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Clinical and Pathological Findings of a Korean Family with Pathogenic Variants of the TTN Gene

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Dear Editor,

Titinopathies are a group of clinical and pathologically heterogeneous muscle disorders. These diseases have been frequently reported in the Finnish population, but have been rarely found in Asian populations.[1] We previously reported recessive *TTN* variants as the genetic cause in a large Korean cohort of inherited muscular disorders.[2] However, the detailed clinical phenotype was not investigated. Here we present clinical and pathological findings of a Korean family with rigid spine syndrome and respiratory difficulty carrying pathogenic variants of *TTN*.

The proband (a 43-year-old man) (Fig. 1A and B, II-5) complained of muscle weakness, scoliosis, and respiratory difficulty. He demonstrated muscle weakness, faint crying, and weak sucking at birth. Since childhood he had experienced difficulty in bending his neck and spine. He was first hospitalized at the age of 30 years for respiratory difficulty, since when he used noninvasive positive pressure ventilation via a nasal mask intermittently, mainly at nighttime. When we examined him at the age of 43 years, he could walk independently. He displayed proximal weakness, lordosis, scoliosis, ankle contracture, and limited bending of the neck (Fig. 1C). He did not have extraocular movement limitation or craniofacial dysmorphism. His forced vital capacity was 0.76 L (20%), his $PaCO_2$ was 47.4 mm Hg, and his serum creatine kinase level was 89 IU/L (reference value <185 IU/L). The electromyography findings were compatible with chronic myopathy, while his electrocardiography and echocardiography findings were normal. A biceps brachii muscle biopsy was performed when he was 30 years old. Staining with hematoxylin and eosin revealed moderate variations of fiber size and shape, in addition to many fibers having internalized nuclei (Fig. 1D). Intracytoplasmic inclusions and subsarcolemmal depositions were not found by modified Gomori trichrome staining (Fig. 1E). Staining with nicotinamide adenine dinucleotide-tetrazolium reductase revealed that type I fibers predominated (Fig. 1F). The older sister of the proband (a 50-year-old woman) (Fig. 1A and B, II-2) had a similar clinical presentation that included proximal weakness, lordosis, scoliosis, ankle contracture, and limited bending of the neck. Although she did not use a ventilator, she experienced morning headaches and daytime somnolence. Her forced vital capacity was 0.8 L (22%) and she exhibited limited extraocular movement.

We performed targeted sequencing of 69 myopathy-related genes, including *TTN*, to obtain a confirmative diagnosis in the proband (Supplementary Table 1, 2, and 3 in the online-only Data Supplement). We identified two compound heterozygous *TTN* variants: c. 14372-2A>G and c.102523C>T (Fig. 1B) (Supplementary Information in the online-only Data Supplement). Capillary sequencing showed that the *TTN* variants cosegregated completely with the two affected family members (Fig. 1A and B). The c.14372-2A>G variant has previously been reported as a pathogenic variant,[3] while the c.102523C>T (p.Arg34175*) variant is a novel truncating variant that was not found in 298 healthy controls, the dbSNP138

database, or the 1,000 Genomes Database.

Titin, the protein encoded by *TTN*, is the largest human protein and the third most common type of filament in both cardiac and skeletal human muscle. Titin connects the Z-line to the M-line and interacts with many other proteins, including actin, myosin, nebulin, α-actinin, telethonin, tropomyosin, and calpain-3. However, the pathomechanism of titinopathy is unclear. Both dominant-negative and loss-of-function

