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CASE REPORT

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비정형 임상 양상을 보인 *de novo* BSCL2 Asn88Ser 변이 dHMN-5 환자: 진행 초기의 감별 진단의 어려움

김현기* 이정현[a]* 원동주[b] 최종락[b] 신하영[a†] 김승현[†]

한양대학교 의과대학 신경과학교실, 연세대학교 의과대학 신경과학교실[a], 진단검사의학교실[b]

Identification of *de novo* BSCL2 Asn88Ser Variant with Atypical Presentation of Distal Hereditary Motor Neuropathy Type 5: Clinical Challenge in Diagnosis of Motor Neuron Diseases

Hyunkee Kim, MD*, Jung Hyun Lee, MD[a]*, Dongju Won, MD[b], Jong Rak Choi, MD, PhD[b], Ha Young Shin, MD, PhD[a†], Seung Hyun Kim, MD, PhD[†]

Department of Neurology, Hanyang University College of Medicine, Seoul, Korea
Department of Neurology, Yonsei University College of Medicine, Seoul, Korea[a]
Department of Laboratory Medicine, Yonsei University College of Medicine, Seoul, Korea[b]

Address for correspondence
Ha Young Shin, MD, PhD
Department of Neurology, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel: +82-2-2228-1600
Fax: +82-2-393-0705
E-mail: hayshin@yuhs.ac

Seung Hyun Kim, MD, PhD
Department of Neurology, Hanyang University College of Medicine, 222-1 Wangsimni-ro, Seongdong-gu, Seoul 04763, Korea
Tel: +82-2-2290-8371
Fax: +82-2-2296-8370
E-mail: kimsh1@hanyang.ac.kr

*These authors contributed equally to the manuscript.
†These authors contributed equally in this article as the corresponding author.

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Diagnosing amyotrophic lateral sclerosis (ALS) is challenging and requires distinguishing it from conditions like distal hereditary motor neuropathy type 5 (dHMN-V). A 21-year-old female initially diagnosed with ALS showed progressive upper limb weakness extending to the lower limbs. Trio exome sequencing revealed a *de novo* pathogenic Berardinelli-Seip congenital lipodystrophy 2 variant (c.263A>G, p.Asn88Ser), confirming dHMN-V. Minipolymyoclonus of small amplitudes in bilateral wrists and ankles was an atypical presentation. This case underscores the importance of considering dHMN-V as a differential diagnosis in ALS-like distal upper extremity weakness.
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Key Words: Distal hereditary motor neuropathy, type V, *BSCL2*, Amyotrophic lateral sclerosis

Diagnosing amyotrophic lateral sclerosis (ALS) is a complex and challenging task, requiring careful consideration of various factors. Differential diagnosis for conditions that mimic ALS is critical to ensure accurate and timely treatment. Among these conditions, distal hereditary motor neuropathy type 5 (dHMN-V) stands out as

a significant differential diagnosis due to its clinical resemblance to ALS. dHMN-V is associated with a specific gene variant in the Berardinelli-Seip congenital lipodystrophy 2 (*BSCL2*) gene.[1] It presents with distinct clinical features: progressive distal muscle weakness, pure motor involvement primarily in the upper limbs, and absence of sensory disturbances. These resemblance of clinical phenotypes makes it important to differentiate dHMN-V from ALS. In this case report, we present a 21-year-old female patient whose clinical journey underscores the significance of distinguishing dHMN-V as a potential alternative diagnosis in cases initially resembling ALS.

CASE

A 21-year-old female visited our neurology department with 6 years history of progressive muscle weakness in the distal muscles of the upper limbs (III-1 in Fig. A). Four years later from the initial onset date, the patient reported difficulty walking, frequent tripping, and weakness in foot dorsiflexion and plantarflexion. She also complained of tremor-like involuntary movements in both hands. She denied any sensory disturbances, sphincter dysfunction. There was no significant family history of neurological disorders.

