Neurology Asia 2023; 28(4) : 1069 – 1072

Centronuclear myopathy with a novel variant (p.Asp646Tyr) in the *DNM2* gene exhibits mild clinical manifestations: A case report

[1]Youngho Kim, [2]Mi Hee Kwack, [1,3]Jong-Mok Lee

[1]*Department of Neurology, Kyungpook National University Hospital, Daegu, South Korea;*
[2]*Department of Immunology, School of Medicine, Kyungpook National University, Daegu, South Korea;*
[3]*Department of Neurology, School of Medicine, Kyungpook National University, Daegu, South Korea*

Abstract

Centronuclear myopathy (CNM) is one of the congenital myopathies characterized by centrally located nuclei in the muscle fibers. Currently, more than 30 pathogenic variants in the dynamin 2 (*DNM2*) genes have been identified. Here, we describe a 63-year-old female who presented with slowly progressive limb weakness with no facial weakness or ophthalmoplegia. Electromyographical myotonia without clinical myotonia was noted. In the *DNM2* gene, whole-genome sequencing revealed the heterozygous variant c.1936G>T (p.Asp646Tyr), which was not reported previously. Muscle pathology identified many fibers with centrally located nuclei, with the predominance of type 1 fibers. Thus, the patient was finally diagnosed with *DNM2*-associated CNM with a novel pathogenic variant and with unusually mild phenotype.

Keywords: Whole-genome sequencing, muscle weakness, myotonic disorders

INTRODUCTION

Centronuclear myopathy (CNM) is a group of congenital myopathies characterized by centrally located nuclei in the muscle fibers. Mutations in the gene dynamin 2 (*DNM2*) are the second most common etiology of CNM with autosomal dominant inheritance.[1] Gain-of-function research in such mutations results in transverse tubule and sarcoplasmic reticulum reduction, ultimately decreasing muscle force.[1] Here, we describe a pathogenically and genetically confirmed case of CNM with a novel *DNM2* mutation in a 63-year-old female who presented with a mild phenotype (lower-limb weakness).

CASE REPORT

A 63-year-old female proband, who was born from nonconsanguineous parents, visited our neurology department with slowly progressive lower-limb weakness bilaterally for 3 years. She denied having previously diagnosed diseases or medications. Regarding family history, her mother showed gait disturbance in her 40s but died undiagnosed. The medical status of other family members was undisclosed.

On neurological examination, she had a distal dominant bilateral leg weakness. Using the Medical Research Council grading system, we graded her ankle dorsiflexion and plantarflexion weakness as 3 and her right proximal leg weakness as 4. The upper extremities remained normal. Facial muscle weakness, including ophthalmoplegia and ptosis, was not noted. However, her deep tendon reflex was absent in her lower extremities and reduced in the upper extremities. Neither handgrip nor percussion myotonia was observed.

Blood examination revealed normal serum creatine kinase level (103 U/L, normal range: 0–192 U/L). Nerve conduction study (NCS) showed reduced compound muscle action potential amplitude in the bilateral lower extremities, with normal sensory NCS findings. Electromyography (EMG) detected myotonic discharges ubiquitously. Motor unit action potentials were of short duration and low amplitude, particularly in the right tibialis anterior and first dorsal interosseous

Address correspondence to: Jong-Mok Lee, MD, PhD, Department of Neurology, School of Medicine, Kyungpook National University, 680 Gukchaebosang-ro, Jung-gu, Daegu, 41944, South Korea. Tel: +82-53-200-5765, E-mail: azulmar@gmail.com

Date of Submission: 26 May 2023; Date of Acceptance: 21 August 2023

https://doi.org/10.54029/2023feu

muscles. Moreover, computed tomography showed severe fatty infiltration in the gluteus maximus, posterior thigh, and entire part of the lower extremities bilaterally. Considering the electrophysiological findings, genetic analysis of the myotonic dystrophy protein kinase (*DMPK*) gene and Pompe disease was conducted to avoid invasive procedure initially; however, the results were negative.

