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【 CASE REPORT 】

Sporadic Amyotrophic Lateral Sclerosis Due to a FUS P525L Mutation with Asymmetric Muscle Weakness and Anti-ganglioside Antibodies

Masanobu Tanemoto, Shin Hisahara, Kazuna Ikeda, Kazuki Yokokawa, Tatsuo Manabe, Reiko Tsuda, Daisuke Yamamoto, Takashi Matsushita, Akihiro Matsumura, Syuuichirou Suzuki and Shun Shimohama

Abstract:
Amyotrophic lateral sclerosis (ALS) due to a fused in sarcoma (FUS) P525L mutation is characterized by a rapidly progressive course. Multifocal motor neuropathy (MMN) may resemble ALS in early stage and is associated with anti-ganglioside antibodies. A 38-year-old woman was admitted to our hospital because of progressive muscle weakness in the right limbs. She had mild mental retardation and minor deformities. Initially, we suspected MMN given the asymmetric muscle weakness and detection of anti-ganglioside antibodies. However, physical and electrophysiological tests did not support MMN, instead suggesting ALS. We confirmed a heterozygous P525L mutation and finally diagnosed this case as ALS due to an *FUS* mutation.

Key words: amyotrophic lateral sclerosis, fused in sarcoma, FUS, P525L mutation, anti-ganglioside antibody

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Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder characterized by degeneration of both the upper and lower motor neurons. The fused in sarcoma (*FUS*) gene is one of the genes responsible for ALS, and the P525L mutation in particular tends to be associated with a rapidly progressive course (1).

Multifocal motor neuropathy (MMN) is an acquired chronic demyelinating neuropathy characterized by progressive asymmetric muscle weakness and amyotrophy. One of the supportive criteria of MMN is the presence of IgM antibodies to ganglioside GM1 (IgM-anti-GM1) (2). MMN sometimes manifests no overt motor conduction block, which is essential for the electrophysiological diagnosis of the disease (3). It can therefore be difficult to distinguish ALS from MMN when symptoms are limited to only one side in the early stage of the disease.

We herein report a case of sporadic ALS due to an *FUS* P525L mutation with remarkable asymmetric muscle weakness and positivity for anti-ganglioside antibodies. This is the first reported case of ALS due to an *FUS* mutation with anti-ganglioside antibodies.

Case Report

A 38-year-old woman was admitted to our hospital because of weakness originating in the right lower limb and extending to the right upper limb within a month. Her medical history was unremarkable. None of her family members had neurological disorders. She had been born via normal delivery.

Her height was 160 cm. She weighed 45.4 kg, and there was no apparent weight loss. Her body temperature was 36.7 °C, blood pressure was 114/64 mmHg, and heart rate was 96 beats per minute. Her respiratory rate was 12 breaths per minute, and SpO_2 was 97% in room air. She had mild mental retardation, low-set ears, micrognathia, cubitus valgus, and scoliosis (Fig. 1). Her consciousness was clear.

Department of Neurology, Sapporo Medical University, School of Medicine, Japan
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Correspondence to Dr. Shin Hisahara, hisahara@sapmed.ac.jp

