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A homozygous *SH3TC2* mutation in a Korean patient with Charcot–Marie–Tooth disease type 4C

[1]Je-Young Shin, [2]Jong-Mok Lee

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

Abstract

Charcot–Marie–Tooth disease type 4C (CMT4C) is an autosomal recessive neuropathy associated with *SH3TC2* mutations, resulting in slow conduction velocity via hypomyelination. The occurrence of CMT4C in demyelinating Charcot–Marie–Tooth (CMT) varies among ethnicities, and several variants have been reported as the founder mutation. In Korea, the incidence of CMT4C was calculated as approximately 2%, and all patients have compound heterozygous mutations, which is partly due to the prohibition of consanguineous marriage. Herein, we describe a 25-year-old male who presented a slowly progressive limb weakness and impaired vibration sensation. Whole-exome sequencing revealed homozygous variants c.929G>A of *SH3TC2* after identifying negative multiplex ligation-dependent probe amplification results of *PMP22*. Based on our literature review, this is the first CMT4C patient with a homozygous variant with each allele inherited from both the parents.

Keywords: whole-exome sequencing, inherited peripheral neuropathy, heterozygote, muscle weakness

INTRODUCTION

Charcot–Marie–Tooth disease (CMT) type 4C has been known to be associated with *SH3TC2* mutations, which encodes the Src homology-3 (SH3) domain and tetratricopeptide repeat motifs located in the plasma membrane of the Schwann cells in the peripheral nerves. Loss of functional SH3TC2 protein widens Ranvier nodes and thinning of myelin sheaths result in slow conduction velocity.[1] Law and tradition have prohibited consanguineous marriage in Korea. Therefore, the prevalence of autosomal recessive (AR) disease is relatively low and reported patients with CMT4C harbor compound heterozygote mutations in the *SH3TC2*.[2] In this report, a CMT4C case of homozygous *SH3TC2* mutation is reported.

CASE REPORT

The proband, a 25-year-old man, was born from nonconsanguineous parents. He visited the Department of Neurology with complaints of slowly progressive limb weakness since infancy. He was able to walk at the age of 24 months. He was unable to run with speed similar to other children. At seven years of age, he noted the foot deformity. He had complained of weakness but remained undiagnosed. Neurologic examination at 25 years revealed weakness of the distal part of bilateral arms and legs. The Medical Research Council (MRC) grade was 4 for both finger extension and ankle dorsiflexion. Other limb movements were normal. Overall deep tendon reflex was reduced. Vibration sense was impaired below both ankles. There was pes cavus and hammertoes on both feet. However, spine deformities were not observed. Nerve conduction studies (NCS) demonstrated slow motor and sensory conduction velocity (Table 1). Brainstem auditory evoked potentials were normal. Based on his medical history, examination, and laboratory findings, the patient was graded as 9 by the CMT neuropathy score (CMTNS).[3] His sensory, arm and leg motor symptoms, and arms and leg strength score was 1, and vibration and ulnar CMAP score was 2. CMT1A was screened using the multiplex ligation-dependent probe amplification (MLPA, MLPA kit P033 CMT1 probemix, MRC-Holland). Once results of MLPA are negative, commercial whole-exome sequencing (WES) was performed to identify other causative genes for CMT beyond CMT1A. In case of point mutation, bioinformatics programs, including

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

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Table 1: Nerve conduction studies of the patient

Nerves	Stimulation site	Nerve Conduction Study		
Motor		Latency (msec)	CMAP (mV)	NCV (m/sec)
Median	Wrist	6.98	5.1	
	Elbow		1.0	26.8
	Axilla		0.8	12.1
Ulnar	Wrist	4.48	7.7	
	Below elbow		2.4	27.6
	Above elbow		2.5	16.7
	Axilla		2.7	23.0
Peroneal	Ankle		NR	
	Knee		NR	
Tibial	Ankle	9.11	0.3	
	Knee		0.1	8.1
Sensory			SNAP (μV)	NCV (m/sec)
Median	Wrist		18.7	30.6
Ulnar	Wrist		9.8	29.5
Sural	Ankle		2.8	36.3

CMAP; compound muscle action potential, NCV: nerve conduction velocity, NR; no response, SNAP; sensory nerve action potential.

SIFT/PROVEAN and Polyphen2 systems, were used to evaluate variants. Furthermore, pathogenic mutation has been confirmed using a direct Sanger sequence in proband and family members. MLPA for CMT1A showed neither *PMP22* duplication nor deletion. WES was performed after negative MLPA results identified homozygous variants c.929G>A (p.Gly310Glu, exon 8, NM_024577.3, NG_007947.2) of *SH3TC2* in a proband, which is already reported to be pathogenic as a compound heterozygous CMT4C mutation.[2] This variant was also identified as a heterozygote from both the parents (Figure 1).

