM9/B339].

Discussion

Juvenile patients with ALS have high phenotypic heterogeneity, and more than ten causative genes have been identified in JALS to date. *FUS* mutations are most frequently seen in JALS patients.[10] We identified seven unrelated JALS patients (43.8%, 7/16) carrying *FUS* mutations in our previous studies,[11,12] and the current study. Combined with the results of the literature review, there were 43 JALS patients carrying 17 different mutations in total. The majority of *FUS* mutations occurs in the C-terminus (exons 14 and 15), affecting the nuclear localization signal of FUS. Among them, mutation c.1574C>T (p.P525L) accounted for 44.2% (19/43). Previous studies have shown phenotypic heterogeneity in patients carrying different mutations within *FUS*.[11,14] However, Chen[15] demonstrated that JALS patients with p.P525L/p.Y526C mutations had no difference in AAO and disease duration compared to those with other *FUS* mutations.

In a German cohort, *FUS* mutations were detected in four JALS patients (66.7%, 4/6), and three of them had the same mutation of c.1574C>T (p.P525L) (75.0%, 3/4).[10] Similar results were verified in another Chinese JALS cohort. Zou *et al*[16] identified four *FUS* mutations in 16 JALS patients, and the mutation of c.1574C>T (p.P525L) accounted for half (50.0%, 2/4). In our cohort, *FUS* mutations were the most common genetic cause and among them, the mutation of c.1574C>T (p.P525L) accounted for 42.9% (3/7), which was consistent with reports worldwide. Other disease-causing genes have rarely been reported in JALS patients; therefore, more studies are needed to depict the genetic and mutation spectrum of JALS patients.

Recently, *SPTLC1* was reported to be associated with JALS[7] which was first identified as a causative gene of HSAN1.[5] HSAN1-associated mutations were distributed in exons 5, 6, and 11, while ALS-associated mutations were mainly located in exon 2. Mutations in exon 2 enhanced SPT activity by weakening feedback inhibition of ORMDL3,[7,17] leading to disruption of sphingolipid homeostasis. JALS patients with *SPTLC1* mutations present with lower limb spasticity manifesting as toe walking or gait abnormalities at an early age, commonly before the age of 10 years, which can be easily misdiagnosed as hereditary spastic paraplegia (HSP) at an early stage. However, diffuse lower motor neuron involvement and EMG showing extensive neurogenic damage help to differentiate between ALS and HSP. In this study, we identified a novel mutation within *SPTLC1* (c.58G>A, p.A20T) in a sporadic patient with JALS. The patient with the *SPTLC1* mutation exhibited lower limb spasticity and weakness without sensory or cognitive impairment at the age of 7 years, and symptoms spread progressively within a 12.3-year disease course. In addition, our patient presented symmetrically remarked muscle weakness in distal areas of the lower limbs accompanied by severe scoliosis and pes cavus, which might be caused by an onset of the distal lower extremity and long disease duration. The mutation (c.58G>A, p.A20T) in *SPTLC1* was in exon 2 and identified as a *de novo* mutation. Altogether, the clinical or genetic characteristics of the patient were consistent with previous reports.[7,8]

After comparing the clinical features, we found that JALS patients with *SPTLC1* mutations showed earlier AAO and longer survival than those with *FUS* mutations. Interestingly, patients with *SPTLC1* mutations had no onset of bulbar, which may explain the mild progression they had, as patients with bulbar onset showed rapid progression.[18] These results help clinicians to distinguish the genotypes of JALS patients from their phenotypes at a clinical level, and genetic tests can support the diagnosis, which provides valuable prognostic information and therapeutic targets.

There are some limitations in this study. First, the sample size of newly recruited JALS was small. Furthermore, patients with *SPTLC1* mutations were relatively fewer than those with *FUS* mutations. Finally, to comprehensively summarize the clinical features, five JALS cases with *FUS* mutations from three articles without a detailed phenotypic description (disease duration) were excluded

during the literature retrieval. These limitations may affect the statistical results, which need to be confirmed by more studies.

