


A Novel Dynamin 2 Mutation Causing Dominant Intermediate Charcot-Marie-Tooth Neuropathy: Case Report

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Abstract

Dynamin 2 mutations are associated with Charcot-Marie-Tooth neuropathy. We report two siblings with a novel missense heterozygous point mutation (c.1609 G>A) in the highly conserved pleckstrin homology domain in exon 15 of Dynamin 2 presenting with progressive length-dependent sensorimotor polyneuropathy with mixed demyelinating and axonal features on electrodiagnostic studies. The previously unrecognized missense point mutation, which was inherited from their symptomatic but previously undiagnosed mother, was determined to be likely pathogenic based on a non-conservative amino acid substitution (p.Gly537Ser) that is predicted to damage secondary protein structure or function. This report emphasizes the importance of recognizing inherited neuropathies in clinical practice and evaluating suspected pathogenic gene variants initially classified to be of undetermined clinical significance in family cohorts. These cases add to the spectrum of pathogenic Dynamin 2 mutations associated with dominant-intermediate Charcot-Marie-Tooth neuropathy.

Keywords

case report, Charcot-Marie-Tooth neuropathy, Dynamin 2, familial genetic studies, pathogenic gene mutations

Introduction

Charcot-Marie-Tooth (CMT) neuropathy is a heterogeneous group of hereditary sensory and motor neuropathies that typically present with a phenotype of foot deformities such as pes cavus (abnormally high plantar longitudinal foot arches) and hammertoes, progressive distal muscle weakness and atrophy that preferentially involves the peroneal muscles early in the disease course, multimodal sensory loss, and decreased or absent myotactic stretch reflexes. Different gene mutations that impair Schwann cell, myelin, and axonal structure or function cause CMT neuropathy.¹⁻³ Over 60 genes associated with CMT neuropathy have been discovered to date. The most common subclass, CMT Type 1, or hereditary motor and sensory neuropathy type 1 (HMSN 1) consists of primary demyelinating polyneuropathies with diffuse reduction in motor nerve conduction velocities (NCV; <38 m/s in the upper limbs). Axonal CMT or CMT2 is characterized by preservation or mild reduction of NCVs with reduced motor amplitudes. There are also subclasses with histopathological evidence of demyelination and prominent axonal degeneration on nerve biopsies with mildly decreased (25–45 m/s) or normal median NCV, classified as dominant-intermediate (DI)-CMT.¹⁻³

Dynamin 2 (DNM2) is a guanosine triphosphatase (GTPase) that mediates vesicle budding, organelle fission

and fusion, and clathrin-coated endocytosis and acts with other proteins such as actin, endophilin, and amphiphysin. It is composed of 5 domains: (1) N-terminal GTPase domain, (2) middle domain, (3) the lipophilic pleckstrin homology [PH] domain that interacts with membrane phosphatidylinositol 4,5-bisphosphate, (4) GTPase effector domain, and (5) proline/arginine-rich domain at the C-terminus.⁴⁻⁷ *DNM2* mutations are commonly associated with axonal CMT neuropathy type 2M (CMT2M; inherited in an autosomal dominant pattern) or DI-CMT neuropathy type B (DI-CMTB),^{1-3,7-12} as well as centronuclear myopathy (CNM), lethal congenital contractures syndrome type 5, and hereditary spastic paraplegia,^{7,8,13,14} implying phenotypic variability in inherited neuromuscular disorders.

We report 2 cases of a progressive sensorimotor polyneuropathy in adult siblings harboring a previously unrecognized *DNM2* mutation that was inherited from their

