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ORIGINAL ARTICLE

Complete Loss of Myelin protein zero (*MPZ*) in a patient with a late onset Charcot-Marie-Tooth (CMT)

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Abstract

Charcot-Marie-Tooth (CMT) comprises a group of hereditary neuropathies with clinical, epidemiological, and molecular heterogeneity in which variants in more than 80 different genes have been reported. One of the important genes which cause 5% of all CMT cases is Myelin protein zero (P0, *MPZ*). Variants in this gene have been reported in association with different forms of CMT including classical CMT1, severe DSS (CMT3B), DI-CMT, CMT2I and CMT2J with autosomal dominant (AD) inheritance. To our knowledge, *MPZ* variants have not been described in autosomal recessive (AR) form of CMT in previous studies. Moreover, its complete deletion has not been reported in human. Here, we described clinical characteristics of a patient with CMT symptoms who demonstrated manifestations of the disease late in his life. We performed exome sequencing for identifying CMT subtype and its associated gene, and follow that co-segregation analysis has been done to characterize inheritance pattern of the disorder. Through using exome sequencing, we identified a novel 4074 bp homozygote deletion which encompasses all 6 exons of the *MPZ* gene in this patient. After identifying the alteration, variant confirmation and co-segregation analysis have been performed by using specific primers. Our result revealed that the patient's parents were heterozygous for the alteration and they did not show any symptoms of CMT. Although most *MPZ* variants have been described with early onset CMT with AD pattern of inheritance, the reported patient in our study had late onset form and his parents did not show any symptoms. Considering substantial role of *MPZ* protein in the biogenesis of peripheral nervous system (PNS) myelin, we proposed that there should be another protein in PNS that compensates for lack of *MPZ* protein. Taken together, our finding is the first report of *MPZ* association with AR form of CMT with late onset features. Moreover, our results propose the presence of another protein in PNS myelin biogenesis and its assembly. However, functional studies alongside with other molecular studies are needed to confirm our results and identify the proposed protein.

Keywords Charcot-Marie-Tooth · Myelin protein zero · Exome sequencing · Peripheral nervous system · Myelin

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Introduction

Charcot-Marie-Tooth (CMT) hereditary peripheral neuropathy collectively refers to a group of disorders usually characterized by symmetrical distal muscle weakness and atrophy, hereditary sensory and motor neuropathy (HSMN), high arched feet, frequently depressed tendon reflexes, and abnormal electrophysiological testing (Azevedo et al. 2018). The prevalence of CMT is 1:2439, although it may range from 1:10,310 to 1:1215 depending on the regions. Norway and Eastern Akershus County have the highest prevalence whereas in Japan, there is a lower reported prevalence (Lousa et al. 2019; Morena et al. 2019). Molecular genetics research showed that CMT has heterogeneous manifestations. Moreover, variants in more than 80 different genes with different patterns of inheritance (autosomal dominant, autosomal recessive, X-linked) have been reported in association with distinct electrophysiological phenotypes (axonal, demyelinating, intermediate) (Stojkovic 2016, Blair et al. 1996). The most frequent pattern is autosomal dominant inheritance. Three electrophysiological classes have been classified by mode of inheritance and nerve conduction velocity (NCV) (Stojkovic 2016). Demyelinating (CMT1) is defined as NCV below 35 m/s with slowly progressive clinical manifestation and affects individuals between ages five and 25 years. Axonal (CMT 2) is defined as NCV above 45 m/s and shows extensive clinical overlap with CMT1. However, patients with CMT2 tended to have less sensory loss and disability compared with individuals with CMT1. A third form of CMT (Dominant intermediate CMT (DI-CMT)) has NCV 35–45 m/s and affected individuals show a relatively typical CMT phenotype (Braathen 2012). Recently, with identifying novel CMT associated genes and defining detailed overlap of modes of inheritance and neuropathy phenotypes, the above classification is substituted with a gene-based classification in which a patient's findings can be described in terms of inheritance pattern, involved gene, and neuropathy type (Magy et al. 2018, TD 2019).

Various genetic alterations have been implicated in the clinical picture of CMT. Linkage between CMT1 and chromosome 1 (1.q22-1.q23) has been identified in 1982. In 1986, linkage between CMT2 and Xq13 markers has been recognized (Bird et al. 1982; Beckett et al. 1986). Two years later, locus heterogeneity for CMT1 has been further validated with the observed linkage between CMT1 and chromosome 17 (Vance et al. 1989). The first molecular genetic cause of these neuropathies was duplication of the 17p11.2 locus, encompassing the peripheral myelin protein 22 gene (PMP22) (Birouk et al. 1997; Reilly et al. 2011; Thomas et al. 1997). While numerous CMT associated genes have been identified, point variants in five genes (*PMP22*, *MPZ*, *GJB1*, *GDAP1*, and *MFN2* genes) comprise over 90% of genetically confirmed cases of CMT (Murphy et al. 2012; Bergoffen et al. 1993; Saporta et al. 2011).

Despite a great number of studies on CMT-associated genes and pathophysiologic mechanisms of this neuropathy, identification of a novel pathogenic alteration with different phenotypic effects makes it difficult to suggest a firm clinical scoring system. Herein, we describe the characteristics of a patient with CMT disease carrying the *MPZ* alteration in homozygous and showed late onset CMT. Additionally, we proposed some reasons for our findings.