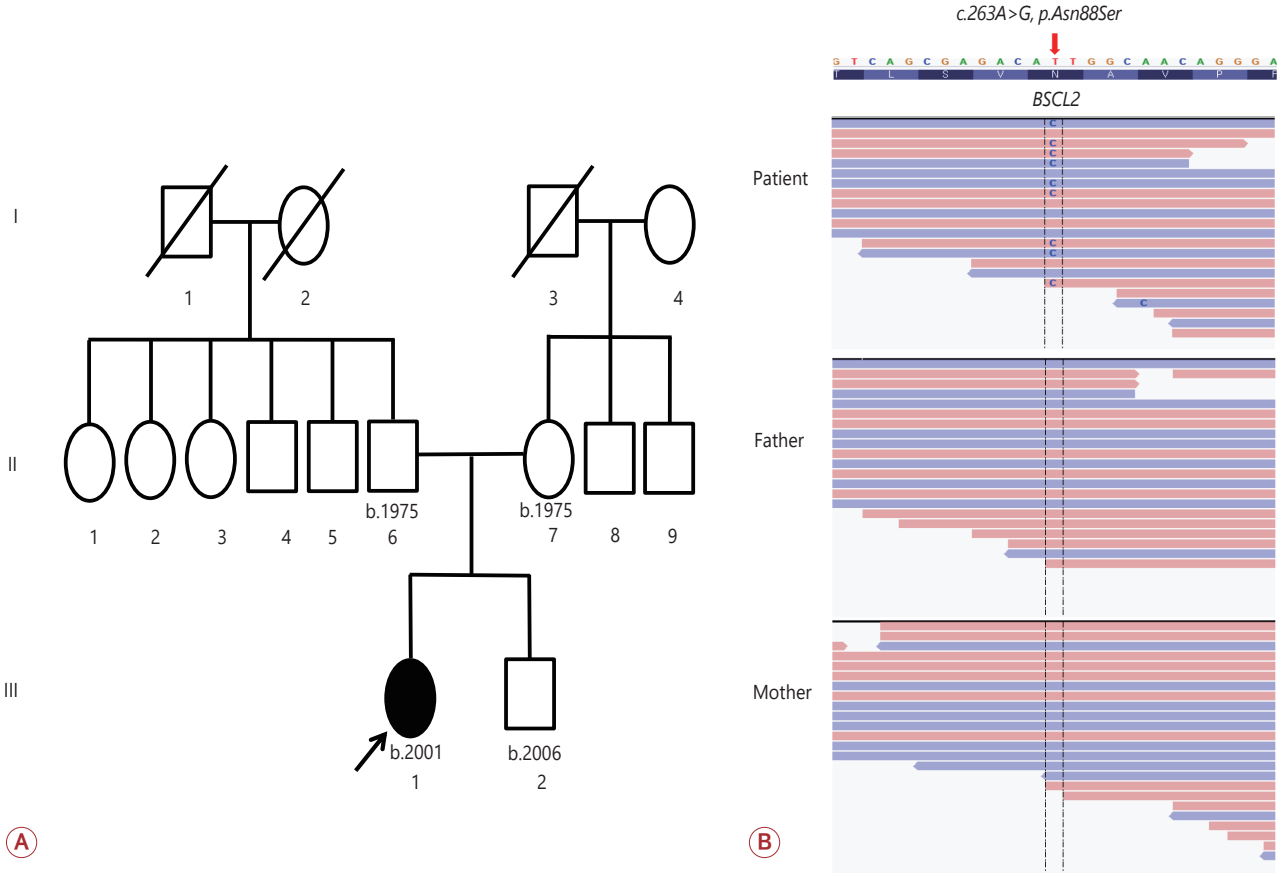

Figure. Pedigree of the patient and trio-whole exome sequencing. (A) Pedigree of the patient (III-1, black arrow). She had heterozygous pathogenic variant (c.263A>G, p.Asn88Ser) in the Berardinelli-Seip congenital lipodystrophy 2 (*BSCL2*) gene. Her parents (II-6 and II-7) did not have gene variant implying the variant was *de novo*. (B) The red arrow indicates a specific point mutation in the *BSCL2* gene, identified as c.263A>G leading to an amino acid change p.Asn88Ser, shown in the sequencing data for the patient, father, and mother. Visual confirmation of the variant with Integrative Genomic Viewer. This proves that the variant identified in the patient was in *de novo* form. Read depth at the position where the variant was found was 305x for the patient, 185x for the father, and 190x for the mother. The variant was found in the patient with a variant allele frequency of 53% (161/305).

Upon examination, the patient showed muscle wasting and weakness, predominantly in upper extremity especially intrinsic hand muscles. Marked weakness in finger flexion and extension of Medical Research Council (MRC) grade 3 was recorded, with mild weakness (MRC grade 4+) in right hip flexion. Pes cavus was also present while the knee extensors and flexors, as well as other upper limbs, appeared unaffected. Deep tendon reflexes were normoactive to hyperactive on upper and lower extremities. Sensory examination was unremarkable. Upon close examination, irregular and repetitive jerky movements resembling

Table. Nerve conduction study of the patient. The study revealed low amplitude of compound muscle action potential recorded over right APB with median nerve stimulation