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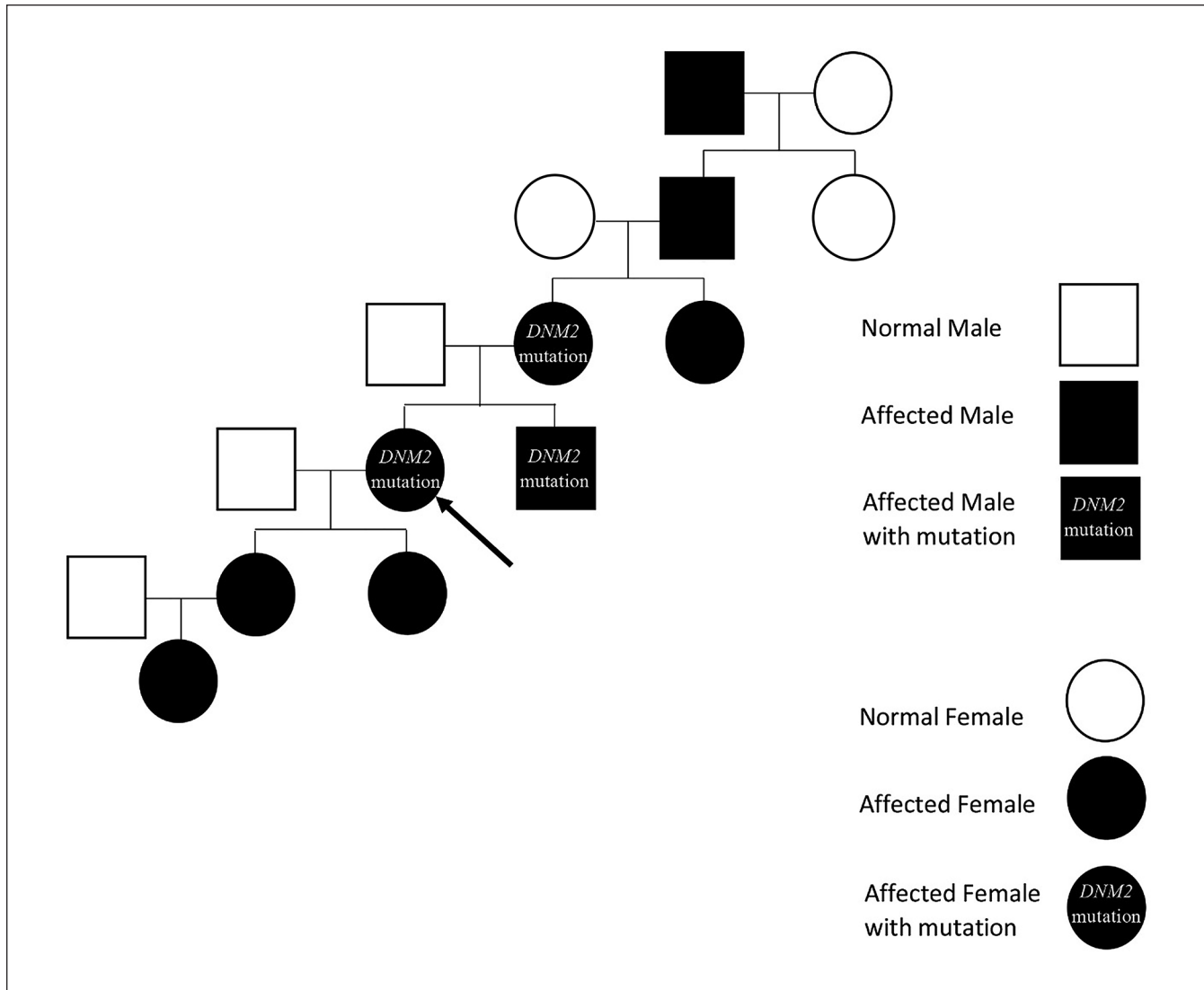


Figure 1. Family pedigree. The Proband's family pedigree demonstrates an autosomal dominant inheritance pattern in the genetically confirmed and clinically suspected individuals indicated.

symptomatic but previously undiagnosed mother, consistent with DI-CMTB. This report further emphasizes the importance of recognizing CMT neuropathy to provide genetic counseling while excluding other chronic neuropathies for which treatment options are available. Performing familial genetic studies in clinical practice to evaluate variants of undetermined significance in potentially relevant genes that are hypothesized to alter transcribed protein structure or function is important to confirm a CMT neuropathy diagnosis.

Case Report

Case 1 (Proband)

This is a 59-year-old woman diagnosed with CMT neuropathy at 16 years of age based on clinical assessment and

electrodiagnostic (EDX) studies performed in 1979. Data from that clinical assessment were not available for review. She returned to the neuromuscular clinic after a long absence requesting confirmatory genetic testing. She reported a family history of presumed CMT neuropathy based on foot drop and intrinsic hand weakness in her maternal grandfather, mother, brother, two daughters, and one granddaughter, although genetic testing or EDX studies had not been performed on extended family members (Figure 1). She complained of progressive weakness, numbness, and tingling in her hands and feet, associated with pain and swelling in her feet, shoulders, and arms. She had been using ankle-foot orthoses (AFOs) since age 19 and denied any falls or need for a cane or walker while using the AFOs.

Neurologic examination showed muscle atrophy in the hands and feet, with finger flexion contractures. Confrontational strength examination (based on the Medical

Table 1. Case 2 Nerve Conduction Study Data.

