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A recurrent *MORC2* mutation causes CMT2Z

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Abstract

Background and Aims—We found a p.Ala406Val (c.1217C>T) mutation in *MORC2* in three individuals, from two families.

Methods—All three individuals were evaluated and clinical electrophysiology was completed.

Results—The neuropathy began in childhood to early adulthood, with distal weakness progressing to proximal weakness. Vinblastine (for Hodgkin lymphoma) acutely worsened the weakness in one patient.

Interpretation—This finding confirms that that the p.Ala406Val mutation in *MORC2* causes severe neuropathy. In addition, we report the first case of vinblastine neurotoxicity in CMT2Z.

Keywords

Charcot-Marie-Tooth disease; axonal CMT; neuropathy; vinblastine

Introduction:

More than 20 different mutations in *MORC2* cause Charcot-Marie-Tooth disease type 2Z (CMT2Z), a dominantly inherited axonal neuropathy (Sancho, et al., 2019). p.Arg252Trp is the most common, with onset of distal weakness and sensory loss in the first or second decade progressing to proximal weakness, cramps, and extensor plantar responses but not frank spasticity (Albulym, et al., 2015). Other mutations (e.g., p.Ser25Leu) may have an infantile onset of a spinal muscular atrophy-like presentation, and electrophysiological evidence of asymmetric axonal loss, myokymia, and fasciculations (Sevilla, et al., 2016). A different set of *MORC2* mutations are associated with respiratory insufficiency and even encephalopathy and cerebellar atrophy (Ando, et al., 2017; Schottmann, et al., 2016; Zanni, et al., 2017). *De novo* mutations may present with developmental delay, intellectual disability, growth retardation, microcephaly, and variable craniofacial dysmorphism in which neuropathy has not been recognized as a predominant feature (Guillen Sacoto, et al., 2020). Here, we report a p.Ala406Val mutation in *MORC2* in three individuals from two unrelated

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families, one of whom had severe worsening after undergoing vinblastine treatment for Hodgkin lymphoma.

Materials and Methods:

A father and a son were evaluated at the University of Pennsylvania (by S.S.S.), and an unrelated woman was evaluated at Johns Hopkins University (by D.R.C). Clinical electrophysiology was performed as part of their evaluation.

Results:

A 33-year-old woman presented with fatigue and cramping. She was clumsy as a child and was unable to roller skate or ice skate. She had severe distal wasting and moderate to severe weakness in the intrinsic hand muscles and toe extensors, mild weakness in bilateral elbow flexion and extension, wrist flexion and extension, finger flexion, and ankle plantar flexion. Vibration was absent at the toes and 4 at the knees using the Rydel-Seiffer tuning fork. Pinprick was reduced to the dorsum of the foot, and joint position was normal at the toes. She was areflexic. The left sural, ulnar, right radial, and bilateral median sensory responses were absent (Table 1). The left and right median motor responses were absent; the left and right ulnar motor responses were normal. Needle EMG was not done. The patient's father had neuropathy: his nerve conductions were reviewed and revealed no responses in the lower limbs and a pattern of axonal neuropathy in the upper limbs.

An unrelated man developed foot drops in his late 20s, but in his early 20s he was able be a captain in the Marines. His strength slowly worsened to the point that he had difficulty getting out of a car and using his arms in his 50s. At age 61, he had severe proximal and distal weakness. Ankle plantar and dorsiflexion were 0–1/5 (MRC scale), and biceps and deltoid were 2/5. Vibratory sensation was absent in his toes and 2 at the thumbs. He was areflexic. Clinical electrophysiology was not done.

