Case Report

J Genet Med 2020;17(2):89-91
https://doi.org/10.5734/JGM.2020.17.2.89
ISSN 1226-1769 (Print) 2383-8442 (Online)

JGM Journal of Genetic Medicine

Axonal Charcot-Marie-Tooth case with a novel heterozygous variant in *MFN2* assessed by the MutationDistiller

Ho-Sung Ryu[1], Yun-Jeong Lee[2], and Jong-Mok Lee[1,3,*]

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

Charcot-Marie-Tooth (CMT) disease can be divided mainly into demyelination and axonopathy based on the results of the electrophysiological study. Mitofusin 2, encoded by *MFN2* gene, has a crucial role in the fusion of mitochondria, which is known to associate with CMT type 2A as one of the axonal forms. We describe a 44-year-old man with progressive weakness on bilateral legs after noticing foot drop in his early teen. When we examined him at 45 years of age, he presented atrophy on entire legs and with distal muscle weakness on limbs. The nerve conduction study revealed severely decreased amplitude on motor nerve ranging from 0.2 to 4.5 mV, while conduction velocity remained more than 30.4 m/s. The whole-exome sequencing revealed a novel variant c.2228G>T in *MFN2* by efficient genetic analysis tool, MutationDistiller. This report will not only expand the mutation spectrum of CMT2A but also introduce a time-saving genetic analysis tool.

Key words: Muscular atrophy, Whole exome sequencing, Hereditary sensory and motor neuropathy.

Introduction

Charcot-Marie-Tooth (CMT) disease type 2A is known to be associated with mutations of *MFN2*, which is one of the leading causative genes for axonal CMT [1]. *MFN2* encodes mitofusin 2 protein in the outer mitochondrial membrane, which has a crucial role in mitochondrial fusion by initiating the formation of antiparallel dimers between their second heptad repeat (HR2) domains [2]. Therefore, the loss-of-function of mitofusin 2 results in the failure of mitochondrial fusion and transport [2]. So far, more than 150 mutations in MFN2 have been identified (https://databases.lovd.nl/shared/genes/MFN2). Here, we report a CMT2A case with a novel mutation in *MFN2*. We believe this report may expand the mutation spectrum of CMT2A.

Case

The proband, a 44-year-old man, was born from non-consanguineous parents. He visited the department of neurology presenting with slowly progressive weakness of the limbs. At the age of 10, he noticed the dropping of feet while walking on a flat surface. At the age of 20, Achilles tendon lengthening was undergone to minimize ankle contracture. At the age of 37, he noticed atrophy on the distal part of bilateral limbs. At the age

Received: 3 July 2020, Revised: 17 July 2020, Accepted: 21 July 2020, Published: 31 December 2020
*Corresponding author: Jong-Mok Lee, M.D., Ph.D. https://orcid.org/0000-0002-2918-6166
Department of Neurology, School of Medicine, Kyungpook National University, 680 Gukchaebosang-ro, Jung-gu, Daegu 41944, South Korea.
Tel: +82-53-200-5765, Fax: +82-53-422-4265, E-mail: azulmar@gmail.com
Conflict of interest: The authors declare that they do not have any conflicts of interest.

of 43, he experienced difficulties writing, using chopsticks, and zipping up the jacket. He denied family history.

A neurologic examination at 45 years of age revealed a weakness in the distal part of bilateral arms and legs. Individually, the patient was not able to move the ankle joint, including dorsi/plantar flexion at all. The motor power of flexion/extension in fingers and wrists and knee extension were four as the Medical Research Council (MRC) grade. The MRC grade of knee flexion was three. The power of the shoulder and hip joints remained normal. Strikingly, the atrophy was severe on the lower legs, in which the circumference was 23 cm at the point of 15 cm below the patella (Fig. 1A). Overall deep tendon reflexes were decreased. Vibration sense was disturbed below both ankles. The hammertoes on both feet were revealed, but pes cavus was not evident. The nerve conduction studies (NCS) demonstrated severely decreased amplitude of compound muscle action potential (CMAP) ranging from 0.2 to 4.5 mV in upper extremities and sensory nerve action potentials ranging from 2.0 to 3.6 μV in lower extremities. The CMAPs were not elucidated in the lower extremities. In contrast, the conduction velocity remained more than 30.4 m/s (Table 1). According to the findings of history, examination, and laboratory, this patient was graded as 14 by the CMT neuropathy score (CMTNS). Based on the results of NCS, we proceeded directly to whole-exome sequencing. To identify the pathogenic variant, we uploaded the variant call format file to the MutationDistiller website (https://www.mutationdistiller.org). Once uploaded, we queried "Charcot-Marie-Tooth" in the phenotype inquiry. The MutationDistiller system identified heterozygous variant c.2228G>T (p.Ser743Ile, NM_014874.3, Fig. 1B) of *MFN2* in the proband, but is not listed in the Genome Aggregation Database (gnomAD) or the Exome Aggregation Consortium. And this variant was predicted to be "damaging" with a score of 0.018 by SIFT, "deleterious" with a score of -3.18 by PROVEAN, and "possibly damaging" with a score of 0.945 by PolyPhen-2 systems. Also, this variant is categorized as "likely pathogenic" satisfying two moderate and two supporting evidences based on ACMG/AMP guidelines [3].

