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First Case of *TARDBP*-Related Amyotrophic Lateral Sclerosis in Korea

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Dear Editor

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by the progressive degeneration of motor neurons. The cause of most cases of ALS is unknown, but 5−10% of them can be attributed to genetic alterations.[1] Currently, 71 causative genes have been identified as causing familial ALS (www.musclegenetable.fr). Among them, *C9ORF72* and *SOD1* are the most common causative genes in European and Asian populations, respectively. Additionally, alterations in *TARDBP* and *FUS* each account for approximately 5% of patients with familial ALS.[1,2] However, a pathogenic variant of *TARDBP* has not been reported in Korea.[3,4] Herein we report a pathogenic variant of *TARDBP* in a Korean patient with familial ALS.

A 52-year-old male (II-11) (Fig. 1A) was referred to our institute with progressive muscle weakness. He had a family history of ALS in his mother (I-2) and elder sister (II-4), who had progressive asymmetric muscle weakness and died from respiratory failure in their 60s and 50s, respectively. The muscle weakness and wasting in the index patient had started in his right leg at the age of 50 years and progressed to his left leg and arm. A physical examination showed muscle weakness, wasting, and fasciculations in both legs and the left arm. The deep tendon reflexes in the bilateral knees and left arm were hyperactive. However, cognitive dysfunction, sensory deficits, and ataxia were not found. Magnetic resonance imaging showed only mild parenchymal atrophy in the brain and spinal cord. An electrophysiological examination revealed a widespread neurogenic process without sensory nerve involvement in the cervical, thoracic, and lumbosacral segments. The patient was diagnosed with clinically probable ALS, after which we performed targeted sequencing of 172 neuropathy-related genes (Supplementary Table 1 in the online-only Data Supplement) and identified a heterozygous pathogenic variant of *TARDBP* (NM_007375.4: c.1009A>G; NP_031401.1:p.M337V) (Fig. 1B). This variant was previously reported as a pathogenic variant in ALS.[2]

We speculate that the c.1009A>G variant should be classified as a likely pathogenic variant based on the following evidence: 1) located in a mutational hotspot without benign variation, 2) not in Genome Aggregation Database (gnomAD), 3) low rate of benign missense variation in *TARDBP*, 4) multiple lines of computational evidence supporting a deleterious effect on the gene, 5) a well-established in-vivo functional study having supported a damaging effect on the gene, and 6) many previous reports of it being a pathogenic variant.[2,5,6]

The TDP-43 protein encoded by *TARDBP* is a widely expressed RNA/DNA-binding protein involved in the regulation of RNA processing and other cellular functions.[7] Most pathogenic variants of *TARDBP* (including c.1009A>G) are located in the C-terminal glycine-rich domain. An abnormal C-terminal domain is believed to improve the aggregation propensity of the TDP-43 protein, which results in neurodegeneration. However, it is unclear whether the pathogenesis is linked to aggregates of the TDP-43 protein or impairment of the normal

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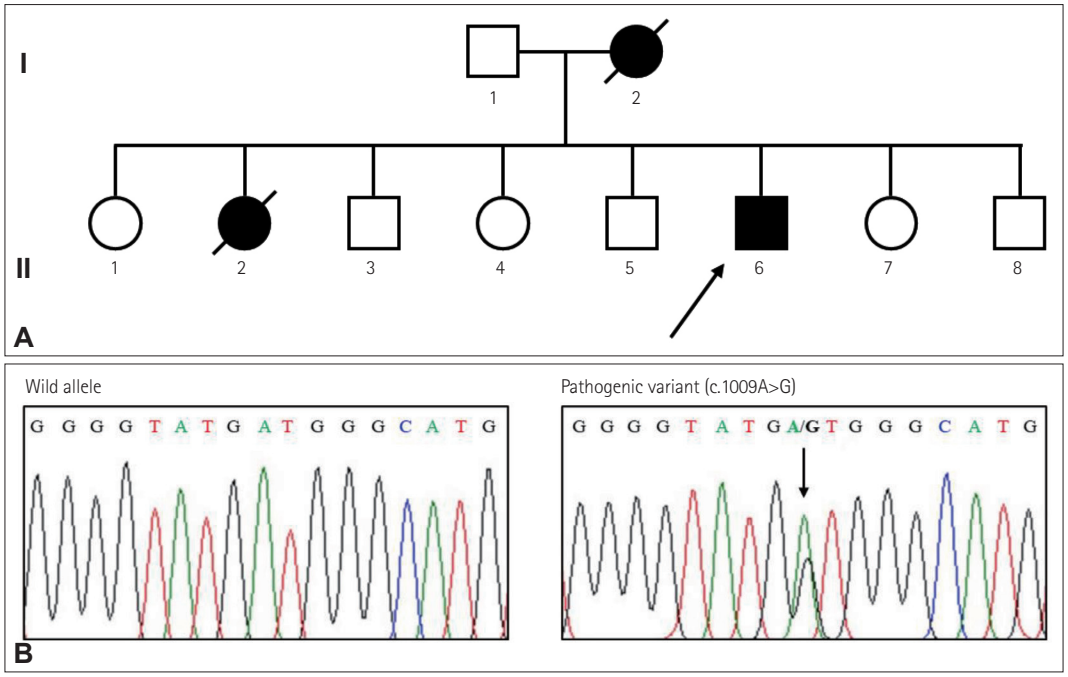

Fig. 1. Pedigree and sequencing chromatogram. A: Pedigree of a patient with familial amyotrophic lateral sclerosis. Arrow indicates the proband (square, male; circle, female; filled, affected; unfilled, unaffected). B: Sequencing chromatograms of the c.1009A>G variant of TARDBP. Arrow indicates the site of the pathogenic variant.

function of this protein.[7]

We have herein reported the first case of pathogenic variant of *TARDBP* in a Korean patient with familial ALS. Our patient showed adult-onset asymmetric muscle weakness without cognitive impairment. His muscle weakness began at the age of 50 years, which is similar to the onset ages in previous reports. However, *TARDBP*-related ALS is well known to have a highly variable clinical presentation, including in the distribution of muscle weakness, severity of the disease, and presence of cognitive impairment.[6] These characteristics make *TARDBP*-related ALS indistinguishable from sporadic or other genetic ALS based on clinical and electrophysiological features. It is essential to perform genetic testing on as many ALS-related genes as possible when diagnosing familial ALS.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2020.16.4.709.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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