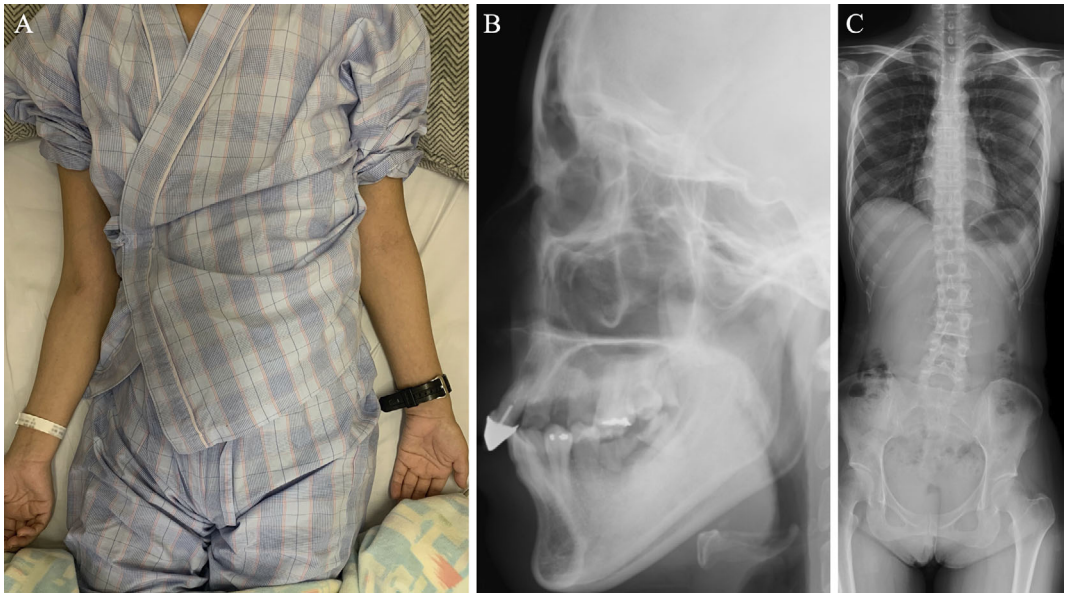

Figure 1. Clinical photographs. The patient showed cubitus valgus (A), micrognathia (B), and scoliosis (C).

Cranial nerves were normal. A physical examination revealed muscle weakness and mild amyotrophy and fasciculations in the right limbs but no definite symptoms in the left limbs. Sensory disturbance was absent. The autonomic nervous function was normal. The deep tendon reflexes were diffusely brisk, but the jaw jerk reflex was normal. Pathologic reflexes were absent. She was able to walk with a walker. Intelligence test using the Wechsler Adult Intelligence Scale III (WAIS-III) showed mildly reduced scores as follows: full-scale intelligence quotient (IQ), 70; verbal IQ, 71; and performance IQ, 71.

A complete blood count and routine biochemical tests were within normal ranges. Anti-acetylcholine receptor antibodies, anti-muscle specific tyrosine kinase antibodies, and anti-human T-cell lymphotropic virus type 1 antibodies were all negative. Cerebrospinal fluid examinations were normal. Magnetic resonance imaging (MRI) findings of the brain and cervical spine were normal. MRI findings of the brachial plexus were also normal. The vital capacity and forced vital capacity were reduced to 68% and 72%, respectively; however, the results of a blood gas analysis were normal. Needle electromyography showed widespread polyphasic motor unit potentials (Fig. 2), along with fasciculation potentials in the right limbs. A nerve conduction study revealed a decline in the compound muscle action potential (CMAP) amplitude in the right median, ulnar and tibial nerves but no conduction block and no delayed conduction velocity (Table 1). Sensory nerve action potentials (SNAPs) were normal in the bilateral median, ulnar, and sural nerves. These findings suggested motor axonal neuropathy or lower motor neuron degeneration followed by motor axonal degeneration limited to the right limbs.

We initially suspected MMN, partially because 8% of patients with MMN show brisk tendon reflexes (4), and it has been reported that MMN sometimes does not show overt motor conduction block (3). Serum antibodies against 10 glycolipids comprising GM1, GM2, GM3, GD1a, GD1b, GD3, GT1b, GQ1b, galactocerebroside (Gal-C), and GalNAc-GD1a were investigated using an enzyme-linked immunosorbent assay (ELISA) as described previously (5, 6). A serum sample was positive for IgM-anti-GM 1 antibodies, which supported a diagnosis of MMN, and was also positive for IgM antibodies to ganglioside GalNAc-GD1a (IgM-anti-GalNAc-GD1a) and IgG antibodies to GalNAc-GD1a (IgG-anti-GalNAc-GD1a). However, motor evoked potentials revealed a prolonged central motor conduction time (CMCT) monitored in the right abductor pollicis brevis (Table 2), indicating upper motor neuron abnormalities, which did not support a diagnosis of MMN.

ALS was then suspected because of the combination of both lower and upper motor neuron abnormalities. We analyzed the antibody against the serum sulfoglucuronosyl paragloboside (SGPG) using an ELISA because about 10% of patients with ALS have this antibody (7), and it was below the cut-off value (1:3,200). An *FUS* mutation was suspected due to the young onset and rapid progression, and *FUS* was analyzed by Sanger sequencing after obtaining the patient's informed consent. We confirmed a heterozygous p.P525L (c.1574C>T) mutation in exon 15 and finally diagnosed the patient with ALS due to an *FUS* mutation (*FUS*-ALS) (Fig. 3). Within five weeks after admission, muscle weakness had spread to the left limbs, and she needed support to stand up because of muscle weakness in both lower limbs. In addition, dysphagia appeared as a bulbar symptom.