DISCUSSION

To date, four patients from two families were reported as CMT4C in Korea, who harbor compound heterozygous variants in the *SH3TC2*, c.929G>A, C.2831A>G, c.929G>A, and c.3272G>T.[2] Our study demonstrated that patients with CMT4C carry homozygous variants of c.929G>A, in which each mutated allele was inherited from asymptomatic heterozygous parents. To our best knowledge, this study describes the first patient with CMT4C with homozygous variants of the *SH3TC2* in Korea.

With regard to clinical severity, majority of patients with CMT4C manifested distal predominant weakness of <4 (MRC grade).[2,4] Furthermore, multiple phenotypes besides limb weakness or vibration-dominant sensory symptoms were identified; namely, deafness, diplopia, nystagmus, facial sensory loss, trigeminal neuralgia, cerebellar ataxia, and scoliosis.[1,2,4] To compare with reported typical patients, our patient presented with a mild phenotype. He did not show spine deformity, atrophy, or cranial nerve involvement, with CMTNS and distal weakness scores of 9 and 4, respectively. However, the vibration-dominant sensory deficit in our patient was consistent with the previously reported cases.[2]

The prevalence of CMT4C varies among countries. Patients with CMT4C associated with *SH3TC2* mutation accounted for 15.7% of patients with intermediate AR-CMT in France.[5] and 11.7% in patients with demyelinating CMT in Czech. In contrast, CMT4C frequency in patients with demyelinating and intermediate CMT has been reportedly to be low in Germany (1.7%), Japan (1.76%), and Korea (2.02%).[2,4] Moreover, several founder mutations were also described in European Gypsies (p.Arg1109*) and French–Canadians (p.Arg954*).[4] In Korea, all reported patients with CMT4C harbor c.929G>A variant in the *SH3TC2*; therefore, this variant can be a

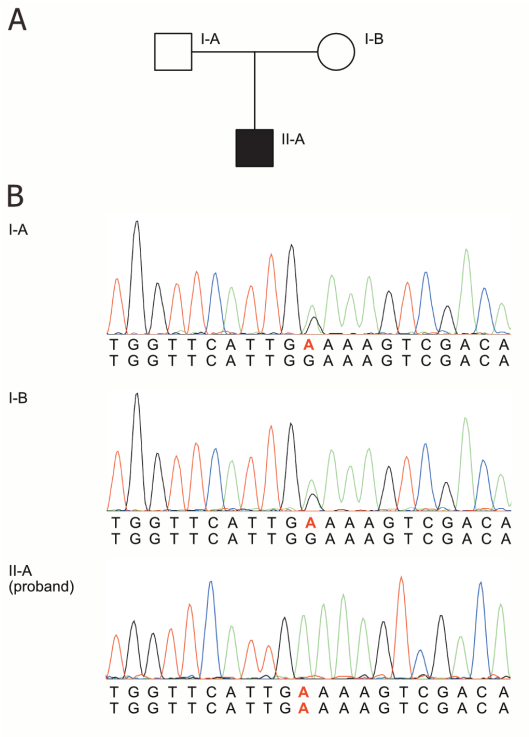

Figure 1. Pedigree and chromatography of Sanger sequence in family members. (A) Only the proband reports the symptom. (B) A homozygous variant of c.929G>A (p.Gly310Glu, NM_024577.3) in SH3TC2 is confirmed using a Sanger sequence in the proband.

founder mutation. In addition, parents of proband married from different families carry the same pathogenic variant as a heterozygote in a single allele, which is likely to be inherited from a common ancestor.

With regard to treatment, symptoms are conservatively treated. Recently, gene replacement therapy was introduced by applying a lentiviral vector of human SH3TC2 cDNA in *Sh3tc2*$^{-/-}$ mice.[6] In treated mice, motor performance, motor nerve conduction velocities, and myelin thickness improved.[6]

WES is extensively used to diagnose rare genetic disease that show Mendelian inheritance pattern.[7] CMT1A characterized by slow conduction velocity accounts for majority of the CMT cases.[8] Therefore, MLPA of the PMP22 gene should be performed as the first genetic test in patients with demyelinating CMT. Once the MLPA of the PMP22 gene is negative, WES can be monitored to investigate point mutation in the MPZ or PMP22 gene. If the motor conduction velocity is normal or intermediate, *GJB1*, *MPZ*, or *MFN2* mutations are explored although WES is highly recommended.[8,9] In this report, the patient with CMT4C was easily diagnosed using WES.

This study has a few limitations. First, haplotype analysis on the association of founder mutation was not performed. Second, pathologic findings from the affected peripheral nerve were not observed. In conclusion, this study demonstrated the first Korean patient with CMT4C harboring homozygous pathogenic variants inherited from both the parents.

DISCLOSURE

Informed consent was obtained from the patient included in this study.

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Conflict of interest: None

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