Side/nerve	Stimulation site	Recording site	Distal latency (ms)	Amplitude (mV)	Normal amplitude (mV)	Negative waveform duration (ms)	Conduction velocity (m/s)
Motor nerve conduction studies							
R Median	Wrist	APB	4.4	0.1	>7	17.9	
	Elbow	APB	12.6	0.1		29.3	30^a (≥50)
R Ulnar	Wrist	ADM	3.2	10.1	>7	15.4	
	Below elbow	ADM	8.9	9.4		22.7	37^a (≥50)
	Above elbow	ADM	12.1	8.5		22.7	31
R Peroneal	Ankle	EDB	NR		>2.5		
	Fibula	EDB	NR				NR (≥40)
R Peroneal	Fibula	TA	4.2	2.4	>4	45.8	
	Popliteal fossa	TA	6.3	2.4		43.7	38 (≥40)
R Tibial	Ankle	AHB	5.2	0.2	>4	24.8	
	Popliteal fossa	AHB	NR				NR (≥40)
Sensory nerve conduction studies							
R Median	Wrist	Digit II	4.1	3.0	>15	1.2	30^a (≥50)
R Ulnar	Wrist	Digit V	3.6	4.0	>12	1.6	28^a (≥50)
R Radial	Forearm	Snuff box	3.0	4.0	>15	1.8	33^a (≥50)
R Sural	Foreleg	Ankle	NR		>3		NR (≥40)
R Superficial Peroneal	Foreleg	Ankle	NR		>3		NR (≥40)

Motor and sensory nerve conduction data from case 2 demonstrate a moderately severe, chronic length-dependent predominantly axonal sensorimotor polyneuropathy with several conduction velocities in the demyelinating range without conduction block, consistent with intermediate forms of CMT neuropathy. Abnormal values indicated in bold type. Brackets indicate normal conduction velocity values.

Abbreviations: R, Right; APB, abductor pollicis brevis; ADM, abductor digiti minimi; EDB, extensor digitorum brevis; NR, not recordable; TA, tibialis anterior; AHB, abductor hallucis brevis; CMT, Charcot-Marie-Tooth.

^aDemyelinating range conduction velocity.

Research Council [MRC] scale) showed normal proximal upper and lower limb muscle strength with wrist and finger extension 3/5, finger abduction and adduction 1/5, ankle dorsiflexion 1/5, and plantarflexion 3/5 weakness bilaterally. Sensation to pinprick, proprioception, and vibration were all subjectively decreased from feet to mid-shins. Myotactic stretch reflexes were absent at the knees and ankles, diminished at brachioradialis and normal at the biceps and triceps on both sides.

Case 2

The Proband's brother is a 58-year-old man who presented with appendicular and low back pain with progressive reduced manual dexterity and imbalance since childhood. Due to work-related difficulties and a clinical suspicion of CMT neuropathy, he was referred to the neuromuscular clinic for specialist evaluation. He had elective carpal tunnel decompression surgeries at a private clinical facility (data not available for review) and underwent magnetic resonance imaging of the lumbar spine with and without contrast at an external facility that showed broad-based disk bulge, bilateral facet joint degeneration changes, and mild-to-moderate bilateral neuroforaminal narrowing at the L4-L5 and L5-S1 levels, associated with Grade 1 L5-S1 anterior spondylolisthesis. Prior to his initial neuromuscular clinic evaluation, he underwent lumbar epidural spinal injections at a private practice pain clinic that improved the pain and numbness in

his feet. He mentioned that his older sister had been diagnosed with CMT neuropathy as a teenager.

Examination revealed muscle atrophy of the hands, feet, and distal legs with high arched feet and high steppage gait. Confrontational strength testing based on the MRC scale showed finger abduction, adduction and extension (4/5), ankle plantarflexion (3/5), and ankle dorsiflexion (2/5) weakness bilaterally. All other muscle groups were normal. Sensory examination revealed subjectively decreased proprioception and absent vibratory sense at the hallux with decreased light touch and pinprick sensation below the knees bilaterally. Myotactic stretch reflexes were absent at the ankles and normal elsewhere.

Comprehensive laboratory tests for acquired causes of polyneuropathy (comprehensive metabolic panel; complete blood count with differentials; hemoglobin A1c; thyroid function tests; vitamins B1, B6, B12, and D levels; serum electrophoresis; serum immunofixation; Lyme disease serology; autoimmune neuropathy panel [antiganglioside IgG/IgM, anti-myelin-associated glycoprotein IgM; and anti-sulfate-3-glucuronidyl paragloboside IgM antibodies]), and 24-hour urine heavy metal screen was normal. EDX studies (Table 1) demonstrated a moderately severe, chronic length-dependent predominantly axonal sensorimotor polyneuropathy with some demyelinating features and no conduction block, as seen in DI-CMTB.