The patient eventually chose to undergo tracheostomy on day 229 and gastrostomy on day 252 and was transferred to a long-term care hospital.

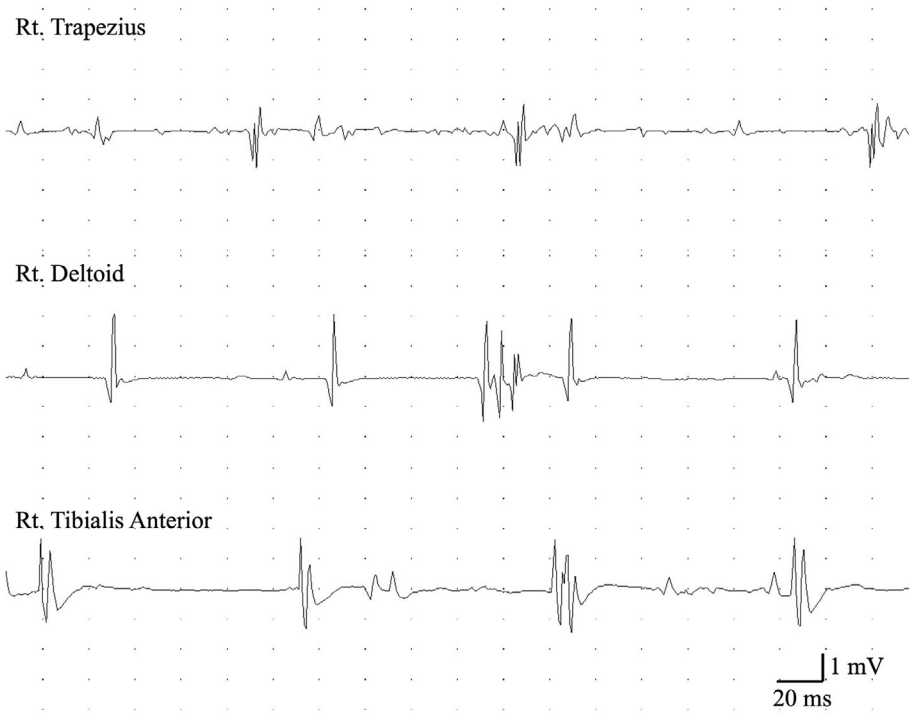

Figure 2. **Needle electromyography showed widespread polyphasic motor unit potentials in the right trapezius, deltoid, and tibialis anterior muscles.**

Table 1. **Results of Motor Nerve Conduction Study.**

	DL (ms)	Amp (mV)	CV (m/s)
Rt. Median	3.3	4.5	56
Lt. Median	2.8	9.5	59
Rt. Ulnar	2.4	5.5	54
Lt. Ulnar	NR	NR	NR
Rt. Tibial	4.4	3.2	45
Lt. Tibial	3.3	10.4	49

DL: distal latency; Amp: amplitude, CV: conduction velocity; NR: not recorded

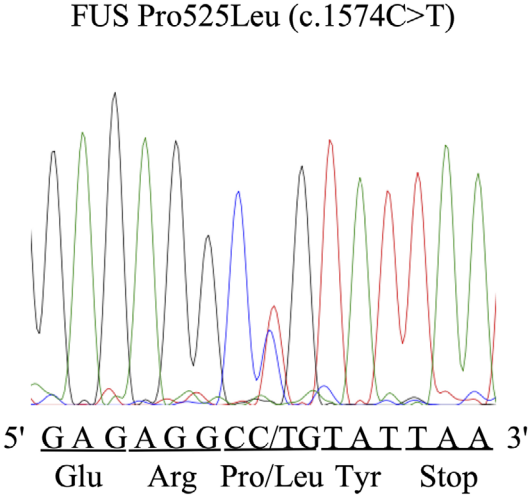

Figure 3. **The results of a genetic analysis of *FUS*. The heterozygous p.P525L (c.1574C>T) mutation was detected.**

Table 2. **Results of Motor Evoked Potentials in the Abductor Pollicis Brevis.**

	Threshold (%)	Latency (ms)	CMCT (ms)
Lt. Cortical stim	58	22.0	9.3
Rt. Cervical stim	30	12.7	
Rt. Cortical stim	70	17.9	7.0
Lt. Cervical stim	15	10.9	

CMCT: central motor conduction time

Discussion

We reported a case of sporadic ALS due to an FUS P525 L mutation with asymmetric muscle weakness and anti-ganglioside antibodies. *FUS* mutations are responsible for approximately 1% of clinical sporadic ALS cases, and FUS P525L mutation has been identified in some sporadic cases (1, 8). In addition, this mutation has been reported to be associated with a juvenile onset (mean age of onset: 21 years old) and severely rapid progression (mean disease duration: 13.7 months) (9). The present patient showed two atypical findings compared with previously reported cases of ALS with an *FUS* P525L mutation. First, this was the first reported case of *FUS*-ALS with anti-ganglioside antibodies. Second, the patient had minor deformities accompanied by mild mental retardation.