In conclusion, we reported a novel *SPTLC1* mutation in a Chinese JALS patient, which expands the mutational and phenotypic spectrum of JALS. In addition, we summarized that JALS patients carrying *SPTLC1* mutations had an earlier AAO, longer survival and no onset of bulbar than those with *FUS* mutations, which helps to better understand the genotype–phenotype correlation of JALS.[19-40]

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Conflicts of interest

None.

References

1. van Es MA, Hardiman O, Chio A, Al-Chalabi A, Pasterkamp RJ, Veldink JH, *et al*. Amyotrophic lateral sclerosis. Lancet 2017;390:2084–2098. doi: 10.1016/S0140-6736(17)31287-4.
2. Orban P, Devon RS, Hayden MR, Leavitt BR. Chapter 15 juvenile amyotrophic lateral sclerosis. Handb Clin Neurol 2007;82:301–312. doi: 10.1016/S0072-9752(07)80018-2.
3. Lehky T, Grunseich C. Juvenile amyotrophic lateral sclerosis: a review. Genes 2021;12:1935. doi: 10.3390/genes12121935.
4. Breslow DK, Weissman JS. Membranes in balance: mechanisms of sphingolipid homeostasis. Mol Cell 2010;40:267–279. doi: 10.1016/j.molcel.2010.10.005.
5. Dawkins JL, Hulme DJ, Brahmbhatt SB, Auer-Grumbach M, Nicholson GA. Mutations in SPTLC1, encoding serine palmitoyltransferase, long chain base subunit-1, cause hereditary sensory neuropathy type I. Nat Genet 2001;27:309–312. doi: 10.1038/85879.
6. Penno A, Reilly MM, Houlden H, Laurá M, Rentsch K, Niederkofler V, *et al*. Hereditary sensory neuropathy type 1 is caused by the accumulation of two neurotoxic sphingolipids. J Biol Chem 2010;285:11178–11187. doi: 10.1074/jbc.M109.092973.
7. Mohassel P, Donkervoort S, Lone MA, Nalls M, Gable K, Gupta SD, *et al*. Childhood amyotrophic lateral sclerosis caused by excess sphingolipid synthesis. Nat Med 2021;27:1197–1204. doi: 10.1038/s41591-021-01346-1.
8. Johnson JO, Chia R, Miller DE, Li R, Kumaran R, Abramzon Y, *et al*. Association of variants in the SPTLC1 gene with juvenile amyotrophic lateral sclerosis. JAMA Neurol 2021;78:1236–1248. doi: 10.1001/jamaneurol.2021.2598.
9. Lone MA, Zeng S, Bourquin F, Wang M, Huang S, Lin Z, *et al*. SPTLC1 p.Leu38Arg, a novel mutation associated with childhood ALS. medRxiv 2022. doi: 10.1101/2022.02.07.22269609.
10. Hübers A, Just W, Rosenbohm A, Müller K, Marroquin N, Goebel I, *et al*. De novo FUS mutations are the most frequent genetic cause in early-onset German ALS patients. Neurobiol Aging 2015;36:3117.e1–3117.e6. doi: 10.1016/j.neurobiolaging. 2015.08.005.
11. Liu ZJ, Lin HX, Liu GL, Tao QQ, Ni W, Xiao BG, *et al*. The investigation of genetic and clinical features in Chinese patients with juvenile amyotrophic lateral sclerosis. Clin Genet 2017;92:267–273. doi: 10.1111/cge.13015.
12. Liu ZJ, Lin HX, Wei Q, Zhang QJ, Chen CX, Tao QQ, *et al*. Genetic spectrum and variability in Chinese patients with amyotrophic lateral sclerosis. Aging Dis 2019;10:1199–1206. doi: 10.14336/AD.2019.0215.
13. Ludolph A, Drory V, Hardiman O, Nakano I, Ravits J, Robberecht W, *et al*. A revision of the El Escorial criteria-2015. Amyotroph Lateral Scler Frontotemporal Degener 2015;16:291–292. doi: 10.3109/21678421.2015.1049183.
14. Naumann M, Peikert K, Günther R, van der Kooi AJ, Aronica E, Hübers A, *et al*. Phenotypes and malignancy risk of different FUS mutations in genetic amyotrophic lateral sclerosis. Ann Clin Transl Neurol 2019;6:2384–2394. doi: 10.1002/acn3.50930.
15. Chen L. FUS mutation is probably the most common pathogenic gene for JALS, especially sporadic JALS. Rev Neurol 2021;177:333–340. doi: 10.1016/j.neurol.2020.06.010.
