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DE NOVO *FUS* P525L MUTATION IN JUVENILE AMYOTROPHIC LATERAL SCLEROSIS WITH DYSPHONIA AND DIPLOPIA

OPEN

Juvenile amyotrophic lateral sclerosis (jALS) is characterized by progressive upper and lower motor neuron degeneration leading to facial muscle spasticity, spastic dysarthria, and spastic gait with an early onset (before 25 years old). Unlike adult-onset amyotrophic lateral sclerosis (ALS), patients with jALS tend to have slower progression of motor neuron disease and prolonged survival to a normal life expectancy. Mutations in *FUS* gene have been reported in jALS,¹ including p.P525L mutation that has been consistently associated with early onset and aggressive presentation.² Here, we report a patient carrying p.P525L *FUS* mutation and experiencing an aggressive course of ALS presenting with dysphonia and diplopia.

The patient was a 21-year-old woman who initially reported progressive dysphonia followed by the development of diplopia. She was previously healthy with no known family history of neuromuscular disorders. Four months after her initial presentation, she developed bilateral ptosis and weakness of her upper extremities. Her weakness was initially subtle in the right deltoids (4+/5 strength), with ptosis and dysphonia being her primary concerns. MRI of brain and cervical spine were reported as normal. Six months after her initial presentation, she developed a viral upper respiratory tract infection and a new head droop and dyspnea, which prompted her intubation only days after her hospitalization. Repeat brain and cervical spine MRI were negative; however, EMG disclosed lower motor neuron dysfunction with no sensory involvement. She received several courses of IV immunoglobulin and plasma exchange with no clinical improvement. The condition of the patient continued to worsen, and she was transferred to our institution for further workup. Clinically, she was alert, with no obvious signs of cognitive impairment. Examination of the cranial nerves revealed limited upgaze and substantially slowed saccades. Extraocular (EO) movements were restricted in all directions, and she reported diplopia in all extremes of vision. She had bilateral ptosis and facial, tongue, and sternocleidomastoid weakness with extensive fasciculations. Motor examination revealed spasticity of the lower extremities,

with decreased bulk in the upper extremities and diffuse fasciculations. She had substantial proximal weakness in the upper extremities, with no observable movement in the deltoids, but somewhat greater strength in her hands and lower extremities. There were brisk reflexes in all 4 extremities, with downgoing plantar reflexes. The rest of the neurologic examination was unremarkable.

Structural, inflammatory, toxic, paraneoplastic, and other causes were ruled out. A repeat EMG was performed and revealed active denervation with intact sensory nerve conduction. The p.P525L *FUS* mutation was identified in the patient by Sanger sequencing, and segregation analysis across the family showed that the mutation appeared de novo (figure, appendix e-1 at Neurology.org/ng).

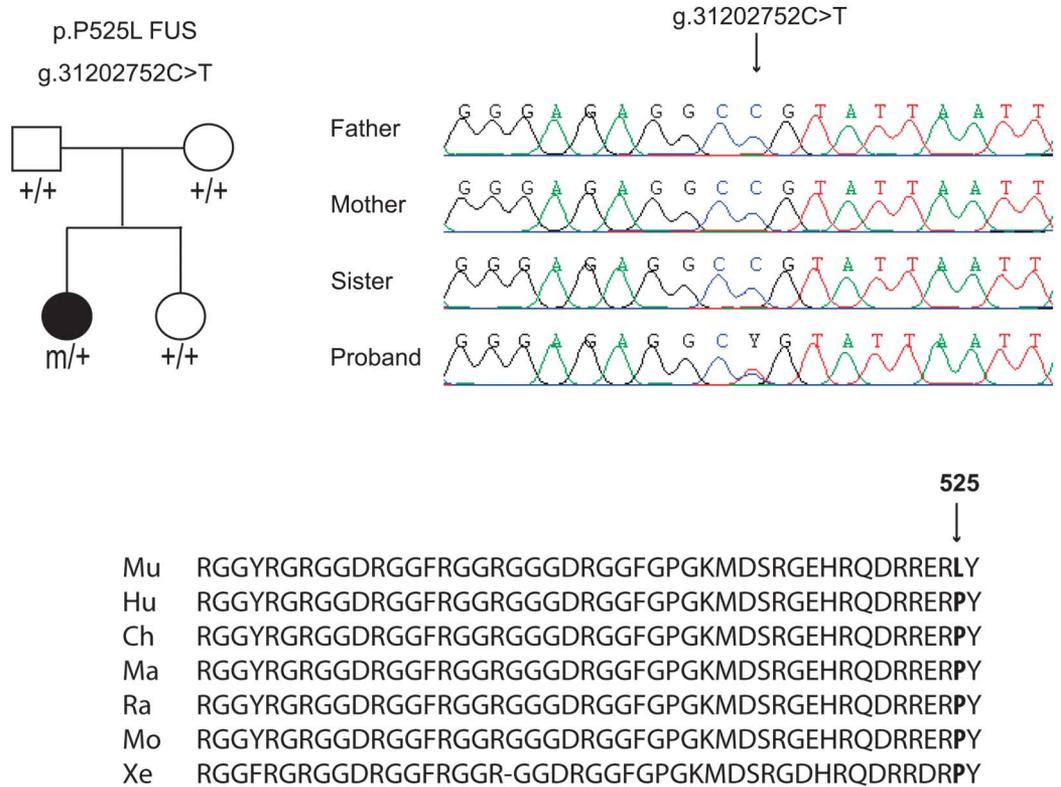
On follow-up examination 1.5 years later, the patient remained in a long-term care hospital, ventilated. She was able to follow commands, although her responses were limited to minimal cranial nerve functions only. She had very slow saccades with limitations of her EO movements in all directions. Cranial nerve examination revealed only +2/5 strength in the buccinator muscle and a flicker of tongue movement. The motor examination revealed flaccid tone, profound wasting in all muscle groups, and no movement in the upper and lower extremities, without elicitation of reflexes. Her parents and siblings at the time of follow-up were asymptomatic and otherwise healthy.

This case is an atypical presentation of ALS because of the involvement of the EO muscles, including slow saccades and diplopia. The involvement of EO muscles has been reported in patients with ALS, but it is a rare presentation,^{3,4} which probably caused the delay in diagnosis. The rapid progression to ventilation only 6 months after the initial presentation is exceptional compared with previously reported cases. This was complicated by a respiratory tract infection, which seemed to accelerate the disease progression. To our knowledge, the association of p.P525L *FUS* mutation and clinical EO muscle involvement is rare.

This case report strengthens the role of *FUS* in jALS and the association of the p.P525L mutation with an aggressive course of jALS. Although genetic testing in individuals with no family history is controversial, it is becoming increasingly clear that *FUS* mutation screening and more precisely p.P525L

Supplemental data
at Neurology.org/ng

Figure Pedigree of the family and segregation analysis of the *FUS* p.P525L mutation



Nucleotide and protein positions are according to NM_004960 from GRCh37/hg19 on the positive DNA strand (chromosome 16). Mu = Mutant; Hu = Human; Ch = Chimpanzee; Ma = Macaque; Ra = Rat; Mo = Mouse; Xe = Xenopus.

genotyping of sporadic jALS should be done in clinical practice considering the increasing number of cases reported carrying *FUS* mutation. Further studies are needed to better assess the prevalence of EO muscle involvement in patients carrying p.P525L *FUS* mutation and more generally in patients with jALS to determine whether this phenotype could be used as an early diagnostic criterion in aggressive forms of jALS.

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