

# *TNNI1* Mutated in Autosomal Dominant Proximal Arthrogryposis

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## Abstract

### Objectives

The main objective of this case report is to identify a gene associated with a Japanese family with autosomal dominant arthrogryposis.

### Methods

We performed clinicopathologic diagnosis and genomic analysis using trio-based exome sequencing.

### Results

A 14-year-old boy had contractures in the proximal joints, and the serum creatine kinase level was elevated. Muscle biopsy demonstrated a moth-eaten appearance in some type 1 fibers, and electron microscopic analysis revealed that type 1 fibers had Z disk streaming. We identified a heterozygous nonsense variant, c.523A>T (p.K175\*), in *TNNI1* in the family.

### Discussion

The altered amino acid residue is within the tropomyosin-binding site near the C-terminus, in a region homologous to the variational hotspot of Troponin I2 (*TNNI2*), which is associated with distal arthrogryposis type 1 and 2b. Compared with patients with *TNNI2* variants, our patient had a milder phenotype and proximal arthrogryposis. We report here a case of proximal arthrogryposis associated with a *TNNI1* nonsense variant, which expands the genetic and clinical spectrum of this disease. Further functional and genetic studies are required to clarify the role of *TNNI1* in the disease.

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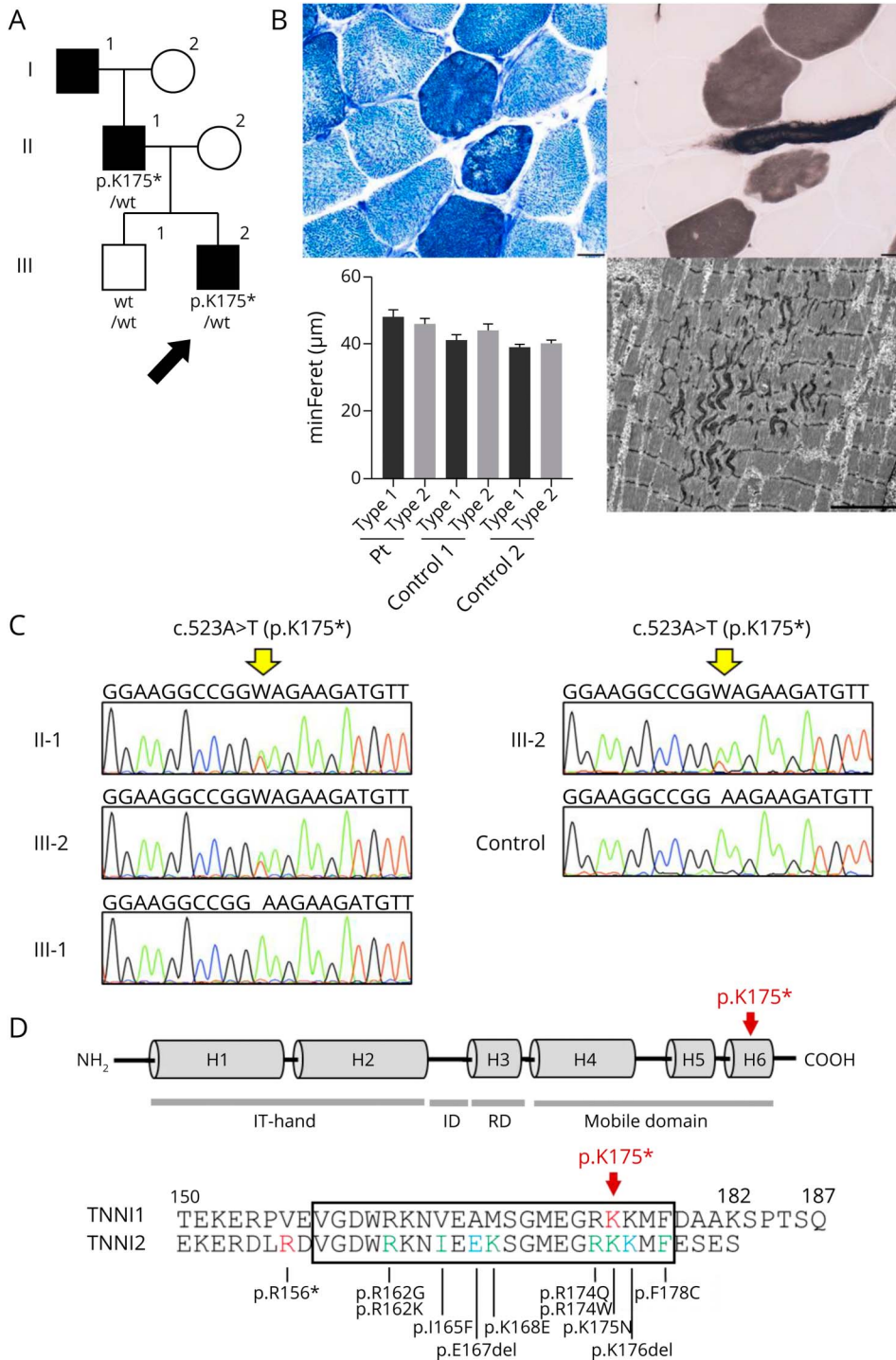
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Among the 3 troponin I genes, *TNNI2*, encoding fast skeletal troponin I2, and *TNNI3*, encoding cardiac troponin I3, were reported as causative genes of distal arthrogryposis and cardiomyopathy, respectively (HGMD Professional 2021.1). In contrast, *TNNI1*, encoding slow skeletal troponin I1, has not been shown to be associated with any disorders. We identified a heterozygous nonsense variant in *TNNI1* by exome sequencing in a Japanese family with autosomal dominant proximal arthrogryposis.