Site	Lat (ms)	Amp (mV)	CV (m/s)	Distance (cm)	Duration (ms)	Area (%)	F-lat (ms)
Median motor left							
Wrist	3.0	19.1	-	5.0	5.8	100.0	-
Median motor right							
Wrist	3.8	3.0	-	5.0	6.4	100.0	-
Elbow	8.8	2.5	43.0	21.5	6.3	83.3	
Axilla	11.1	2.3	56.5	13.0	6.7	76.7	
Ulnar motor left							
Wrist	2.3	17.1	-	5.0	7.4	100.0	-
Ulnar motor right							
Wrist	2.4	14.6	-	5.0	7.0	100.0	26.2
Elbow (below)	6.6	14.5	54.8	23.0	7.3	99.3	
Elbow (above)	8.0	14.4	67.1	8.0	7.3	98.6	
Axilla	9.4	14.0	57.1	8.0	7.2	95.9	
Tibial motor left							
Ankle	3.9	5.2	-	5.0	7.0	100.0	-
Tibial motor right							
Ankle	3.3	6.1	-	5.0	6.3	100.0	44.1
Knee	10.4	4.9	47.9	34.0	6.4	80.3	
Peroneal motor left							
Ankle	4.3	26.9	-	5.0	5.6	100.0	-
Peroneal motor right							
Ankle	4.3	30.3	-	5.0	6.1	100.0	-
Knee	11.4	22.6	54.2	38.5	6.9	74.6	
Median sensory right[a]							
Finger-wrist	2.8	31.9	44.6	12.5			
Wrist-elbow	3.2	43.9	53.1	17.0			
Elbow-axilla	2.0	143.6	62.5	62.5			
Ulnar sensory right[a]							
Finger-wrist	2.2	24.4	47.7	10.5			
Wrist-elbow	4.4	56.9	54.5	24.0			
Elbow-axilla	1.8	59.9	66.7	12.0			
Sural sensory right[a]							
Calf	2.5	51.9	40.0	10.0			

APB; abductor pollicis brevis, Lat; terminal temporal latency, Amp; amplitude, CV; conduction velocity, F-lat; f-wave latency.
[a]Amp unit, μV

dystonic tremor were seen in the fingers and the toes. There were also minipolymyoclonus of small amplitudes in bilateral wrists and ankles. The clinical presentation of progressive distal muscle weakness and atrophy as a lower motor neuron sign coincided with hyperreflexia as an upper motor neuron sign raised suspicion of a motor neuron disease, especially ALS.