Discussion

We recognized axonal CMT based on the electrophysiological findings, and the diagnosis was confirmed by detecting a novel mutation in *MFN2* c.2228G>T (p.Ser743Ile). Moreover, we have discovered the pathogenic mutation efficiently through MutationDistiller [4]. Also, different amino acid substitutions at the same position (c.2229T>A, p.Ser743Arg) had been reported to be pathogenic, which can support the pathogenicity of a variant in our study [1].

WES is currently considered to be a powerful tool for genetic analysis. However, the more we perform WES, the more we get tons of variants to be sifted. To determine the pathogenic muta-

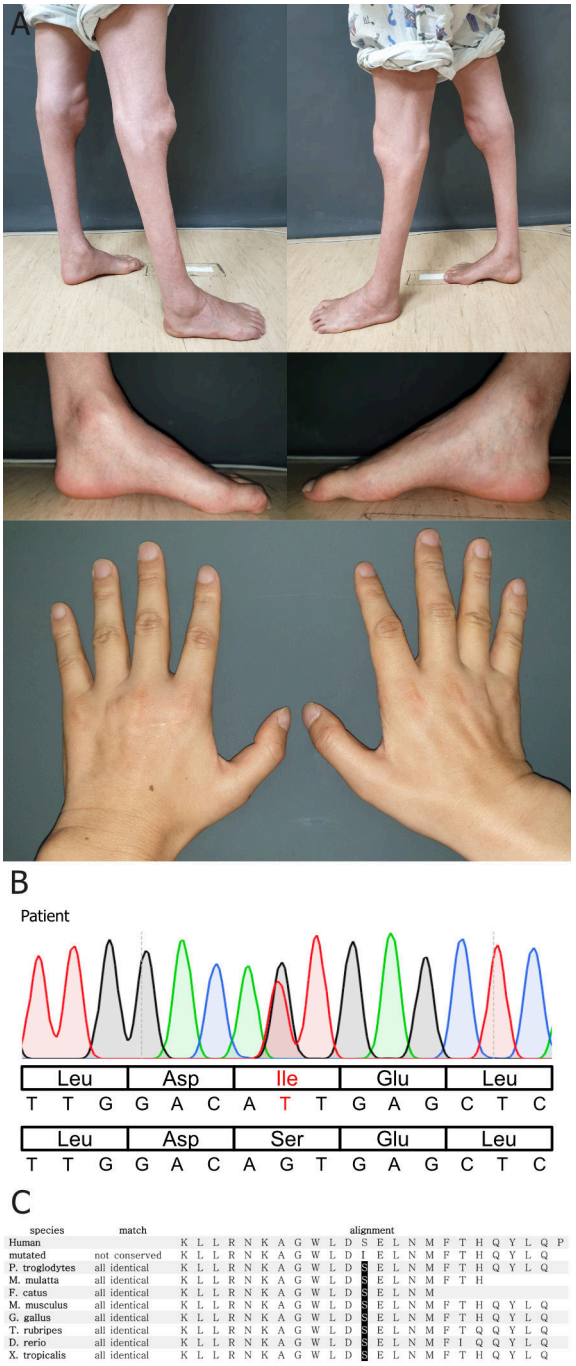

Fig. 1. Photos and results of genetic analysis from the proband. (A) Atrophy of lower extremities, intrinsic muscles of hand, and the distal part of feet is evident. (B) A heterozygous variant c.2228G>T (p.Ser743Ile, NM_014874.3) in *MFN2* is confirmed by Sanger sequencing in the proband. (C) Serine at the position 743 in mitofusin 2 protein is highly conserved across the species.