## Case Presentation

A 14-year-old boy presented with contractures of the trunk, hip, and knee joints. The family had an apparent autosomal dominant family history of joint contractures and high creatine kinase affecting the father and paternal grandfather, albeit without muscle weakness (Figure, A). The proband was born with clasped thumbs, inguinal hernia, and testicular hydrocele,

**Figure** Pedigree and Pathologic and Genetic Findings



(A) Pedigree of a Japanese arthrogryposis family. (B) Skeletal muscle pathology of patient III-2. (Upper left) NADHTR staining shows fibers with moth-eaten appearance. (Upper right) Myosin ATPase staining with pH 4.6 pre-incubation demonstrates type 1 fibers. Bar denotes 20 microns. (Lower left) The minimum Feret diameters of type 1 fibers were marginally larger than those of type 2 fibers in patient III-2. (Lower right) Electron microscopical analysis: Z disk streaming was observed in type 1 muscle fibers, with the average width of Z bands of the fibers with Z disk streaming at 95 nm. Bar denotes 5.0 microns. (C) (Left) Electropherograms of genomic DNAs in the family. c.523A>T was identified in patients II-1 and III-2 but not in patient III-1. (Right) Transcript with c.523A>T of *TNNI1* in the patient's skeletal muscle. (D) Schematic structure of troponin I1 consists of 6  $\alpha$ -helices and position of the identified nonsense variant at 175. ID, inhibitory domain; RD, regulatory domain. Lysine residue at 175 in troponin I1 is highly conserved within the C-terminus. The 11 *TNNI2* pathogenic variants reported in patients with distal arthrogryposis are indicated at the bottom. Tropomyosin-binding site is indicated by a rectangle. Green letters, missense; blue letters, deletion; red letters, nonsense variant.

which were corrected by surgery at age 5 months. At elementary school ages, he noticed difficulties with jumping, sitting with his legs crossed, and bending his back. At age 14 years, he visited the hospital seeking medical workup for contractures. On examination, his height and weight were 153 cm (−2.1 SD) and 41.4 kg (−1.5 SD), respectively. He had small mouth and trismus. He had no apparent muscle weakness but had joint contractures of the neck, trunk, and knees. The serum creatine kinase level was 1,689 IU/L (normal range: 25–170 IU/L). No edematous change or fat replacement was observed on muscle MRI. Muscle biopsy from the left biceps brachii demonstrated mild disorganization of the intermyofibrillar network, showing a moth-eaten appearance in some type 1 fibers and mild fiber size variation in the type 1 fibers. The minimum Feret diameters of type 1 fibers were marginally larger than those of type 2 fibers in patient III-2. Electron microscopic analysis revealed that type 1 fibers, identified by the Z-band width, had Z disk streaming (Figure, B).

To genetically diagnose the proband, we performed pathogenic variant screening using a custom-made targeted gene panel for inherited skeletal muscle diseases, which revealed no pathogenic variant. Trio-based exome sequencing (II-1, III-1, and III-2) identified a heterozygous nonsense variant, c.523A>T (p.K175\*), in *TNNI1* (NM\_003281.4), which was confirmed by Sanger sequencing (Figure, C). The nonsense variant was segregated among II-1, III-1, and III-2. In addition, the reverse transcription-PCR products of mRNA from the patient's muscle showed the presence of both the mutated and normal transcripts. The altered amino acid residue (p.K175) is within the tropomyosin-binding site near the C-terminus, which is highly conserved in the troponin family and is evolutionarily conserved.<sup>1</sup> This variant is not registered in any public databases, including gnomAD, dbSNP151, HGMD Professional 2021.1, Human Genome Variation Database, ToMMo, ClinVar, ESP6500, and 1000 Genomes.

## Discussion

Troponin I is an inhibitory subunit of the troponin complex for myosin on actin binding in relaxed muscles and is important in the thin filament regulation of striated muscle contraction.<sup>1</sup> Eleven pathogenic variants in *TNNI2* have been reported in patients with distal arthrogryposis (HGMD Professional 2021.1), 10 of which were localized to the tropomyosin-binding site (Figure, D).<sup>1</sup> The nonsense variant terminates translation at codon 175, which is also within the tropomyosin-binding site, and eliminates the last 4 amino acids at this site and the remaining 9 C-terminal amino acids. The truncated *TNNI1* might lead to a dominant negative effect and impairment of the inhibitory function. The C-terminal region of troponin I (fast skeletal type) contributes to the binding affinity to tropomyosin and thin filaments to prevent myosin from accessing thin filaments without Ca<sup>2+</sup>.<sup>2</sup> We hypothesize that the *TNNI1* nonsense variant acts in a manner analogous to pathogenic variants in *TNNI2*, which increase the Ca<sup>2+</sup>-sensitivity of myosin-actin interaction and thus cause excessive muscle contraction.

Our patient with the nonsense variant p.K175\* in *TNNI1* had contractures in the proximal joints without apparent abnormality of the feet and face, whereas 10 patients with *TNNI2* variants at the C-terminal region showed distal arthrogryposis type 2B, characterized by congenital contractures of the hands and feet, in addition to facial anomalies such as triangular face and downslanting palpebral fissures.<sup>3-7</sup> Our patient had an apparently milder phenotype and proximal arthrogryposis. Muscle histology determined by histochemistry and electron microscopy revealed abnormalities only in type 1 fibers, possibly because *TNNI1* encodes slow skeletal type troponin I. Phenotypic differences are still unclear between the patients with *TNNI1* and *TNNI2* variants. Further functional studies of truncated troponin II are necessary to prove the pathogenicity of this nonsense variant and how it leads to proximal arthrogryposis.

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## Disclosure

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## Appendix (continued)

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## Appendix (continued)

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