We next conducted whole-genome sequencing, which revealed the variant c.1936G>T (p.Asp646Tyr, NM_001005361, NG_008792) in *DNM2* (Figure 1A). This variant has not been reported in the genome aggregation database. It was predicted to be "probably damaging" with a score of 1.000 by polyPhen-2 and "disease causing" with 0.999 probability by MutationTaster. Furthermore, the amino acid residue at 646 in dynamin was preserved across various species (Figure 1B).

After identifying the potential pathogenic variant, we conducted pathologic analysis. In light microscopy, the muscle biopsied from left biceps brachii had increased fiber size variation, with many fibers containing centrally located nuclei in hematoxylin and eosin staining (Figure 1C). Additionally, several fibers stained with nicotinamide adenine dinucleotide tetrazolium reductase showed radiating sarcoplasmic strands (Figure 1D). In immunohistochemistry against BA-D5 antibody, type 1 fiber was predominant and atrophied (Figure 1E).

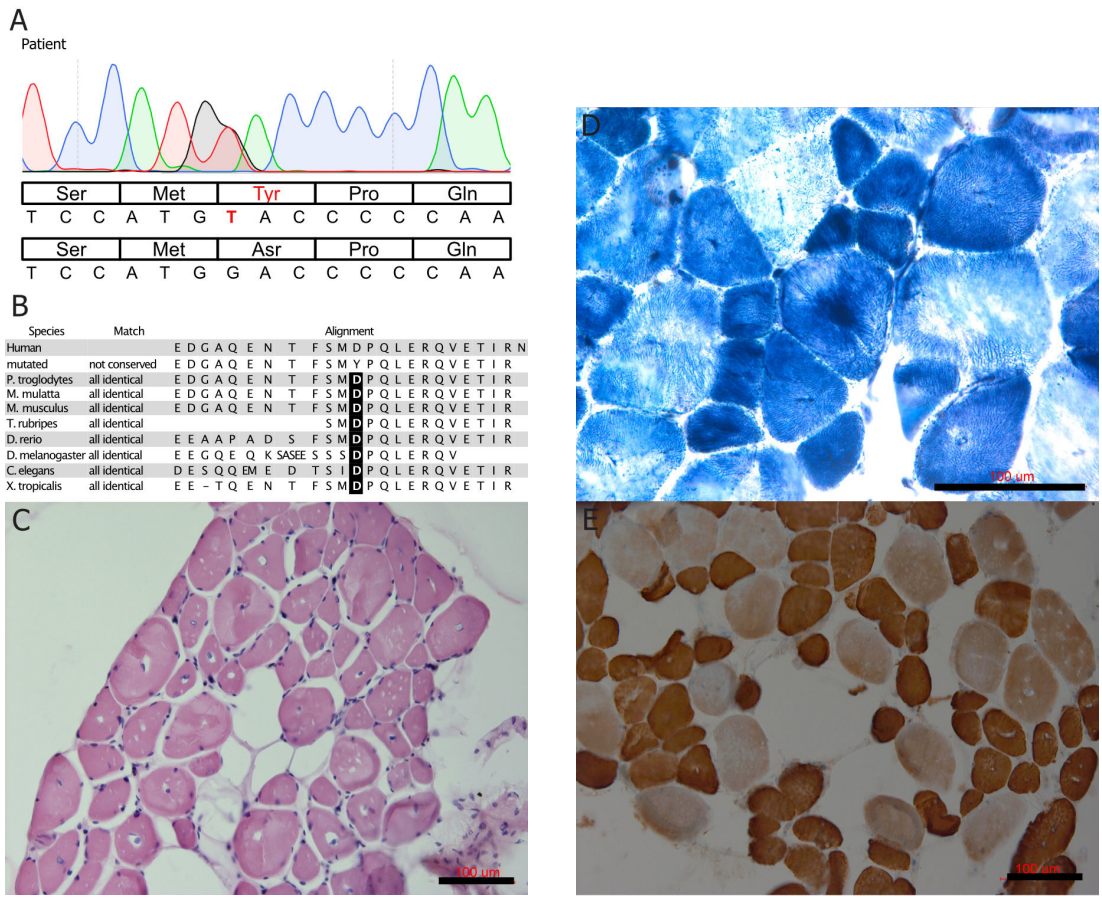

Figure 1. Patient's genetic analysis and muscle pathology results. (A) The Sanger sequencing chromatogram reveals a nucleotide substitution from guanine to thymine at position 1936 of the dynamin 2 (*DNM2*) gene (c.1936G>T, NM_001005361). (B) Asparagine at position 646 in the DNM2 protein is highly conserved throughout the species. (C) Hematoxylin and eosin staining reveals many fibers with centrally located nuclei. (D) Several fibers stained with nicotinamide adenine dinucleotide tetrazolium reductase have radiating sarcoplasmic strands. (E) Immunohistochemistry against BA-D5 antibody shows strongly stained type 1 fiber predominance and atrophy. Scale bar, 100 μm.

DISCUSSION

According to the unique findings of EMG, typical light microscopic features and final confirmation by genetic analysis, the patient was diagnosed with *DNM2*-associated CNM. Concerning the clinical severity of *DNM2*-associated CNM, a recent retrospective study summarized the phenotypic spectrum.[2] The symptoms, which started before childhood in 80% of patients, were mostly both proximal and distal limb weakness. Furthermore, over 90% of patients showed distal weakness.[2,3] Cranial dysfunctions and facial deformities, namely, ptosis, eye movement abnormality, and high arched palate, are also common.[2] Our patient displayed distal bilateral limb weakness and markedly late age of onset, but not respiratory insufficiency, facial weakness, or deformity. Therefore, our patient only had mild phenotypes, which are uncommon in *DNM2*-associated CNM cases.