Table 1. Nerve conduction studies of the patient

Nerves	Stimulation site	Recording site	Nerve conduction study		
Motor			Latency (msec)	CMAP (mV)	NCV (m/sec)
Median	Wrist	Abductor pollicis brevis	4.69 ↑ (<3.6)	0.4 ↓ (>5.0)	
	Elbow			0.2 ↓ (>5.0)	44.6 ↓ (>50)
	Axilla			0.2 ↓ (>5.0)	34.3 ↓ (>55)
Ulnar	Wrist	Abductor digiti minimi	3.91 ↑ (<3.0)	2.6 ↓ (>5.0)	
	Below elbow			1.4 ↓ (>5.0)	52.6
	Above elbow			1.3 ↓ (>5.0)	45.2
	Axilla			0.7 ↓ (>5.0)	30.4 ↓ (>52)
Peroneal	Ankle	Extensor digitorum brevis		NR	
	Knee			NR	
Tibial	Ankle	Abductor hallucis		NR	
	Knee			NR	
Sensory				SNAP (μV)	NCV (m/sec)
Median	Finger	Wrist		2.0 ↓ (>10)	33.5 ↓ (>41)
Ulnar	Finger	Wrist		3.1 ↓ (>10)	33.1 ↓ (>39)
Sural	Midcalf	Lateral malleolus		3.6 ↓ (>6)	45.6

CMAP, compound muscle action potential; NCV, nerve conduction velocity; NR, no response; SNAP, sensory nerve action potential, normal ranges are described between parentheses.

tion from the results of WES, we have filtered allele frequency and the score of in-silico analysis such as SIFT, Proven, and Polyphen2 manually. MutationDistiller is a recently introduced online tool for the analysis of WES [4]. It combines MutationTaster's pathogenic predictions with a phenotype database of the Human Phenotype Ontology and provides a list of potential disease mutations [4]. Therefore, this tool can reduce the burden of identifying possible pathogenic variants.

Human MFN2 protein consists of GTPase, first heptad repeat (HR1), transmembrane, and HR2 domains [2]. HR2 is an essential part of the initiation of mitochondrial fusion by tethering each other. And the dimerization of the GTPase domains is responsible for pulling the mitochondrial membrane [2]. The loss-of-function of a novel variant can lead to the failure of mitochondrial fusion by interferences of tethering.

In terms of phenotype-genotype correlation in CMT2A, the type or location of mutation was not associated with severe or mild phenotype [5,6]. The previous study could not reveal any relationship between the site or type of mutation and the age at onset, clinical severity, or additional features [6,7]. However, early-onset patients seem to present with severe phenotype with higher score of CMTNS [5,7].

In conclusion, this study demonstrated the CMT2A patient with a novel mutation c.2228G>T in *MFN2*, analyzed by an efficient tool of MutationDistiller.

References

1. Bombelli F, Stojkovic T, Dubourg O, Echaniz-Laguna A, Tardieu S, Larcher K, et al. Charcot-Marie-Tooth disease type 2A: from typical to rare phenotypic and genotypic features. JAMA Neurol 2014;71:1036-42.
2. Filadi R, Pendin D, Pizzo P. Mitofusin 2: from functions to disease. Cell Death Dis 2018;9:330.
3. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al.; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405-24.
4. Hombach D, Schuelke M, Knierim E, Ehmke N, Schwarz JM, Fischer-Zirnsak B, et al. MutationDistiller: user-driven identification of pathogenic DNA variants. Nucleic Acids Res 2019;47:W114-20.
5. Choi BO, Nakhro K, Park HJ, Hyun YS, Lee JH, Kanwal S, et al. A cohort study of MFN2 mutations and phenotypic spectrums in Charcot-Marie-Tooth disease 2A patients. Clin Genet 2015;87:594-8.
6. Verhoeven K, Claeys KG, Züchner S, Schröder JM, Weis J, Ceuterick C, et al. MFN2 mutation distribution and genotype/phenotype correlation in Charcot-Marie-Tooth type 2. Brain 2006;129(Pt 8):2093-102.
7. Chung KW, Kim SB, Park KD, Choi KG, Lee JH, Eun HW, et al. Early onset severe and late-onset mild Charcot-Marie-Tooth disease with mitofusin 2 (MFN2) mutations. Brain 2006;129(Pt 8):2103-18.