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Mitofusin 2 Variant Presenting With a Phenotype of Multiple System Atrophy of Cerebellar Subtype

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Abstract

Objectives

To investigate the etiology of cerebellar ataxia in an adult male patient.

Methods

We performed standard neurologic assessment and genome sequencing of a 62-year-old man with rapidly progressive balance and gait abnormalities.

Results

The propositus exhibited cognitive dysfunction, mild appendicular bradykinesia, prominent appendicular ataxia, dysarthria, and hypomimia with minimal dysautonomic symptoms. Nerve conduction studies showed mild peripheral sensory neuropathy and normal motor nerve conduction velocities. Brain imaging showed progressive cerebellar atrophy and gliosis of the olivopontocerebellar fibers, characterized by T2 hyperintensity within the pons. Genetic testing revealed a likely pathogenic germline variant in *MFN2* (NM_014874: c.[838C>T];[=], p.(R280C)) in the GTPase domain (G) interface; pathogenic variants of *MFN2* typically cause hereditary sensory and motor neuropathy VI or Charcot-Marie-Tooth disease 2A. The presence of progressive ataxia, "hot cross bun" sign, and dysautonomia has been associated with multiple system atrophy, cerebellar type (MSA-C).

Discussion

We describe progressive cerebellar ataxia in an individual with a deleterious variant in *MFN2*. Our findings suggest that pathogenic variants in *MFN2* can result in a spectrum of phenotypes including cerebellar ataxia with cerebellar-pontine atrophy in the absence of significant neuropathy and in a manner closely resembling MSA-C.

Introduction

Multiple system atrophy (MSA) is a synucleinopathy characterized by parkinsonism, cerebellar atrophy, and autonomic failure. Like Alzheimer disease, amyotrophic lateral sclerosis, and Parkinson' disease, MSA is largely considered a sporadic and multifactorial disease, and the genetic contributions are not well-understood.[1,2]

Dysfunction of mitochondria, energy-producing organelles with content-sharing and network dynamics regulated by membrane fusion, is involved in several neurodegenerative disorders. Mitofusins (MFNs) are transmembrane GTPase proteins essential for mitochondrial membrane fusion.[3] Pathogenic variants in *MFN2* are the cause of Charcot-Marie-

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Tooth disease 2A (CMT2A), a progressive peripheral motor and sensory neuropathy characterized by variable age at onset, severity, and disease progression.[4] MRI often detects hyperintensities in the periventricular, subcortical, and centrum semiovale white matter.[5] Progressive cerebellar ataxia, which is a core clinical feature of MSA, cerebellar type (MSA-C), is a rare feature of *MFN2*-related disorders[6,7] (Table 1).

We report an individual with a likely pathogenic *MFN2* variant who presented with cognitive dysfunction, ataxia, progressive cerebellar atrophy, and degeneration of the olivopontocerebellar tracts. We propose consideration of *MFN2* variation as a contributor to MSA-C and of ataxia and cerebellar atrophy as presenting features of *MFN2*-related disorder, even in the absence of significant axonal neuropathy.

Methods

This study was approved by the University of British Columbia Clinical Research Ethics Board (H09-01228). The patient provided informed written consent for genome sequencing and publication of findings. Long-read genome sequencing was performed as previously described on the Oxford Nanopore Technologies PromethION.[8]

Case Description

A 62-year-old man presented to the movement disorder clinic with a 12-month history of progressive gait imbalance and recent worsening of speech and mentation. He experienced loss of concentration and forgetfulness, loss of dexterity, and recent onset of depression and anxiety without features of psychosis. He did not complain of swallowing problems, arthralgias, rashes, fever, or weight loss. He denied sensory loss or problems with his bowel or bladder function. He had well-controlled type 2 diabetes, hypertension, dyslipidemia, sleep apnea, and hypothyroidism. The propositus was of South Asian descent; from a nonconsanguineous sibship of 10; and had no family history of ataxia, dementia, or parkinsonism.

