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Letter to the Editor

A juvenile sporadic amyotrophic lateral sclerosis case with P525L mutation in the FUS gene: A rare co-occurrence of autism spectrum disorder and tremor

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Dear Editor,

p.P525L mutation in the *fused in sarcoma* (*FUS*) gene has been detected in patients with amyotrophic lateral sclerosis (ALS), characterized by early onset and a severely progressive course. We describe a 19-year-old woman who was admitted to our hospital because of rapidly progressive dysarthria and dysphagia, developing over the course of 3 months. She had no family history of neurological diseases including essential tremor and no consanguineous history. Her delivery was non-eventful. In elementary school, her school records were not so bad, but she was not able to get along with her classmates. In addition, she was given a diagnosis of learning disability and autism spectrum disorder by a pediatrician. She therefore went to a special school for handicapped children, instead of junior high school and high school. On admission, she showed dysarthria, a nasal voice, dysphagia, and atrophied tongue with fasciculation. She could not close her eyes perfectly or elevate both corners of the mouth, indicating facial muscle weakness. The muscle strength of the proximal upper limbs and neck were grade 4, and that of the distal upper limb and lower limbs were grade 5 according to the Medical Research Council scale. Deep tendon reflexes were increased, but pathological reflexes were absent. She had showed postural tremor since before onset of any weakness, especially when using a pen or chopsticks. There was no evidence of Parkinsonism, sensory disturbance, or autonomic dysfunction. On laboratory tests, the complete blood count, biochemical screening, lactic acid, and pyruvic acid were all negative for abnormalities. Cerebrospinal fluid tests, MRI of brain and spine were also normal. A spirogram disclosed decreased forced vital capacity (FVC; 54%), while the results of an arterial blood gas test were normal (pH 7.403, $PaCO_2$ 38.8 mm Hg, PaO_2 97.5 mm Hg). The results of a nerve conduction study were normal, and needle electromyography showed no acute or chronic denervation in the limbs. A biopsy of the left biceps muscle showed large group atrophy and no vacuoles, suggesting a neurogenic process. The immunohistochemical stains, including p62/SQSTM1, Tau, SMI-31, TDP-43, and FUS, showed no abnormal aggregation in muscle fibers (Fig. 1). After obtaining informed consent, genomic DNA was extracted from peripheral blood. All exons of the *SOD1* and *FUS* genes, whose mutations are popular in familial ALS in Japan, were analyzed by polymerase chain reaction (PCR) followed by direct DNA sequencing. The patient was negative for *SOD1* mutation, but had an identical p.P525L (c.1574C > T) variant, resulting in a missense mutation in exon 15 (Fig. 1B). On the basis of these findings, we diagnosed amyotrophic lateral sclerosis caused by *FUS* gene mutation.

Bulbar symptoms and muscle weakness, particularly remarkable in the proximal upper limb and neck, progressed very rapidly. Six months after onset, she could not walk alone because of instability of the neck and trunk. She complained of dyspnea and of difficulty in oral intake. At that time, an arterial blood gas test revealed hypercapnia (PCO_2 54.9 mm Hg). Thus, she received tube feeding and tracheostomy. Eight months after onset, she became bedridden and required mechanical ventilation.

FUS mutations have been reported to be responsible for 4% of familial ALS [1] and for less than 1% of sporadic ALS [2], illustrating their rarity. Among these mutations, p.P525L *FUS* mutation has been reported to be consistently associated with young onset, rapid disease course, and high proportions of *de novo* mutations in sporadic patients [3]. In previous studies, Conte et al. presented 10 patients (7 unrelated patients) [3], Sproviero et al. 2 patients [4] and Leblond et al. 1 patient [5] with p.P525L mutations in *FUS*. Seven of these patients (54%) were sporadic ALS. The mean age at disease onset was 22.1 years old, and the disease progression was very rapid in all patients, with a mean interval between onset and death or tracheostomy of 16.7 months.