EMG is valuable for myotonic discharge assessment. Clinical myotonia is a unique symptom in many myotonia-associated disorders, including myotonic dystrophy, myotonia congenita, paramyotonia congenita, and Schwartz–Jampel syndrome, which are usually accompanied with EMG myotonia.[4] However, EMG myotonia without clinical myotonia can only be seen in rare diseases, such as myofibrillary myopathy, CNM, drug-induced myopathy, and Pompe disease[5], indicating a valuable sign for the differential diagnosis.

Regarding genotype–phenotype correlation, several pathogenic variants in *DNM2* were associated with more severe phenotypes.[2] Most patients with a p.Phe372Ser, p.Ser619Leu, p.Ala618Asp, or p.Glu368Lys variant exhibit a congenital or infantile onset and early ambulation difficulty.[2] Patients with p.Phe372Ser or p.Ser619Leu also need respiratory and feeding assistance.[2] Conversely, patients with p.Arg522His or p.Arg369Trp showed milder severity.[2] Our patient harboring p.Asp646Tyr revealed late age of onset, with no respiratory or swallowing difficulties. Therefore, the protein variant p.Asp646Tyr can be associated with a milder phenotype in *DNM2*-related CNM. Further research on patients with p.Asp646Tyr is necessary to elucidate the correlation between severity and genotype.

DNM2 is a ubiquitously expressed GTPase with high expression levels in the skeletal muscles.[6] Located in T-tubules at development, DNM2 is essential for membrane fission.[1,6] Wild-type DNM2 lowers the GTPase activity to stabilize T-tubule–like structures.[6] In *DNM2*-associated CNM, most of the pathogenic variants located in the middle or pleckstrin-homology domains can cause formation of abnormally stable polymers and increase the GTPase activity though a gain-of-function manner. This mechanism is supported by in vivo and in vitro experiments. In cultured cells with *DNM2* pathogenic variants, T-tubule-like structures were fragmented[7], while in the body wall muscle of a fruit fly model with *DNM2* mutations, the T-tubule collapsed.[8] Interestingly, a higher GTPase activity in DNM2 pathogenic variants correlates with increased fragmentation of T-tubule-like structures and more severe pathogenicity by vitro assay.[6] Therefore, T-tubule disruption resulting in defective excitation–contraction coupling, or abnormal membrane fission may be involved in eliciting myotonia in *DNM2*-associated CNM.[8-10]

Concerning treatment, reduction of gain-of-function features in DNM2 has been tried to diminish the GTPase activity. In addition, gene slicing approaches, shRNA targeting *DNM2* mRNA, or antisense oligonucleotides against *DNM2* mRNA were positively effective in a *DNM2* mouse model.[11] Tamoxifen also demonstrated positive effects not only on muscle power but also histologic findings in both *DNM2* and *BIN1* mouse models through DNM2 level regulation.[12] Presently, a clinical trial of the antisense medication DYN101 (NCT04033159) for *DNM2*-related CNM is ongoing.

