

adult onset symmetrical pelvic and shoulder girdle weakness and predominant lower motor neuron involvement, which has been confirmed pathologically.^{3,4} In contrast, other *FUS* mutations present more frequently with flail arm syndrome or with typical limb or bulbar onset ALS. Our patient with juvenile-onset ALS, an R521C missense mutation, and a flail leg presentation represents an unusual combination. *FUS* mutations should be assessed in young patients who present with rapidly progressive flail leg syndrome, even in the absence of upper motor neuron signs.

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AN UNUSUAL PRESENTATION FOR SOD1-ALS: ISOLATED FACIAL DIPLEGIA

Approximately 20% of familial amyotrophic lateral sclerosis (fALS) cases are linked to mutations in the superoxide dismutase 1 gene (*SOD1*). More than 160 mutations have been reported.^{1–3}

A 63-year-old man developed insidious onset of lower facial weakness. The initial symptom was difficulty speaking. One year later, he noticed difficulty smiling and handling food in the mouth due to weakness in his cheeks. No laterality of symptoms was reported, and neurological examination showed no tongue or limb involvement. Two years after onset, he noted progressive left hand weakness and loss of dexterity. Examination demonstrated bilateral lower facial weakness and atrophy, sparing the frontalis muscle. There were no tongue fasciculations. Articulation was normal except for labial consonants. There was a positive jaw jerk. The remainder of the cranial nerve examination was normal. There was mild distal left upper extremity atrophy

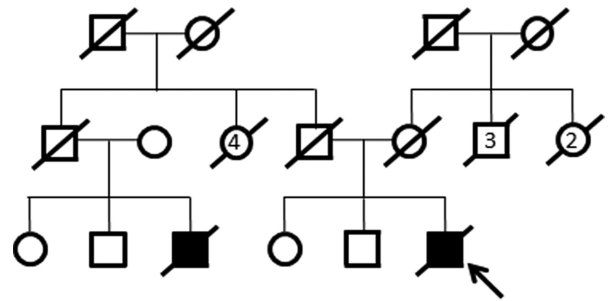


FIGURE 1. Pedigree of the family. Arrow identifies the proband. The proband's father and paternal uncle are potential obligate carriers of the mutation. The proband's father died of ischemic heart disease at age 77 years. No information is available for the proband's paternal uncle.

and weakness. In the lower limbs, tone was increased, but power was normal. Reflexes were brisk in all limbs. The Hoffman sign was absent, and plantar reflexes were extensor.

A first cousin on his father's side died of ALS. Blood tests and cerebrospinal fluid were unremarkable. MRI scan of brain and spine were normal. Electrodiagnostic studies supported a diagnosis of motor neuronopathy. Needle examination revealed chronic neurogenic changes in the face, widespread and frequent polymorphic fasciculation potentials in the limbs, less frequent fasciculation potentials in the paraspinal and trapezius muscles, and very mild and patchy neurogenic abnormalities in the limbs. Nerve conduction studies were normal except for a mild ulnar neuropathy at the left elbow. Central motor conduction times showed prolonged latency in the upper left limb. Sequencing of *SOD1* revealed a heterozygous T>C point mutation resulting in the substitution of Isoleucine for Threonine at amino acid 113 (Ile113Thr).

In the following 6 months, the patient developed spasticity and widespread fasciculations in all limbs. He did not develop emotional lability. He died 3 years after symptom onset.

The Ile113Thr mutation was among the first *SOD1* mutations described¹ and is the third most common *SOD1* mutation.² Its penetrance was shown to be low in fALS families⁴ making it plausible that the proband's cousin, who died of ALS, also had this mutation and that both the patient's father and uncle were obligate carriers who did not develop ALS (Figure 1). Previous reports of the *SOD1* Ile113Thr mutation indicate a mean age of onset of 57.8 ± 15.1 years and a disease duration of 4.2 ± 2.5 years, which are both compatible with the described patient.⁵ This mutation has been linked recently to a patient with ALS/FTD, another very atypical finding for *SOD1* ALS.⁶

In a previous report, a patient with the *SOD1* A4V mutation presented with facial diplegia, but this also involved upper face muscles and was accompanied by dysarthria, dysphagia, and unilateral vocal cord paralysis.⁷ The striking feature of the patient reported here is that the facial diplegia was the only finding for the first 2 years.