To evaluate a clinical suspicion of autosomal dominant CMT neuropathy in our patients, the Hereditary Neuropathy

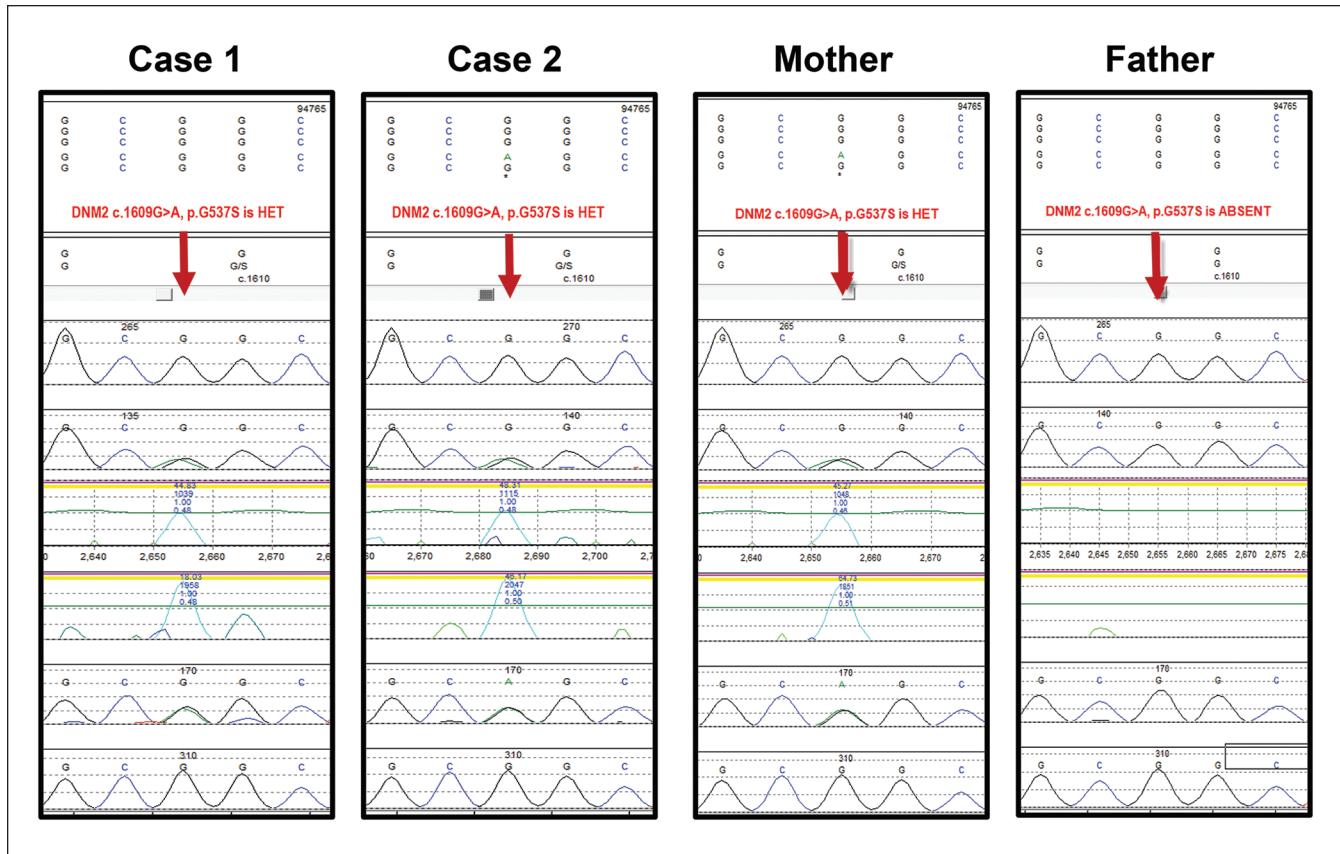


Figure 2. DNA electropherograms. The clinically likely pathogenic heterozygous *DNM2* mutation (c.1609 G>A) is demonstrated in the Proband (case 1), her brother (case 2), and their clinically affected mother. The normal allele is present in their unaffected father, indicating maternal dominant gene transmission. HET = Heterozygous.

genetic test panel was performed by GeneDx (Gaithersburg, Maryland) using oral rinse specimens. Using genomic DNA from the submitted specimens, the coding regions and splice junctions of the genes in the panel were enriched via GeneDx's proprietary-targeted capture system. These targeted regions were sequenced simultaneously using massively parallel (NextGen) sequencing on an Illumina platform using pair-end reads. Bi-directional sequence was assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19, and analyzed for sequence variants.