16. Zou ZY, Liu MS, Li XG, Cui LY. Mutations in FUS are the most frequent genetic cause in juvenile sporadic ALS patients of Chinese origin. Amyotroph Lateral Scler Frontotemporal Degener 2016;17:249–252. doi: 10.3109/21678421.2016.1143012.
17. Han G, Gupta SD, Gable K, Bacikova D, Sengupta N, Somashekarappa N, *et al*. The ORMs interact with transmembrane domain 1 of Lcb1 and regulate serine palmitoyltransferase oligomerization, activity and localization. Biochim Biophys Acta Mol Cell Biol Lipids 2019;1864:245–259. doi: 10.1016/j.bbalip.2018.11.007.
18. Wolf J, Safer A, Wöhrle JC, Palm F, Nix WA, Maschke M, *et al*. Variability and prognostic relevance of different phenotypes in amyotrophic lateral sclerosis-data from a population-based registry. J Neurol Sci 2014;345:164–167. doi: 10.1016/j.jns.2014.07.033.
19. Yu X, Zhao Z, Shen H, Bing Q, Li N, Hu J. Clinical and genetic features of patients with juvenile amyotrophic lateral sclerosis with Fused in Sarcoma (FUS) mutation. Med Sci Monit 2018;24:8750–8757. doi: 10.12659/MSM.913724.
20. Zou ZY, Cui LY, Sun Q, Li XG, Liu MS, Xu Y, *et al*. De novo FUS gene mutations are associated with juvenile-onset sporadic amyotrophic lateral sclerosis in China. Neurobiol Aging 2013;34:e1–8. doi: 10.1016/j.neurobiolaging.2012.09.005.
21. Zhou B, Wang H, Cai Y, Wen H, Wang L, Zhu M, *et al*. *FUS* P525L mutation causing amyotrophic lateral sclerosis and movement disorders. Brain Behav 2020;10:e01625. doi: 10.1002/brb3.1625.
22. Wu Y, Li C, Yang T, Lin J, Shang H. A case of juvenile-onset amyotrophic lateral sclerosis with a de novo frameshift FUS gene mutation presenting with bilateral abducens palsy. Amyotroph Lateral Scler Frontotemporal Degener 2022;23:313–314. doi: 10.1080/21678421.2021.1927100.
23. Deng J, Wu W, Xie Z, Gang Q, Yu M, Liu J, *et al*. Novel and recurrent mutations in a cohort of Chinese patients with young-onset amyotrophic lateral sclerosis. Front Neurosci 2019;13:1289. doi: 10.3389/fnins.2019.01289.
24. Chen L, Li J, Lu H, Liu Y. A de novo c.1509dupA:p R503fs mutation of FUS: report of a girl with sporadic juvenile amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener 2020;21:635–637. doi: 10.1080/21678421.2020.1775256.
25. Eura N, Sugie K, Suzuki N, Kiriyama T, Izumi T, Shimakura N, *et al*. A juvenile sporadic amyotrophic lateral sclerosis case with P525L mutation in the FUS gene: a rare co-occurrence of autism spectrum disorder and tremor. J Neurol Sci 2019;398:67–68. doi: 10.1016/j.jns.2019.01.032.
26. Hikiami R, Yamakado H, Tatsumi S, Ayaki T, Hashi Y, Yamashita H, *et al*. Amyotrophic lateral sclerosis after receiving the human papilloma virus vaccine: a case report of a 15-year-old girl. Intern Med 2018;57:1917–1919. doi: 10.2169/internalmedicine.0285-17.
27. Hirayanagi K, Sato M, Furuta N, Makioka K, Ikeda Y. Juvenile-onset sporadic amyotrophic lateral sclerosis with a frameshift FUS gene mutation presenting unique neuroradiological findings and cognitive impairment. Intern Med 2016;55:689–693. doi: 10.2169/internalmedicine.55.5569.
28. Yamashita S, Mori A, Sakaguchi H, Suga T, Ishihara D, Ueda A, *et al*. Sporadic juvenile amyotrophic lateral sclerosis caused by mutant FUS/TLS: possible association of mental retardation with this mutation. J Neurol 2012;259:1039–1044. doi: 10.1007/s00415-011-6292-6.
29. Leblond CS, Webber A, Gan-Or Z, Moore F, Dagher A, Dion PA, *et al*. De novo FUS P525L mutation in juvenile amyotrophic lateral