Gangliosides are sialylated glycosphingolipids that are most abundant in the nervous system and are reported to play an important role in neuroplasticity (10). Autoantibodies against gangliosides are found in several immune-

Table 3. The Previous Reports of ALS Due to FUS P525L Mutation with Characteristic Findings.

Reference	Case	Sex	Age Onset (year)	Survival (m)	Family History	Onset site	Bulbar	LMN	UMN	EMG	Characteristic findings
(27)	1	F	13	20	-	Limb	-	+	+	Acute, chronic	Developmental delay, learning difficulty
(28)	2	F	13	15	+	Limb	+	+	NR	NR	Developmentaldelay, ophthalmoparesis
(29)	3	F	21	6	-	Bulbar	+	+	+	Acute, chronic	Ptosis, diplopia
(30)	4	F	19	8	-	Bulbar	+	+	-	Normal	Autism, learning disability, postural tremor
(9)	5	M	19	7	-	Limb	-	+	+	Acute, chronic	Ophthalmoplegia, tremor, developmental delay, learning difficulty, adventitious movements
(9)	6	M	34	13	-	Bulbar	+	+	+	Acute, chronic	Adventitious movements
This case	7	F	38	7	-	Limb	+	+	+	Acute, chronic	Developmental delay, minor deformities, anti-ganglioside antibodies

LMN: lower motor neuron, UMN: upper motor neuron, EMG: electoromyography, NR: not recorded

mediated diseases, such as Guillain-Barré syndrome (11), MMN, and chronic inflammatory demyelinating polyradiculoneuropathy (12). The presence of IgM-anti-GM1 is a supportive criterion for a diagnosis of MMN (2), and the detection of IgM-anti-GalNAc-GD1a and IgG-anti-GalNAc-GD1a has been reported for this disease (13). GM1 is expressed at higher concentrations in ventral roots than in dorsal roots (14), and GalNAc-GD1a is also expressed in the ventral roots and intramuscular nerves (15). In contrast, anti-ganglioside antibodies can be found in various neurodegenerative disorders, such as Parkinson's disease, Alzheimer's disease, and ALS (16). In ALS, IgM-anti-GM1 was reported to be present in 9-57% of the cases (16), while IgG-anti-GalNAc-GD1a was reported in only 1 case (17). Furthermore, the presence of anti-SGPG antibodies has been suggested to be a potential progressive marker of ALS, although these antibodies were not detected in the present case (7).

Our case was positive for IgM-anti-GM1, IgM-anti-GalNAc-GD1a, and IgG-anti-GalNAc-GD1a and had remarkable asymmetric progressive muscle weakness. In familial ALS with *FUS* mutations, an onset in bulbar, neck, or proximal upper limbs with subsequent spreading to the lower limbs is a characteristic feature (18, 19). Several cases of *FUS*-ALS showed an asymmetric onset in the case series (20). In the present case, symptoms manifested in the lower limbs at the onset and then spread to include bulbar involvement in the later stage. These clinical findings made a diagnosis of ALS difficult. However, motor evoked potentials showed prolonged CMCT, indicating upper motor neuron abnormalities (21), and a nerve conduction study confirmed the absence of motor conduction block. In addition, dysphagia appeared as a bulbar symptom, and muscle atrophy spread throughout the whole body. These findings did not support a diagnosis of MMN, instead suggesting ALS.

