TNNI1 Mutated in Autosomal Dominant Proximal Arthrogryposis

Yukako Nishimori, MD, Aritoshi Iida, PhD, Masashi Ogasawara, MD, Mariko Okubo, MD, PhD, Yuki Yonenobu, MD, Makoto Kinoshita, MD, PhD, Kazuma Sugie, MD, PhD, Satoru Noguchi, PhD, and Ichizo Nishino, MD, PhD

Correspondence

Dr. Iida
iidaa@ncnp.go.jp

Neurol Genet 2022;8:e649. doi:10.1212/NXG.0000000000000649

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.

From the Department of Neuromuscular Research (Y.N., M.O., M.O., S.N., I.N.), National Institute of Neuroscience, National Center of Neurology and Psychiatry (NCNP), Tokyo, Japan; Department of Clinical Genome Analysis, Medical Genome Center, NCNP, Tokyo, Japan (Y.N., A.I., I.N.); Department of Neurology (Y.N., K.S.), Nara Medical University, Nara, Japan; Department of Neurology (Y.Y., M.K.), Osaka University Graduate School of Medicine, Osaka, Japan.

Go to [Neurology.org/NG](https://www.neurology.org/NG) for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by the authors.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

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 microscopic 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 α -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.¹ 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.¹ 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).¹ 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 Ca²⁺.² We hypothesize that the *TNNI1* nonsense variant acts in a manner analogous to pathogenic variants in *TNNI2*, which increase the Ca²⁺-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.^{3–7} 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 I are necessary to prove the pathogenicity of this nonsense variant and how it leads to proximal arthrogryposis.

Study Funding

This study was supported partly by Intramural Research Grants (2-5 and 30-9) for Neurological and Psychiatric Disorders of NCNP and by AMED under Grant Number 20ek0109490h0001.

Disclosure

Y. Nishimori reports no disclosures relevant to the manuscript. A. Iida received grants from Intramural Research Grants (2-5 and 30-9) for Neurological and Psychiatric Disorders of NCNP and AMED under Grant Numbers 20ek0109490h0001 and Joint Usage and Joint Research Programs, the Institute of Advanced Medical Sciences, Tokushima University grant number 2020, 2A19. M. Ogasawara, M. Okubo, Y. Yonenobu, M. Kinoshita, and K. Sugie report no disclosures relevant to the manuscript. S. Noguchi received grants from Intramural Research Grants (2-6 and 3-9) for Neurological and Psychiatric Disorders of NCNP and AMED under Grant Number 20ek0109490h0001. I. Nishino received a grant from Intramural Research Grant (2-5) for Neurological and Psychiatric Disorders of NCNP and AMED under Grant Number 20ek0109490h0001. Go to Neurology.org/NG for full disclosures.

Publication History

Received by *Neurology: Genetics* June 17, 2021. Accepted in final form November 10, 2021.

Appendix Authors

Name	Location	Contribution
Yukako Nishimori, MD	Department of Neuromuscular Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry (NCNP), Tokyo, Japan Department of Clinical Genome Analysis, Medical Genome Center, NCNP, Tokyo, Japan Department of Neurology, Nara Medical University, Nara, Japan	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data; additional contributions: evaluated muscle biopsy

Continued

Appendix (continued)

Name	Location	Contribution
Aritoshi Iida, PhD	Department of Clinical Genome Analysis, Medical Genome Center, NCNP, Tokyo, Japan	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data; additional contributions: performed genome analysis, data analysis, and interpretation
Masashi Ogasawara, MD	Department of Neuromuscular Research, National Institute of Neuroscience, NCNP, Tokyo, Japan	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data; additional contributions: evaluated muscle pathology and contributed diagnosis
Mariko Okubo, MD, PhD	Department of Neuromuscular Research, National Institute of Neuroscience, NCNP, Tokyo, Japan	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data; additional contributions: evaluated muscle pathology
Yuki Yonenobu, MD	Department of Neurology, Osaka University Graduate School of Medicine, Osaka, Japan	Drafting/revision of the manuscript for content, including medical writing for content; additional contributions: contributed to the clinical diagnosis and muscle biopsy of the patient
Makoto Kinoshita, MD, PhD	Department of Neurology, Osaka University Graduate School of Medicine, Osaka, Japan	Drafting/revision of the manuscript for content, including medical writing for content; additional contributions: contributed to the clinical diagnosis and muscle biopsy of the patient