sclerosis with dysphonia and diplopia. Neurol Genet 2016;2:e63. doi: 10.1212/NXG.0000000000000063.
30. Belzil VV, Langlais JS, Daoud H, Dion PA, Brais B, Rouleau GA. Novel FUS deletion in a patient with juvenile amyotrophic lateral sclerosis. Arch Neurol 2012;69:653–656. doi: 10.1001/archneurol.2011.2499.
31. Picher-Martel V, Brunet F, Dupré N, Chrestian N. The occurrence of *FUS* mutations in pediatric amyotrophic lateral sclerosis: a case report and review of the literature. J Child Neurol 2020;35:556–562. doi: 10.1177/0883073820915099.
32. Waibel S, Neumann M, Rosenbohm A, Birve A, Volk AE, Weishaupt JH, *et al*. Truncating mutations in FUS/TLS give rise to a more aggressive ALS-phenotype than missense mutations: a clinico-genetic study in Germany. Eur J Neurol 2013;20:540–546. doi: 10.1111/ene.12031.
33. Conte A, Lattante S, Zollino M, Marangi G, Luigetti M, Del Grande A, *et al*. P525L FUS mutation is consistently associated with a severe form of juvenile amyotrophic lateral sclerosis. Neuromuscul Disord 2012;22:73–75. doi: 10.1016/j.nmd.2011.08.003.
34. Lanteri P, Meola I, Canosa A, De Marco G, Lomartire A, Rinaudo MT, *et al*. The heterozygous deletion c.1509_1510delAG in exon 14 of FUS causes an aggressive childhood-onset ALS with cognitive impairment. Neurobiol Aging 2021;103:e1–130. e7. doi: 10.1016/j.neurobiolaging.2021.01.029.
35. Bodur M, Toker RT, Başak AN, Okan MS. A rare case of juvenile amyotrophic lateral sclerosis. Turk J Pediatr 2021;63:495–499. doi: 10.24953/turkjped.2021.03.017.
36. Dodd KC, Power R, Ealing J, Hamdalla H. FUS-ALS presenting with myoclonic jerks in a 17-year-old man. Amyotroph Lateral Scler Frontotemporal Degener 2019;20:278–280. doi: 10.1080/21678421.2019.1582665.
37. Bäumer D, Hilton D, Paine SM, Turner MR, Lowe J, Talbot K, *et al*. Juvenile ALS with basophilic inclusions is a FUS proteinopathy with FUS mutations. Neurology 2010;75:611–618. doi: 10.1212/WNL.0b013e3181ed9cde.
38. Hewitt C, Kirby J, Highley JR, Hartley JA, Hibberd R, Hollinger HC, *et al*. Novel FUS/TLS mutations and pathology in familial and sporadic amyotrophic lateral sclerosis. Arch Neurol 2010;67:455–461. doi: 10.1001/archneurol.2010.52.
39. DeJesus-Hernandez M, Kocerha J, Finch N, Crook R, Baker M, Desaro P, *et al*. De novo truncating FUS gene mutation as a cause of sporadic amyotrophic lateral sclerosis. Hum Mutat 2010;31:E1377–E1389. doi: 10.1002/humu.21241.
40. Huang EJ, Zhang J, Geser F, Trojanowski JQ, Strober JB, Dickson DW, *et al*. Extensive FUS-immunoreactive pathology in juvenile amyotrophic lateral sclerosis with basophilic inclusions. Brain Pathol 2010;20:1069–1076. doi: 10.1111/j.1750-3639.2010.00413.x.

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