His son was evaluated at age 31 and 41. He developed neuropathy as a young child and was diagnosed with CMT in the second grade. He frequently sprained his ankles and had a triple arthrodesis and a tendon transfer on one foot at age 14 and on the other foot at age 17. In college, he was diagnosed with Hodgkin lymphoma and was treated with ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine). Before treatment, he could walk up four floors with a heavy backpack without using a handrail; after treatment, he needed a handrail to help pull himself up the steps. He did not report worsening of sensory symptoms. At 31, he was weak in proximal and distal arm and leg muscles – intrinsic hand muscles were 3/5 and biceps, deltoid, and triceps were 4/5. Vibration was absent in his toes, and he was areflexic. He began using a walker at age 32, and, at age 41, he needed a wheelchair. An EMG at age 41 showed absent left median and ulnar sensory responses, a severely reduced radial sensory amplitude, reduced median and ulnar motor amplitudes (Table 1), and severe, chronic denervation in proximal and distal arm muscles. His CMT Exam Score (CMTES) was 15 (out of a maximum score of 28) and his CMT Neuropathy Score (CMTNS) was 19 (out of a maximum score of 36).

All patients had normal cognition, and did not have cerebellar findings, retinopathy, extensor plantar responses, or spasticity. Genetic testing showed a p.Ala406Val (c.1217C>T) mutation in *MORC2* in all three affected individuals, but not in the mother of the 41-year-old man.

Discussion:

The p.Ala406Val (c.1217C>T) mutation in *MORC2* was not present in gnomAD but was previously described in a patient with proximal and distal weakness (Frasquet, et al., 2018; Sancho, et al., 2019). The identification of two additional, unrelated families with the same p.Ala406Val mutation demonstrates the pathogenic role of this mutation.

The MORC2 protein is a DNA-dependent ATPase that is highly conserved in higher eukaryotes, with GyraseB, Hsp90, MutL (GHL)-ATPase, a CW-type zinc finger domain, and three predicted coiled-coil domains (Sancho, et al., 2019). It functions as an effector of epigenetic transcriptional repression by the human silencing hub (HUSH) complex (Sancho, et al., 2019; Tchasovnikarova, et al., 2017), a regulator of ATP-citrate lyase activity (Sanchez-Solana, et al., 2014), and as a facilitator of chromatin remodeling and repair in response to DNA damage (Xie, et al., 2019). The p.A406V variant is located between the first coiled-coil domain and CW-type zinc finger domain of *MORC2*; variants in this region are speculated to disturb ribonucleic acid metabolism (Zhao, et al., 2016).

In addition, the functional consequences of *MORC2* mutations that cause neuropathy differ from those that cause a more severe phenotype without recognized neuropathy. For instance, functional assays on a series of mutants – p.Thr24Ile, p.Glu27Lys, p.Ser87Leu, p.Arg132Cys, p.Arg266Ser, and p.Val413Phe – hyperactivated HUSH-mediated silencing, albeit to differing extents: the variants with the strongest hyperactivating effects result in the most severe central nervous system symptoms (Guillen Sacoto, et al., 2020). The extent of HUSH complex hyperactivation may have differential phenotypic consequences in the central nervous system as compared to motor and sensory neurons. Because we did not find any central nervous system involvement in either family, we infer that the p.Ala406Val mutation results in a lesser degree of HUSH complex hyperactivation.

This may be the first case of neurotoxicity in a person with CMT2Z. Although vincristine is well documented to cause neuropathy, this complication is less common for vinblastine (Shah, et al., 2018). Similarly, vincristine is well known to cause acute deterioration in people with CMT1A and was also reported to affect one patient with an unknown type of CMT2 (Ibanez-Julia, et al., 2017), but we could not find examples of vinblastine neurotoxicity in someone with CMT. Nevertheless, it seems prudent to carefully monitor a patient with CMT for whom therapy with any vinca alkaloid is being considered.

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Table 1:

Summary of electrophysiology, CMT Exam Score (CMTES), and CMT Neuropathy Score (CMTNS).

	ulnar CMAP			median CMAP			radial SNAP (A)		CMTES/CMTNS
Patient (age)	DL <3.2 ms	amp ≥6 mV	CV ≥49 m/s	DL <4.4 ms	amp ≥4 mV	CV ≥49 m/s	amp ≥15 μV	CV ≥50 m/s	
case 1 (33 y)	2.6	8.9	55	NR	NR	NR	NR	NR	
II-1 (41 y)	3.6	5.0	43	4.5	2.2	50	3.3	43	15/19

A: antidromic; amp: amplitude; CMAP: compound muscle action potential; CV: conduction velocity; DL: distal latency; SNAP: sensory nerve action potential