He exhibited dysarthria with intact language function. His primitive reflexes were negative. He initially scored 21/30 on a Montreal Cognitive Assessment (MoCA, version 1; eFigure 1, links.lww.com/NXG/A660). He had a wide-based gait with an irregular stagger and mild appendicular bradykinesia admixed with prominent appendicular ataxia. There was mild global hypokinesia with facial hypomimia and reduced spontaneity of movement as well as reduced vibration thresholds with normal proprioception and modest deficits on spinothalamic sensory testing. He did not have rigidity, spasticity, or *pes cavus*. He had normal motor strength, reflexes, plantar responses, cranial nerve testing, extraocular movements, and a negative Romberg test. His initial head MRI showed moderate cerebellar atrophy and mild cortical atrophy (Figure 1). Nerve conduction studies found mild length-dependent axonal peripheral sensory neuropathy with absent sural and peroneal sensory nerve action potentials (Table 2, Figure 2). Motor nerve conduction studies were normal, and EMG needle examination of the lower extremity distal and proximal muscles did not reveal features of reinnervation (data not shown).

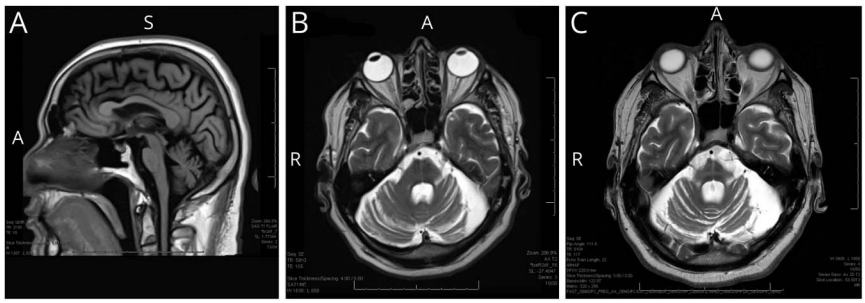
General blood work, which included serum protein electrophoresis, very long chain fatty acids, and levels of vitamin E and B12, was nondiagnostic. Markers for *Borrelia burgdorferi* (IgG/IgM), HIV, hepatitis, and syphilis were negative. Serum

Table 1 Previously Reported Cases With *MFN2* Variants and Cerebellar Abnormalities

NM_014874.4 (*MFN2*) variant *inheritance*	Age at onset (y), sex	Phenotype	Reference
c.[310C>T];[=] p.(Arg104Trp) ***de novo***	17, M	• Early-onset lower limb weakness due to axonal CMT • Progressive cognitive disability • Obesity with glucose intolerance • Diffuse periventricular white matter abnormalities • Mild cortical, pons, spinal cord atrophy • Moderate cerebellar atrophy	19
c.[617C>T];[=] p.(Thr206Ile) ***unknown***	47, F	• Childhood-onset progressive motor and sensory neuropathy • Optic atrophy, normal cognitive function • High signal intensities of bilateral middle cerebellar peduncles on diffusion-weighted and FLAIR MRI	22
c.[1894C>T];[1894C>T] p.(Arg632Trp)[a] ***recessive***	Middle age, F	• Progressive motor and sensory neuropathy • Diffuse atrophy of the spinal cord • Mild atrophy of the parietal lobe and cerebellum	23
c.[314C > T];[=] p.(Thr105Met) ***not maternal***	9, F	• Abnormal gait • Dysarthria • Global developmental delay • Progressive cerebellar ataxia • Axonal neuropathy	6

Abbreviations: F = female; M = male.
[a] There are conflicting interpretations of the pathogenicity of this variant and recessive inheritance pattern.

Figure 1 MRI of the Propositus' Brain



(A) Initial T1 FLAIR sagittal slice in the context of a 12-month history of worsening balance. Note the moderate cerebellar atrophy and mild cortical atrophy. (B) T2 axial image at the level of the pons. At the initial scan, T2 signal within the brain parenchyma was normal. (C) Repeat MRI 32 months after initial scan. T2 signal hyperintensity in cross formation is seen within the pons.

and CSF testing were negative for antibodies associated with paraneoplastic syndrome and paraneoplastic neurologic disorders. SSA and SSb were negative, and anti-TTG antibody was negative. Lupus testing showed elevated serum ANA, ENA, and RNP, but negative dsDNA and Smith antibodies. Antiphospholipid syndrome testing was negative. CSF lupus markers were not elevated. CSF studies were negative for pleocytosis, infection, and oligoclonal bands. He was trialed on a short course of immunosuppression with high-dose oral prednisone without improvement and with systemic side effects.