Interestingly, our patient had two novel findings as compared with previously reported cases of ALS with p.P525L mutation in the *FUS* gene. First, our patient had postural tremor and could not use a pen or chopsticks skillfully. Because her distal-limb muscle strength was

Abbreviations: ALS, amyotrophic lateral sclerosis; FUS, fused in sarcoma

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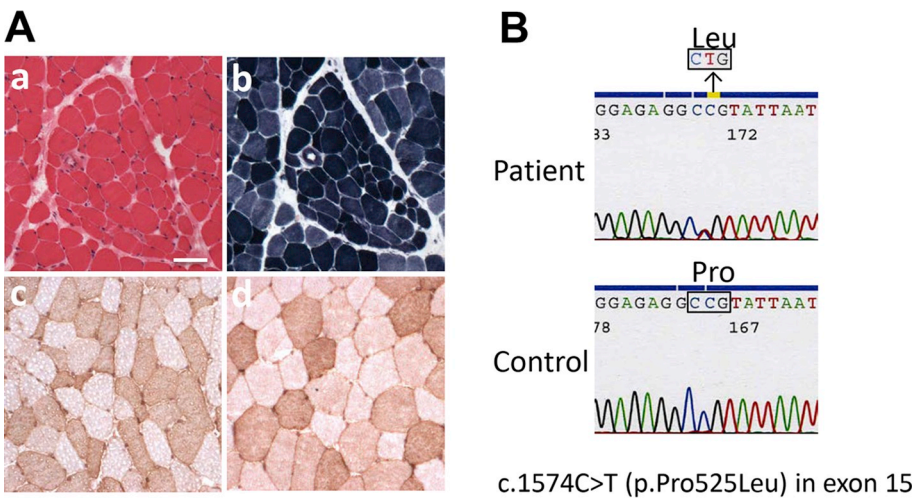

Fig. 1. A. Histochemical and immunohistochemical findings. Transverse sections of skeletal muscle specimens in ALS patients with p.P525L mutation in the *FUS* gene (A, B, C) and in a morphologically normal control (D). Group fiber atrophy and fiber type grouping were detected (A, B). On FUS immunohistochemical staining, FUS was localized in the nuclei of muscle fibers and no abnormal aggregations were seen in the patient (C) or normal control (D). (A) Hematoxylin and eosin stain. (B) Nicotinamide adenine dinucleotide-tetrazolium reductase stain. (C) (D) Immunohistochemical staining with primary antibody against FUS. *Bar* = 10 μm. B. Genetic analysis of *fused in sarcoma* (*FUS*) gene.
A heterozygous missense mutation, c.1574C > T (p.P525L), was identified in the patient.

normal, the tremor couldn't be explained by muscle weakness. Recently, *FUS* gene mutation, p.Gln290*, was shown to be a cause of essential tremor without ALS by Merner et al. [6]. They also showed that nonsense mutation was degraded by nonsense-mediated-decay pathway in essential tremor, but not in ALS. They consequently claimed that the pathological mechanism of essential tremor differs from that of ALS. In our case, both ALS and tremor may have been caused in our patient by p.P525L mutation *via* a distinct mechanism not involving p.Gln290*. Although neuropathological evaluations were not done, our patient may provide important clues to better understanding the relations between ALS and essential tremor with *FUS* mutations.

As the second novel finding, our patient had learning disability and autism spectrum disorder before the onset of ALS. There have been some reports of juvenile ALS with mental retardation or psychiatric disorders. In those reports, various mutations, including S96del, G492EfsX527, G497AfsX527, and R514S, were described, whereas p.P525L mutation was not [7]. Indeed, learning disability or autism spectrum disorder is generally common, but these reports may suggest relations between ALS and intellectual disability. Considering that cases with mental retardation associated with frameshift mutation or mutations at C-terminal of *FUS*, the proline-tyrosine (PY)-type nuclear localization signal may be responsible for intellectual function [7].

In addition, this is the first case report of ALS with p.P525L *FUS* mutation in which muscle pathology was evaluated. As for neuropathology, we previously reported that neuronal and glial FUS-immunoreactive inclusions were found in the brain and spinal cord of 3 autopsy cases of ALS with *FUS* mutation [8]. In our study, the immunohistochemical findings of skeletal muscle, including FUS, showed no abnormal inclusions or aggregations, suggesting *FUS* mutation does not directly affect muscle pathology.

In conclusion, ALS with p.P525L mutation in the *FUS* gene can cause autism spectrum disorder and tremor. *FUS* mutations can affect a broader range of function in addition to motor neuron degeneration. Further studies including pathological evaluations should be performed to establish the genotype-phenotype relations in ALS with p.P525L mutation in the *FUS* gene.

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Ethical standards

Our patient gave fully informed consent before publication.

Conflicts of interest

None of the authors has any conflict of interest to disclose.

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