Recently, lipid metabolism associated with apoptosis as a mechanism of motor neuron degeneration has been intensely studied (22). However, the pathogenicity of anti-ganglioside antibodies in ALS remains controversial (23). In ALS model mice with a superoxide dismutase 1 (*SOD1*) mutation, the activity of hexosaminidase, which is an enzyme that metabolizes some gangliosides, has been shown to be increased in the motor neurons of the spinal cord (24, 25). In addition, the inhibition of glycosphingolipids synthesis in the same model mice exacerbated disease progression (26), suggesting the important role of gangliosides in the pathogenesis of ALS. The relationship between gangliosides and *FUS* mutations has not been studied. In the present case, it is unknown whether the antibodies to GM1 and GalNAc-GD1a were elevated due to the disease or because of the lower degree of motor degeneration. However, antibodies may have been produced against GM1 and GalNAc-GD1a that leaked into the blood because of abnormal metabolism or the degeneration of motor neurons and axons.

The patient had minor deformities accompanied by mild mental retardation. A review of the literature found characteristic clinical findings in some cases of ALS with an *FUS* P525L mutation (Table 3) (9, 27-30). Although ALS due to an *FUS* P525L mutation with congenital deformities has not been reported, a case of *FUS*-ALS due to a c.1554_1557delACAG mutation manifesting congenital deformities in both feet has been reported (31). These deformities were interpreted as a forme fruste of arthrogryposis, and the patient also had mild learning difficulties. Four cases of juvenile ALS with an *FUS* P525L mutation showing mental retardation or developmental disabilities have been described (Table 3). According to a previous report, the loss of proline-tyrosine nuclear localization signal activity may be associated with abnormalities in the intellectual function (32).

This report describes for the first time a case of *FUS*-ALS with anti-ganglioside antibodies. In addition, ALS with an *FUS* P525L mutation may manifest physical and intellectual abnormalities, suggesting the existence of various phenotypes of this mutation. Further biochemical and pathological evaluations are needed to elucidate the association between *FUS* mutations and gangliosides and the effects of *FUS* mu-

tations over a broader area of the central nervous system.

The authors state that they have no Conflict of Interest (COI).