Over the next 32 months, his ataxia progressed rapidly. He required a walker for ambulation, lost the ability to write, and developed oropharyngeal dysfunction. Repeat MRI at this time revealed a T2 hyperintense "hot cross bun" sign within his pons, consistent with gliosis of the olivopontocerebellar fibers (Figure 1). Genetic testing for repeat expansions, multigene panel sequencing for ataxia and episodic ataxia disorders (not including *MFN2*), and mitochondrial genome sequencing were nondiagnostic. Genome sequencing identified a heterozygous variant in *MFN2* (NM_014874: c.[838C>T];[=], p.(Arg280Cys)), classified as likely pathogenic by ACMG criteria (PM2, PP3, PS1). His parents were deceased and, therefore, not available for testing. Follow-up evaluations over the following year revealed mild dysautonomia with urinary urgency and frequency, which improved with mirabegron. Cognitive performance on the MoCA worsened (eFigure 1, links.lww.com/NXG/A660), as did the degree of parkinsonism. A trial of immediate release levodopa/carbidopa 100/25 mg 2 tablets TID led to no significant improvement in rigidity or bradykinesia.

Discussion

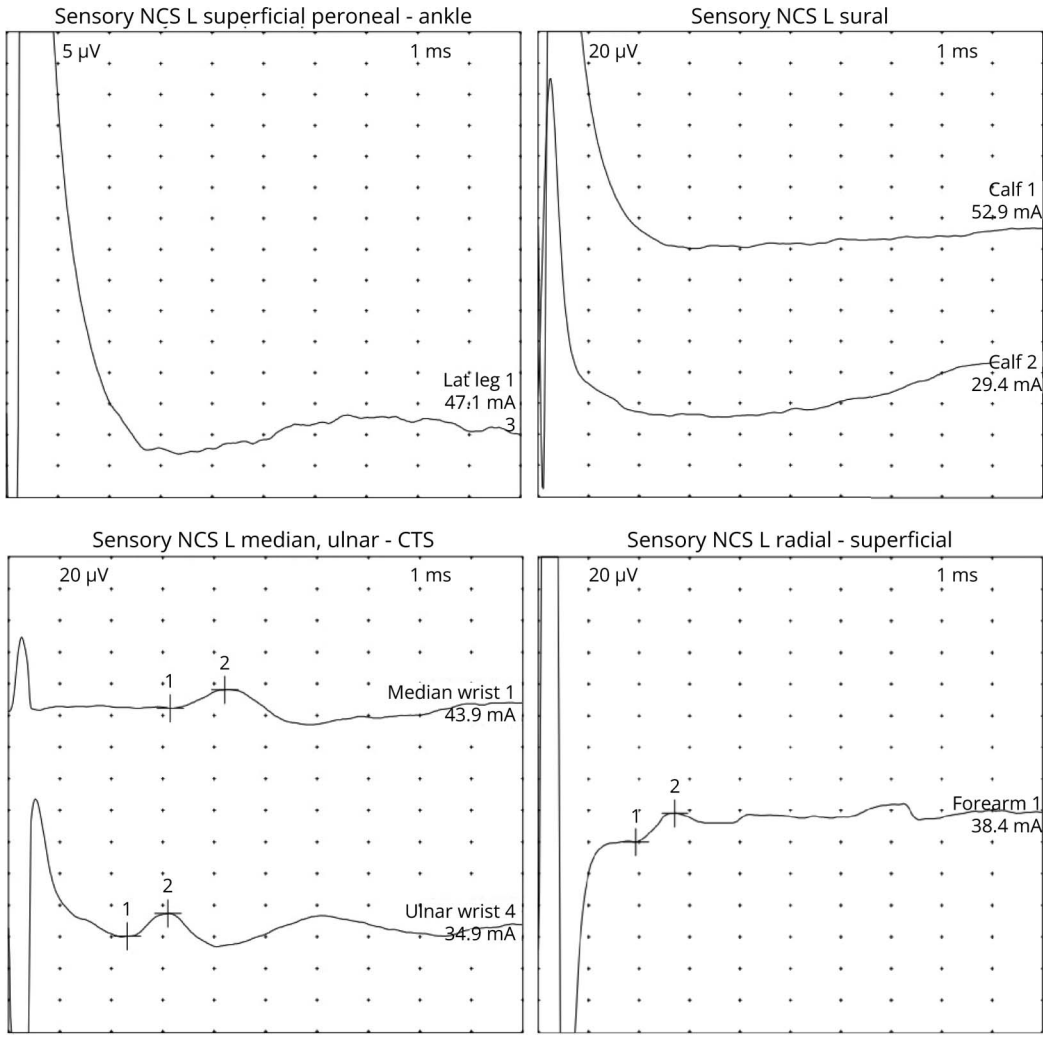
We report an individual with a likely pathogenic variant in *MFN2* presenting with a progressive cerebellar ataxia without significant motor or sensory neuropathy. This report emphasizes ataxia as a presenting feature of an *MFN2*-related disorder (Table 1) identifies radiologic features typically associated with MSA-C. Except for progressive cognitive impairment, the propositus met the 2022 diagnostic criteria for MSA-C, as defined by the Movement Disorder Society.[9] Although dementia is still considered an exclusion criterion for MSA by these guidelines, the same MSA Study Group also reported that multidomain cognitive impairment of executive