In conclusion, physicians may consider Pompe disease, a treatable disorder, as a possible diagnosis for patients showing EMG myotonia without clinical myotonia. If the result for Pompe disease is negative, *DNM2*-related CNM should be included in the differential diagnosis of EMG myotonia. Further study is needed in *DNM2*-associated CNM in order to establish the phenotype–genotype correlation.

DISCLOSURE

Financial support: This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (NRF-2021R1G1A1009123).

Conflict of interest: None

REFERENCES

1. Gomez-Oca R, Cowling BS, Laporte J. Common pathogenic mechanisms in centronuclear and

myotubular myopathies and latest treatment advances. *Int J Mol Sci* 2021; 22(21):11377. doi:10.3390/ijms222111377
2. Hayes LH, Perdomini M, Aykanat A, *et al*. Phenotypic spectrum of DNM2-related centronuclear myopathy. *Neurol Genet* 2022; 8:e200027. doi:10.1212/NXG.0000000000200027
3. Park YE, Choi YC, Bae JS, *et al*. Clinical and pathological features of Korean patients with DNM2-related centronuclear myopathy. *J Clin Neurol* 2014; 10:24-31. doi:10.3988/jcn.2014.10.1.24
4. Miller TM. Differential diagnosis of myotonic disorders. *Muscle Nerve* 2008; 37:293-9. doi:10.1002/mus.20923
5. Dabby R, Sadeh M, Gilad R, Jurkat-Rott K, Lehmann-Horn F, Leshinsky-Silver E. Myotonia in DNM2-related centronuclear myopathy. *J Neural Transm (Vienna)* 2014; 121:549-53. doi:10.1007/s00702-013-1140-8
6. Fujise K, Okubo M, Abe T, *et al*. Imaging-based evaluation of pathogenicity by novel DNM2 variants associated with centronuclear myopathy. *Hum Mutat* 2022; 43:169-79. doi:10.1002/humu.24307
7. Fujise K, Okubo M, Abe T, *et al*. Mutant BIN1-dynamin 2 complexes dysregulate membrane remodeling in the pathogenesis of centronuclear myopathy. *J Biol Chem* 2021; 296:100077. doi:10.1074/jbc.RA120.015184
8. Chin YH, Lee A, Kan HW, *et al*. Dynamin-2 mutations associated with centronuclear myopathy are hypermorphic and lead to T-tubule fragmentation. *Hum Mol Genet* 2015; 24:5542-54. doi:10.1093/hmg/ddv285
9. Li Q, Lin J, Widrick JJ, *et al*. Dynamin-2 reduction rescues the skeletal myopathy of a SPEG-deficient mouse model. *JCI Insight* 2022; 7. doi:10.1172/jci.insight.157336
10. Zhao M, Maani N, Dowling JJ. Dynamin 2 (DNM2) as cause of, and modifier for, human neuromuscular disease. *Neurotherapeutics* 2018; 15:966-75. doi:10.1007/s13311-018-00686-0
11. Buono S, Ross JA, Tasfaout H, *et al*. Reducing dynamin 2 (DNM2) rescues DNM2-related dominant centronuclear myopathy. *Proc Natl Acad Sci U S A* 2018; 115:11066-71. doi:10.1073/pnas.1808170115
12. Gineste C, Simon A, Braun M, Reiss D, Laporte J. Tamoxifen improves muscle structure and function of Bin1- and Dnm2-related centronuclear myopathies. *Brain* 2023; 146:3029-48. doi:10.1093/brain/awac489