Single Case – General Neurology

A Novel Duplication Mutation in the Myelin Protein Zero Gene Causing Mild, Nonprogressive Demyelinating Neuropathy

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Keywords

Myelin protein zero gene · Duplication mutation · Nonprogressive demyelinating neuropathy

Abstract

Mutations in the *myelin protein zero (MPZ)* gene can cause a variety of clinical and electrophysiological forms of genetic neuropathies including Charcot-Marie-Tooth (CMT) type 1B disease which is characterized by demyelinating features. We present a father and daughter with neuropathy carrying a novel 31 base pair duplication mutation in the 5' untranslated region of the *MPZ* gene, c.-23_8dup31. Genetic analysis and protein modeling indicated that this is a frameshift mutation resulting in premature truncation of the encoded protein. The daughter underwent repeat neurological examination and electromyography testing over an 11-year time span demonstrating no clinical or electrophysiological change. Our study expands the clinical and genetic spectrum of mutations that can cause CMT type 1B disease and demonstrates the value of sequence analysis of noncoding portions of a gene that are not intronic.

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Published by S. Karger AG, Basel

Introduction

Myelin protein zero (*MPZ*) protein is required for the maintenance of myelin which facilitates the efficient transmission of nerve impulses and is produced only in the Schwann cells [1]. Mutations in the *MPZ* gene cause a broad spectrum of dominantly inherited neuropathies ranging from mild demyelinating Charcot-Marie-Tooth (CMT) type 1B to axonal CMT type 2I disease. In addition, mutations can also result in severe childhood-onset neuropathies that include Dejerine-Sottas neuropathy and congenital hypomyelinating neuropathy [2]. We report our genetic and electrophysiological analysis of two affected family members carrying a novel mutation in the *MPZ* gene.

Case Report

The index patient reached normal motor milestones as a child and had no specific complaints except that as an adolescent she was a slow runner. In her twenties, she complained of numbness and discomfort in her legs and over the next three decades was evaluated by a number of physicians, but not a neurologist. Ultimately, at the age of 52 years, she was referred for neurological evaluation and underwent electromyography (EMG) testing which showed a demyelinating neuropathy (Table 1). A spinal tap was done which showed an elevated protein and on the basis of these investigations, she was diagnosed with chronic inflammatory demyelinating polyneuropathy and referred for a second opinion.

When she was first examined at the age of 53 years, her neurological examination disclosed a normal mental status and cranial nerve examination. Cerebellar testing was normal. Her biceps, triceps, brachioradialis, patellar, and ankle stretch reflexes could not be elicited and her plantar reflexes were flexor. Power testing revealed that when she provided a full effort, she had grade 5/5 MRC grade strength in her arms and legs. Sensory testing revealed a decrease in pin prick, proprioception, and vibratory sense distally in her feet with no abnormalities in her hands. Tests of the cerebellar system revealed no abnormalities including absence of tremor. She had a positive Romberg test and could not walk on her toes or heels or perform a tandem walk.

A thorough investigation of the potential cause of her neuropathy was performed and the following tests were negative or normal: cell count and comprehensive metabolic panel, vitamin B12, vitamin B1, folate, serum protein electrophoresis and immunofixation, serological tests for HIV and hepatitis C, and antiglycolipid panel which includes anti-MAG antibodies, rheumatoid factor, and antinuclear antibodies test.

She had been diagnosed with chronic inflammatory demyelinating polyneuropathy and was started on intravenous immunoglobulin therapy 2 g/kg monthly for 3 months. There was no response to this treatment, and solumedrol 1 g/week for 6 weeks was added to the regimen. She did not respond to this combination treatment, and therapy was discontinued.

Over the course of the next 11 years, there was no significant change in her neurological examination. A number of EMGs were performed from the age of 52 to 63 years, all of which confirmed a demyelinating polyneuropathy. Inspection of the numerical values during this time span shows no significant change in the electrophysiological parameters (Table 1).

The patient's father, aged 80 years, was evaluated with complaints of numbness in his extremities associated with imbalance he had had for the last 10 years. He had a history of adult-onset diabetes for more than 35 years and had been diagnosed with diabetic neuropathy. EMG revealed a significant demyelinating neuropathy with secondary axonal features. Family history revealed that his mother had had a "clumsy gait" in her seventies, but no history to suggest that any other member was affected. This family history suggested a possible genetic neuropathy and prompted genetic testing.