Genetic testing identified a heterozygous missense point mutation in exon 15 of the *DNM2* gene (c.1609 G>A) on chromosome 19, resulting in substitution of glycine 537 to serine (p.Gly537Ser) in the Proband and her brother (see arrow, Figure 2). This is a non-conservative amino acid substitution, which likely impacts the highly conserved PH domain protein structure and function based on GeneDx's *in silico* analysis. Importantly, a different amino acid substitution at the same position, c.1609 G>T (p.Gly573Cys),¹⁵ and the same point mutation in a nearby residue, c.1597 G>T (p.Gly533Cys),¹⁰ are associated with *DNM2*-related disorders. As the mutation had neither been previously published

as a pathologic variant nor reported as a benign variant, it was initially classified as a variant of undetermined significance.

Due to our high index of suspicion that this mutation was pathogenically significant based on the clinical phenotypes that were consistent with CMT neuropathy and the potential impact of the mutation on secondary protein structure or function, the patients' undiagnosed symptomatic mother and asymptomatic father underwent targeted genetic testing. Their mother possessed the same heterozygous missense *DNM2* point mutation which was absent in their father (Figure 2), supporting our inference that *DNM2* (c.1609 G>A) is causative of DI-CMTB in this family cohort.

Clinical Follow-up

During follow-up neuromuscular clinic visits over the next 2-3 years, the Proband (case 1) reported increased falls despite wearing AFOs; worsening pain in multiple joints, including her hips and knees; progressive weakness in her hands with reduced dexterity; and persistent paresthesias in her feet, adequately treated with Gabapentin. Her brother (case 2) reported worsening hand and leg strength and

progressive difficulty standing for prolonged periods and walking. He decided against using AFOs due to perceived discomfort and walked cautiously to prevent falls without using ambulatory aids.

Discussion

We report a novel heterozygous *DNM2* c.1609 G>A mutation that results in amino acid substitution, p.Gly537Ser, in three family members that expands the repertoire of known mutations associated with autosomal dominant CMT neuropathy. Previously identified pathogenic or likely pathogenic *DNM2* mutations are accessible via the United States of America National Library of Medicine National Center for Biotechnology Information ClinVar website (accessible at <https://www.ncbi.nlm.nih.gov/clinvar>).

The EDX study in case 2 demonstrated absent or markedly low lower limb sensory and distal motor responses with the upper limbs involved but less affected, in keeping with a length-dependent axonopathy. However, minor features of demyelination were noted in the ulnar motor nerve conduction study with a normal compound motor action potential and conduction velocity slowing below the cutoff value of 38 m/s expected in CMT2. In addition, the right median motor, right ulnar sensory, and right superficial radial sensory conduction velocities were in the demyelinating range. The clinical history and physical examination findings, EDX data, and genetic testing were most consistent with DI-CMTB.

Pathogenic *DNM2* mutations, including those associated with DI-CMTB and CMT2M, commonly alter the conserved PH domain,^{10,12-15} consistent with the patients' mutation. These mutations may alter Schwann cell fission, endocytosis, and transport by disrupting the cytoskeleton and Schwann cell and axon interactions^{6,7,12} but could directly affect peripheral nerve axons with or without Schwann cell membrane instability.⁴

Conclusions

In summary, we report a novel heterozygous missense point mutation c.1609 G>A that results in p.Gly537Ser in the highly conserved *DNM2* PH domain in two adult siblings with a CMT neuropathy phenotype, consistent with a diagnosis of DI-CMTB. Identical gene expression in their symptomatic mother, implying an autosomal dominant inheritance pattern in this family, supports that this mutation is pathogenic. This case report emphasizes the importance of pursuing potentially causative gene variants of undetermined significance by targeted familial genetic testing in symptomatic and asymptomatic individuals in clinical practice. Furthermore, the case report adds to the spectrum of clinically likely pathologic *DNM2* mutations associated with DI-CMTB. Functional studies using relevant *in vitro* or animal model systems would further confirm the significance and pathologic relevance of this mutation.

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Declaration of Conflicting Interests

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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