In summary, this atypical presentation for a common SOD1 FALS mutation expands the known clinical spectrum of this mutation.

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INCLUSION BODY MYOPATHY WITH PAGET DISEASE OF BONE AND FRONTOTEMPORAL DEMENTIA ASSOCIATED WITH A NOVEL G156S MUTATION IN THE VCP GENE

Inclusion body myopathy (IBM) with Paget disease of bone (PDB) and frontotemporal dementia (FTD) (IBMPFD) is a progressive autosomal dominant multisystem disorder affecting muscles, bones, and brain. IBMPFD has been attributed to missense mutations in the valosin-containing protein gene (*VCP*) on chromosome 9p13.3. We describe a patient with IBMPFD associated with a novel G156S mutation in *VCP*.

A 65-year-old Japanese man with no family history of PDB, FTD, or myopathic disease was evaluated for a 9-year history of progressive muscle weakness and a 1-year history of irritability and difficulty recalling names of friends. At age 40, he had presented with low back pain and an elevated serum alkaline phosphatase level (750 U/L; normal 30–115). 99m Tc-methylene diphosphonate bone scan showed abnormal accumulations in the skull, spine, iliac bone, and right shoulder joint. An L2 vertebral biopsy revealed PDB. Neurological examination revealed proximal-predominant muscle atrophy and

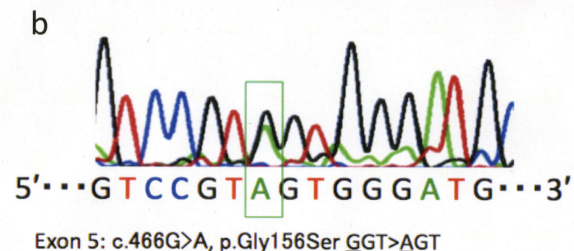
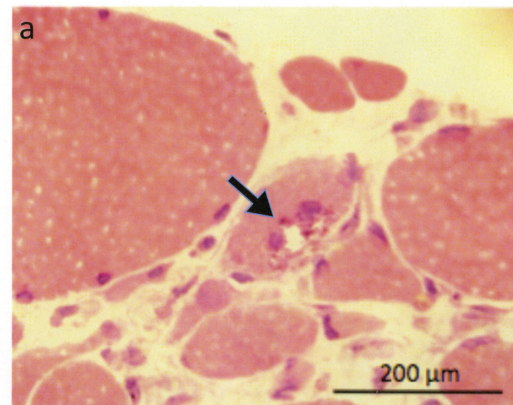


FIGURE 1. (a) A biopsy from the tibialis anterior muscle shows a rimmed vacuole (arrow) with myopathic change on hematoxylin and eosin. (b) Sequence chromatogram of the c.466G>A (p.G156S) mutation in exon 5 of the *VCP*.

weakness in his extremities. His Mini-Mental State Examination and Frontal Assessment Battery scores were 26/30 (normal range, >27/30) and 13/18 (normal range, >14/18),¹ respectively. The Wechsler Adult Intelligence Scale-III revealed a decline in his verbal intelligence quotient from 93 at age 63 to 59 at age 65, and in his performance intelligence quotient from 115 at age 63 to 86 at age 65. Serum creatine kinase levels were normal. Electromyography revealed myopathic features, and a biopsy of the right tibialis anterior muscle revealed myopathic changes with rimmed vacuoles (Fig. 1a). Brain MRI showed bilateral frontotemporal lobe atrophy (Supp. Fig. S1, which is available online), and 99m Tc-methyl cysteinate-dimer single photon emission computed tomography disclosed blood flow reduction in the bilateral parietal and left temporal lobes.

A genomic study was approved by the Ethics Committee for Human Genome/Gene Analysis Research at Kanazawa University Graduate School of Medical Sciences, and informed consent was obtained from the patient. Genomic DNA was isolated from blood. Mutation screening was performed by direct sequencing of PCR products of coding exons 2, 3, 5, and 6 of *VCP*,² and a novel heterozygous base substitution was found in exon 5: c.466G>A (p.G156S), as shown in Figure 1b. This mutation was not observed in 100 healthy Japanese control subjects.

Although more than half of the missense mutations in *VCP* associated with IBMPFD have been reported to cluster in the N-terminal hot spot, R155, in exon 5,³ this G156S mutation is novel. The particular shape and charge distribution within the cleft around R155 of *VCP* may be