Appendix (continued)

Name	Location	Contribution
Kazuma Sugie, MD, PhD	Department of Neurology, Nara Medical University, Nara, Japan	Drafting/revision of the manuscript for content, including medical writing for content; additional contributions: contributed to the clinical diagnosis and muscle biopsy of the patient
Satoru Noguchi, PhD	Department of Neuromuscular Research, National Institute of Neuroscience, NCNP, Tokyo, Japan	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data; additional contributions: supervised muscle pathology and electron microscopy analysis
Ichizo Nishino, MD, PhD	Department of Neuromuscular Research, National Institute of Neuroscience, NCNP, Tokyo, Japan; and Department of Clinical Genome Analysis, Medical Genome Center, NCNP, Tokyo, Japan	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data; additional contributions: supervised clinical diagnosis, muscle pathology, and electron microscopy analysis and supervised manuscript preparation

References

- Sheng JJ, Jin JP. TNNI1, TNNI2 and TNNI3: evolution, regulation, and protein structure-function relationships. *Gene*. 2016;576(1Pt3):385-394.
- Ramos CH. Mapping subdomains in the C-terminal region of troponin I involved in its binding to troponin C and to thin filament. *J Biol Chem*. 1999;274(26):18189-18195.
- Beck AE, McMillin MJ, Gildersleeve HI, et al. Spectrum of mutations that cause distal arthrogryposis types 1 and 2B. *Am J Med Genet A*. 2013;161A(3):550-555.
- Sung SS, Brassington AM, Grannatt K, et al. Mutations in genes encoding fast-twitch contractile proteins cause distal arthrogryposis syndromes. *Am J Hum Genet*. 2003;72(3):681-690.
- Kimber E, Tajsharghi H, Kroksmark AK, Oldfors A, Tulinius M. A mutation in the fast skeletal muscle troponin I gene causes myopathy and distal arthrogryposis. *Neurology*. 2006;67(4):597-601.
- Jiang M, Zhao X, Han W, et al. A novel deletion in TNNI2 causes distal arthrogryposis in a large Chinese family with marked variability of expression. *Hum Genet*. 2006;120(2):238-242.
- Krakowiak PA, O'Quinn JR, Bohnsack JF, et al. A variant of Freeman-Sheldon syndrome maps to 11p15.5-pter. *Am J Hum Genet*. 1997;60(2):426-432.

Neurology[®] Genetics

***TNNI1* Mutated in Autosomal Dominant Proximal Arthrogryposis**

Yukako Nishimori, Aritoshi Iida, Masashi Ogasawara, et al.

Neurol Genet 2022;8;

DOI 10.1212/NXG.0000000000000649

This information is current as of December 17, 2021

Updated Information & Services	including high resolution figures, can be found at: http://ng.neurology.org/content/8/1/e649.full.html
References	This article cites 7 articles, 1 of which you can access for free at: http://ng.neurology.org/content/8/1/e649.full.html##ref-list-1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): All Genetics http://ng.neurology.org/cgi/collection/all_genetics All Pediatric http://ng.neurology.org/cgi/collection/all_pediatric Muscle disease http://ng.neurology.org/cgi/collection/muscle_disease
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://ng.neurology.org/misc/about.xhtml#permissions
Reprints	Information about ordering reprints can be found online: http://ng.neurology.org/misc/addir.xhtml#reprintsus

Neurol Genet is an official journal of the American Academy of Neurology. Published since April 2015, it is an open-access, online-only, continuous publication journal. Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology. All rights reserved. Online ISSN: 2376-7839.