Table 2 Sensory Nerve Conduction Studies

Nerve/Sites	Segment	Onset latency (ms)	Peak latency (ms)	NP Amp (μV)	Distance (mm)	Velocity (m/s)	Temp (°C)
Left superficial peroneal—Ankle							
Lat leg	Ankle	NR	NR	NR	140	NR	33.1
Left sural							
Calf	Ankle	NR	NR	NR	140	NR	33
Calf	Ankle	NR	NR	NR	120	NR	32.9
Left median, ulnar—CTS							
Median wrist	Digit II	3.1	4.2	11.8	130	41	31.5
Ulnar wrist	Digit V	2.3	3.1	14.7	110	48	31.3
Left radial—superficial							
Forearm	Wrist	1.9	2.7	18.5	100	52	31

Abbreviations: C- Celsius; m/s = meters per second; mm = millimeter; ms = milliseconds; μV = microvolt; NR = not recordable.

Figure 2 Sensory Nerve Conduction Studies Across Different Nerve Segments



X-axis is time. Y-axis is the amplitude of the response (µV).

function, visual-spatial function, and memory encoding occur among some individuals diagnosed with MSA-C.[10]

Peripheral neuropathy in *MFN2*-related disorders is known to be incompletely penetrant among older patients who have a milder form of disease.[5,11,12] However, EMG typically reveals reinnervation in CMT2A, suggesting that his electrodiagnostic studies were more reflective of a diabetic peripheral neuropathy. The absence of marked peripheral neuropathy antecedent to or in conjunction with the progressive cerebellar changes in the patient suggests that cerebellar symptoms are possibly a sole presenting feature of *MFN2*-related disorders. Supporting the hypothesis that deleterious *MFN2* variants predispose to progressive cerebellar degeneration similar to that with MSA-C are the observations that loss of mitofusin impairs mitochondrial membrane potential[3] and that MSA-C has been associated with mitochondrial dysfunction.[2,20,21] Furthermore, conditional knockout of *Mfn2* in mice has established that MFN2 is required for cerebellar development and maintenance.[13] It remains a possibility, however, that the MSA-C phenotype is concurrent and unrelated to the *MFN2* variant.

The MFN2 p.Arg280Cys variant has previously been reported in CMT2A and affects a highly conserved amino acid in the G4 motif of the G interface, a domain ensuring specificity for GTP binding.[14-16] The recurrent p.Arg280His variant has been associated with CMT2A of variable age at onset including adult onset.[17,18] Early-onset CMT2A and cerebellar atrophy have been reported in individuals with variants in the G1 motif of the G interface.[6,19] Two previously described cases of *MFN2*-related cerebellar atrophy carried missense changes in the G interface of the MFN2 protein (p.Arg104Trp and p.Thr105Met).[15] Variants within the G interface show variable effects on dimerization and mitochondrial trafficking suggesting that residue-dependent functional effects contribute to disease onset and progression. The factors underlying preferential neurodegeneration of the cerebellum among some individuals with *MFN2* pathogenic

variants are unknown. Further work is required to assess whether, in some contexts, *MFN2* variants interfering with dimerization predispose to cerebellar neurodegeneration.

In summary, pathogenic variants in MFN2 can result in a spectrum of disorders with variable phenotypes ranging from a purely axonal peripheral neuropathy to that of a progressive cerebellar ataxia associated with olivopontocerebellar atrophy that closely resembles MSA-C. These findings emphasize the need to consider *MFN2* variants in the etiology of progressive cerebellar atrophy. Further work is required to assess the role of MFN2 and mitochondrial fusion in MSA-C and to estimate the penetrance of cerebellar atrophy and ataxia in *MFN2*-related disorders. Such insights can potentially provide insights into the disease mechanism and identify therapeutic targets.

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