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References

1. Lattante S, Rouleau GA, Kabashi E. TARDBP and FUS mutations associated with amyotrophic lateral sclerosis: summary and update. Hum Mutat **34**: 812-826, 2013.
2. Join task force of the EFNS and the PNS. European federation of neurological societies/peripheral nerve society guideline on management of multifocal motor neuropathy. Report of a joint task force of the European federation of neurological societies and peripheral nerve society-first revision.. J Peripher Nerv Syst **15**: 295-301, 2010.
3. Pakiam ASI, Parry GJ. Multifocal motor neuropathy without overt conduction block. Muscle Nerve **21**: 243-245, 1998.
4. Cats EA, van der Pol WL, Piepers S, et al. Correlates of outcome and response to IVIg in 88 patients with multifocal motor neuropathy. Neurology **75**: 818-825, 2010.
5. Kusunoki S, Chiba A, Kon K, et al. N-acetylgalactosaminyl GD1a is a target molecule for serum antibody in Guillain-Barré syndrome. Ann Neurol **35**: 570-576, 1994.
6. Kaida K, Kusunoki S, Kamakura K, Motoyoshi K, Kanazawa I. Guillain-Barré syndrome with antibody to a ganglioside, N-acetylgalactosaminyl GD1a. Brain **123**: 116-124, 2000.
7. Li D, Usuki S, Quarles B, Rivner MH, Ariga T, Yu RK. Anti-sulfoglucuronosyl paragloboside antibody: a potential serologic marker of amyotrophic lateral sclerosis. ASN Neuro **8**: 1759091416669619, 2016.
8. Lai SL, Abramzon Y, Schymick JC, et al. FUS mutations in sporadic amyotrophic lateral sclerosis. Neurobiol Aging **32**: 550 (e1-4), 2011.
9. Zhou B, Wang H, Cai Y, et al. FUS P525L mutation causing amyotrophic lateral sclerosis and movement disorders. Brain Behav **10**: e01625, 2020.
10. Wanleenuwat P, Iwanowski P, Kozubski W. Antiganglioside antibodies in neurological diseases. J Neurol Sci **408**: 116576, 2020.
11. Kaida K, Ariga T, Yu RK. Antiganglioside antibodies and their pathophysiological effects on Guillain-Barré syndrome and related disorders-a review. Glycobiology **19**: 676-692, 2009.
12. Antoine JC, Camdessanché JP, Ferraud K, Caudie C. Antiganglioside antibodies in paraneoplastic peripheral neuropathies. J Neurol Neurosurg Psychiatry **75**: 1765-1767, 2004.
13. Kaji R, Kusunoki S, Mizutani K, et al. Chronic motor axonal neuropathy associated with antibodies monospecific for N-acetylgalactosaminyl GD1a. Muscle Nerve **23**: 702-706, 2000.
14. Ogawa-Goto K, Funamoto N, Ohta Y, Abe T, Nagashima K. Myelin gangliosides of human peripheral nervous system: an enrichment of GM1 in the motor nerve myelin isolated from cauda equina. J Neurochem **59**: 1844-1849, 1992.
15. Kaida K, Kusunoki S, Kamakura K, Motoyoshi K, Kanazawa I. GalNAc-GD1a in human peripheral nerve: target sites of anti-ganglioside antibody. Neurology **61**: 465-470, 2003.
16. Ariga T. Pathogenic role of ganglioside metabolism in neurodegenerative diseases. J Neurosci Res **92**: 1227-1242, 2014.
17. Yamazaki T, Suzuki M, Irie T, Watanabe T, Mikami H, Ono S. Amyotrophic lateral sclerosis associated with IgG anti-GalNAc-GD1a antibodies. Clin Neurol Neurosurg **110**: 722-724, 2008.
18. Tateishi T, Hokonohara T, Yamasaki R, et al. Multiple system degeneration with basophilic inclusions in Japanese ALS patients with FUS mutation. Acta Neuropathol **119**: 355-364, 2010.
19. Akiyama T, Warita H, Kato M, et al. Genotype-phenotype relationships in familial amyotrophic lateral sclerosis with FUS/TLS mutations in Japan. Muscle Nerve **54**: 398-404, 2016.
20. Groen EJ, van Es MA, van Vught PW, et al. FUS mutations in familial amyotrophic lateral sclerosis in the Netherlands. Arch Neurol **67**: 224-230, 2010.
21. Vucic S, Ziemann U, Eisen A, Hallett M, Kiernan MC. Transcranial magnetic stimulation and amyotrophic lateral sclerosis: pathophysiological insights. J Neurol Neurosurg Psychiatry **84**: 1161-1170, 2013.
22. Guégan C, Vila M, Rosoklija G, Hays AP, Przedborski S. Recruitment of the mitochondrial-dependent apoptotic pathway in amyotrophic lateral sclerosis. J Neurosci **21**: 6569-6576, 2001.
23. Kollewe K, Wurster U, Sinzenich T, et al. Anti-ganglioside antibodies in amyotrophic lateral sclerosis revisited. PLoS ONE **10**: e 0125339, 2015.
24. Lobsiger CS, Boillée S, Cleveland DW. Toxicity from different SOD1 mutants dysregulates the complement system and the neuronal regenerative response in ALS motor neurons. Proc Natl Acad Sci USA **104**: 7319-7326, 2007.
25. Baker DJ, Blackburn DJ, Keatinge M, et al. Lysosomal and phagocytic activity is increased in astrocytes during disease progression in the SOD1 (G93A) mouse model of amyotrophic lateral sclerosis. Front Cell Neurosci **9**: 410, 2015.
26. Dodge JC, Treleaven CM, Pacheco J, et al. Glycosphingolipids are modulators of disease pathogenesis in amyotrophic lateral sclerosis. Proc Natl Acad Sci USA **112**: 8100-8105, 2015.
27. Huang EJ, Zhang J, Geser F, et al. Extensive FUS-immunoreactive pathology in juvenile amyotrophic lateral sclerosis with basophilic inclusions. Brain Pathol **20**: 1069-1076, 2010.
28. Mochizuki Y, Isozaki E, Takao M, et al. Familial ALS with FUS P 525L mutation: two Japanese sisters with multiple systems involvement. J Neurol Sci **323**: 85-92, 2012.
29. Leblond CS, Webber A, Gan-Or Z, et al. De novo FUS P525L mutation in juvenile amyotrophic lateral sclerosis with dysphonia and diplopia. Neurol Genet **2**: e63, 2016.
30. Eura N, Sugie K, Suzuki 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 **398**: 67-68, 2019.
31. Bäumer D, Hilton D, Paine SML, et al. Jevenile ALS with basophilic inclusions is a FUS proteinopathy with FUS mutations. Neurology **75**: 611-618, 2010.
32. Yamashita S, Mori A, Sakaguchi H, et al. Sporadic juvenile amyotrophic lateral sclerosis caused by mutant FUS/TLS: possible association of mental retardation with this mutation. J Neurol **259**: 1039-1044, 2012.