The initial workup included electrophysiology studies, nerve conduction studies (NCS) and electromyography (EMG). NCS revealed low amplitude of compound muscle action potential recorded over right abductor pollicis brevis (APB) with median nerve stimulation (Table). EMG showed active denervation potentials in bilateral 1st dorsal interossei and right APB, confirming a lower motor neuron involvement. Repeated nerve stimulation test was unremarkable. Routine complete blood test, blood chemistry was normal. Brain and cervical spine magnetic resonance imaging was normal.

Since she was young age onset patient, whole exome sequencing was analyzed for any genetic variants. Interestingly, a heterozygous pathogenic variant (NM_032667.6; c.263A>G, p.Asn88Ser) in *BSCL2* gene was identified. Subsequently genetic test for her parents were done and both her parents (II-6, II-7 in Fig. A) did not have the gene variant, identifying this variant is *de novo* (Fig. B). Based on the clinical presentation, electromyographic findings, and genetic test results, the patient was diagnosed with dHMN-V. She was discharged with a plan for close observation, along with the administration of a vitamin supplement serving as an antioxidant.

DISCUSSION

ALS affects motor neurons leading to the progressive deterioration of both upper motor neurons and lower motor neurons. Diagnosis of ALS relies on the clinical symptoms. Differential diagnosis is crucial because potential curative treatments exist for certain ALS mimic diseases.[2] ALS mimics include wide variety of diseases. dHMN-V caused by *BSCL2* variant is also one of ALS mimics that show progressive degeneration of motor neurons in distal upper limbs, especially hand muscles.[3] dHMN-V is mostly limited to distal upper extremity and very slowly progressed in nature. However, early stage at diagnosing ALS patients with upper extremity weakness is confusing because symptoms could only appear in upper limbs.[2,3]

BSCL2 gene encodes seipin, a protein that plays a vital role in lipid droplets formation and regulation of excitatory synaptic transmission. Variant of seipin is believed to provoke endoplasmic reticulum stress, inducing cell toxicity.[4] Known pathogenic variants are p.N88S and p.S90L and p.S90W variants.[5-8] Patients with the same genetic variant may exhibit different clinical phenotypes and show varying degrees of penetrance.[5,9,10] The variant of this patient, p.N88S variant, also show variable phenotypes. Previous study, Auer-Grumbach et al.[5] subdivided clinical phenotypes into six groups: subtypes 1 (no symptoms), subtypes 2 (subclinical phenotype), subtypes 3 (dHMN-V phenotype), subtypes 4 (Silver syndrome phenotype), subtypes 5 (Charcot-Marie-Tooth phenotype), and subtypes 6 (hereditary spastic paraplegia phenotype).

In this case, the combination of progressive muscle weakness and atrophy in the peripheral areas, suggesting lower motor neuron participation, along with heightened reflexes, which point to upper motor neuron impairment, has raised concerns about the possibility of ALS. Moreover, the disease's progression towards the lower extremities, rather than being confined to the upper extremities, along with its relatively rapid course, poses additional challenges to prompt diagnosis. However,

genetic screening confirmed *de novo* variant of *BSCL2* gene and diagnosis of dHMN-V. The patient exhibited some features of typical dHMN-V, which are slowly progressive weakness predominant in the upper limbs and pes cavus with mild involvement of the lower extremities. In addition to such features, dystonic tremor and minipolymyoclonus in the distal limbs were observed unlike previously reported cases.

This case report firstly highlights the importance of considering dHMN-V as a differential diagnosis in patients presenting with clinical features resembling ALS. Secondly, it expands the clinical spectrum associated with *BSCL2* variant. Minipolymyoclonus, described as an atypical clinical feature in this case, may be one of clinical manifestations associated with dHMN-V. It is essential for healthcare practitioners to consider this phenomenon when conducting examinations on patients. Genetic test plays a crucial role in confirming the diagnosis and guiding appropriate management strategies, including genetic counseling and potential therapies targeting the underlying molecular defect. Early and accurate diagnosis is essential for appropriate patient care, counseling, and support for affected families.

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