Genetic analysis was performed on a DNA sample obtained from the proband's father on two occasions. The first was performed in 2013 through a commercially available test panel for 25 genes known to cause neuropathy. This included DNA sequencing using next-generation sequencing technology analyzing all exons and at least 10 base pairs flanking noncoding nucleotides. In addition, *PMP22* and *GJB1* were tested for deletions or duplications. This testing resulted in the discovery of variants of unknown significance in the following genes: *GARS* (c.1149C>T), *HSPB1* (c.36G>T), and *TRPV4* (c.651G>A). All of these changes were heterozygous and synonymous indicating that there was no change in the encoded amino acid and therefore they were not likely disease-producing. In addition, a mutation was noted in the *SBF2* gene, c.5020_5022: 3 bp deletion of GAA in codon 1674 in which the mRNA reading frame is preserved. Mutations in this gene cause CMT4B2, which follows an autosomal recessive pattern of inheritance. Since no other mutation was found in the other allele of this gene, this is not likely to have caused the neuropathy in this patient. In this panel, the *MPZ* gene was studied and no mutations or variants were reported; overall, these test results were considered negative. Next, in 2017, the analysis was repeated on the same patient with a more extensive genetic neuropathy panel and a different company. In this repeat testing, again using next-generation sequencing, 53 genes were studied and reported. In this analysis, the deletion mutation in the *SBF2* gene was again detected. In addition, a variant in the *DNMT1* gene was noted, c.385C>A categorized as a variant of unknown significance. This is a novel variant leading to nonsynonymous amino acid change, P129T, however this protein is predicted to be a tolerated change by two protein modeling programs, SIFT [3] and Mutation Taster [4]. Mutations in the *DNMT1* gene result in hereditary sensory neuropathy with deafness and dementia, HSN 1E, which is not consistent with the phenotype observed in our family. The combination of our protein modeling analysis and lack of the associated phenotype make it highly unlikely that this *DNMT1* variant is a pathogenic mutation in this family.

Interestingly, in the second analysis, a NM_000530.6:c.-23_8dup31, NC_000001.11:g.161309933_161309934 variant was identified by sequencing up to 50 base pairs in the untranslated portion of the *MPZ* gene. In this variant, the sequence CAT AGC TGG GGC AGG GGC AGG GGC CCG GAG C is duplicated. It is located in the 5' untranslated region adjacent to exon 1 and not in an intron and was found in both the father and daughter. This variant was further analyzed and duplication of this 31-bp sequence was found to cause a frameshift mutation resulting in an Ala5Pro change and premature truncation of the protein at position 62 of the new reading frame, p.Ala5ProfsX62. Furthermore, it is predicted as damaging/disease-producing by three protein modeling programs, SIFT, Mutation Taster, and Polyphen [5]. This variant is not found in any of the publicly available databases (1000 G, ExAC, and NHLBI) or in our internal database, which is a collection of rare gene variants with a frequency of <3% generated from whole-exome sequencing data of 72 individuals with neurological disorders. This variant has been deposited in the ClinVar database, rs1553260017

(former db SNP rs1085307731), and we now provide the associated genotype/phenotype analysis.

Discussion

Mutations in the *MPZ* gene cause 6–10% of all CMT type 1 disorders [6], and currently 81 pathogenic variants and 31 likely pathogenic variants have been reported in this gene. The majority of these are point mutations while 14 are frameshift variants. The c.-23_8 dup variant in our patient results in the loss of a functional allele as it is predicted to result in premature protein truncation. While the wild-type protein has 248 amino acids, this mutation results in a protein of only 62 amino acids. The study of this mutation exemplifies the importance of sequencing not only the exons, but adjacent sequences such as those in the untranslated portion of the gene.

It is likely that the father has a combination of CMT type 1 with a superimposed diabetic neuropathy. In his daughter, remarkably, this mutation results in a relatively mild and non-progressive demyelinating neuropathy as assessed both clinically and electrophysiologically.

The study of this family exemplifies the power of next-generation sequencing enhancing our ability to confirm a genetic diagnosis. It also expands the phenotypic spectrum that can occur with mutations in the *MPZ* gene.

Statement of Ethics

The study was conducted following policies and procedures approved by the local institutional review board. Written informed consent was obtained for the case report publication from the individuals who participated in this study.

Conflict of Interest Statement

The authors have no conflict of interest to report.

Funding Sources

The authors have not received any funding for conduct, authorship, or publication of this study.

Author Contributions

All authors contributed to the initial draft of this publication. L.R. Peddareddygar and K. Oberoi revised the later drafts. All authors reviewed and approved the final draft.

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Table 1. Nerve conduction studies in the index patient

	Distal latencies, m/s		Response amplitude, mV		Conduction velocity, m/s		F-wave latency, m/s	
	52 y.	63 y.	52 y.	63 y.	52 y.	63 y.	52 y.	63 y.
Motor nerve								
R. median	4.7 (<4.2) ^a	5.0	9.9 (>4.0)	9.5	44.0 (>50)	42.0	37.0 (<30)	37.9
R. ulnar	3.7 (<3.3)	4.2	8.3 (>3.5)	8.6	40.0 (>50)	42.0	37.6 (<30)	41.4
R. peroneal	6.2 (<6.2)	4.9	2.8 (>2.6)	4.2	35.2 (>40)	35.0	NR	NR
R. tibial	8.8 (<6.0)	6.3	12.7 (>4.0)	14.1	34.1 (>40)	35.0	67.8	76.5
R. sural	NR ^b	NR	>6.0		>40			
Sensory nerve								
R. median	3.7	3.7	10.7 (>20)	17.0	38.0 (>50)	38.0		
R. ulnar	3.5	3.3	3.2 (>17)	9.0	40.0 (<50)	36.0		
R. radial	ND ^c	1.6	28.0 (>15)		51.0 (>50)			

^a Normal values are given in parentheses. ^b No response; all sensory response latencies are onset latencies. ^c Not done.