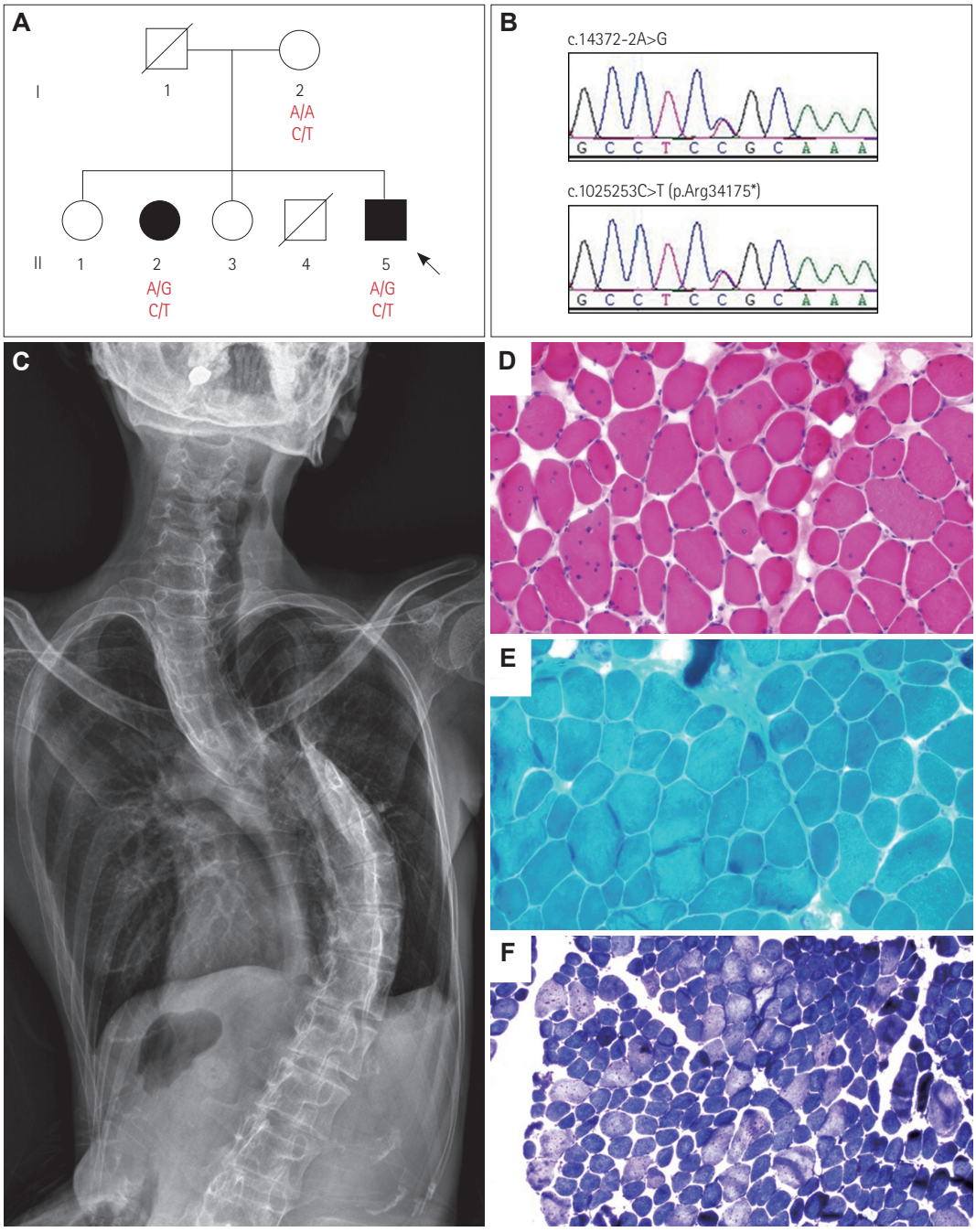

Fig. 1. Pedigree, sequencing chromatograms, whole-spine X-ray images, and pathology results. A: Pedigree of a Korean patient with compound heterozygous pathogenic variants of *TTN*. Arrows indicate the proband (square: male; circle: female; filled: affected; unfilled: unaffected). B: Sequencing chromatograms of the c.14372-2A>G and c.102523C>T (p.Arg34175*) *TTN* variants. Arrows indicate pathogenic or likely pathogenic variant sites. C: Whole-spine X-ray images. D, E, and F: Histopathology of the biceps brachii. D: Hematoxylin and eosin (H&E) staining of biceps brachii muscle tissue revealing moderate variations of fiber size and shape in addition to many fibers having internalized nuclei. E: Intracytoplasmic inclusions and subsarcolemmal depositions were not found in modified Gomori trichrome (GT) staining. F: Staining with nicotinamide adenine dinucleotide-tetrazolium reductase (NADH-tr) demonstrated the predominance of type I fibers (approximately 84%). (D: H&E stain, ×200; E: modified GT stain, ×200; F: NADH-tr stain, ×100).

mechanisms have been described as underlying titinopathy. Actually, titinopathies have highly variable clinical presentations, including dilated cardiomyopathy, tibial muscular dystrophy, limb-girdle muscular dystrophy type 2J, hereditary myopathy with early respiratory failure, and centronuclear myopathy.[4] The skeletal muscle diseases associated with titinopathy have mainly been associated with an autosomal-dominant late-onset distal myopathy. However, centronuclear myopathy has only been reported as a recessive disease. The present family with *TTN* variants demonstrated rigid spine syndrome and respiratory difficulty associated predominantly with muscle fibers with internalized nuclei, which is compatible with a previous report.[3]

In conclusion, this is the first report of the clinical and pathological features of a Korean family with recessive *TTN* variants.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2017.13.1.116.

Conflicts of Interest

The authors have no financial conflicts of interest.

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