Materials and methods

A 34-year-old man with consanguineous parents was referred to our center with spastic paraplegias symptoms such as muscle stiffness and paralysis of the lower limbs. At the age of 18, he had noticed difficulty in walking and weakness in the hands. He did not have any vision or hearing loss and has not experienced numbness and tingling. The subject's parents were consanguineous and one of his brothers had been died due to muscle atrophy, pulmonary disorder and physical disabilities such as scoliosis, severe weakness and walking disability over uneven surfaces. His niece suffered from congenital hypotonia (Fig. 1).

Neurophysiological examination particularly motor nerve conduction, F-wave studies, H waves and right median and left facial recordings demonstrated very severe chronic demyelination polyneyropathy, that was consistent with CMT type 1 (Table 1, Fig. 2).

Exon sequencing

We performed exome sequencing in Gharehsouran Medical Genetics Center, Tabriz, Iran, for identifying the subtype of CMT and the corresponding gene, due to heterogenous nature of the disorder (Oliveira et al. 2015). Genomic DNA was extracted from peripheral blood of the proband, their parents, and relatives according to standard protocols (GeneAll Exgene Blood SV Mini). Once exome sequencing data was analyzed, the co-segregation analysis of the disease-associated variant was done for understanding the inheritance pattern of the disorder by using specific primers (Table 2). After PCR amplification, we load the product on gel electrophoresis. However, as the deletion area was large Sanger sequencing was not performed in this case.

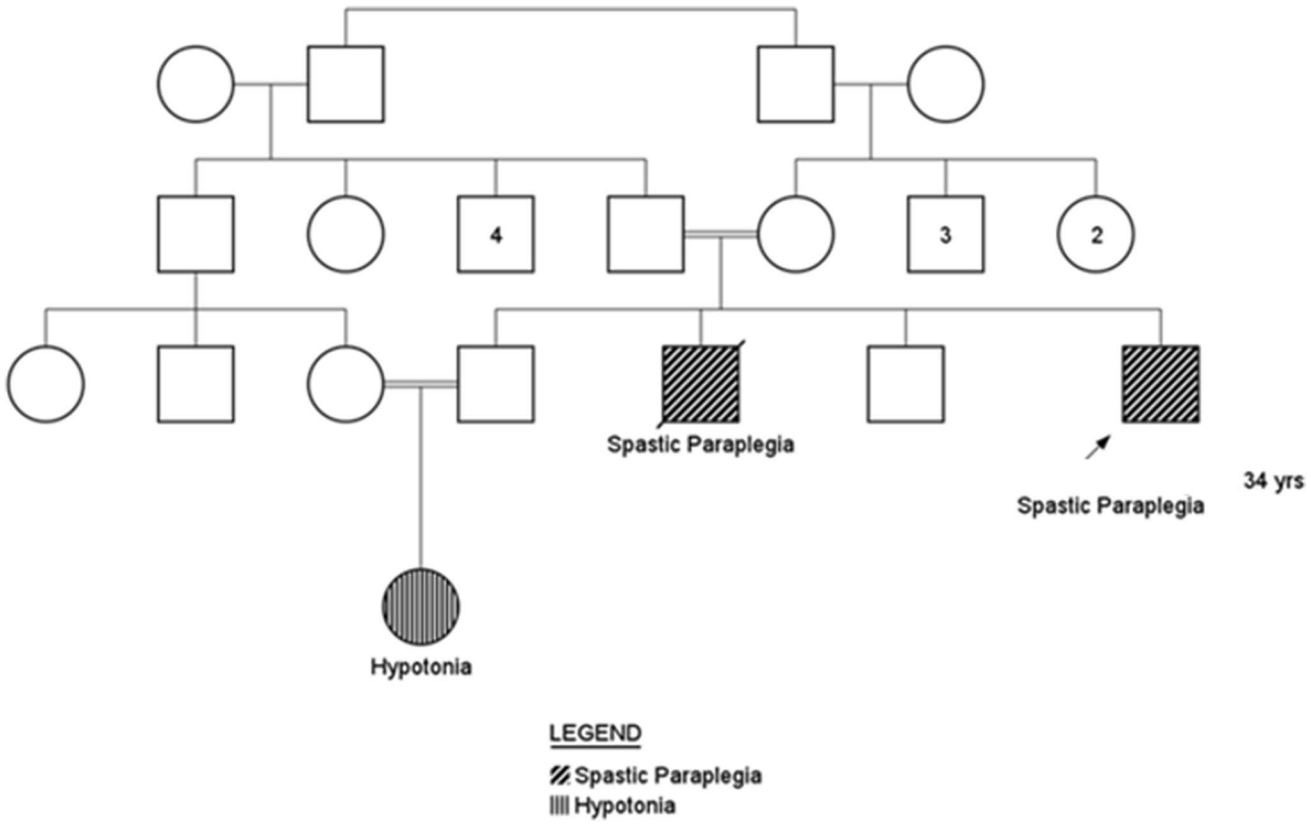

Fig. 1 Family tree of the patient. Numbers inside squares and circle shows the number of siblings

Results

Molecular genetics results

Since CMT is clinically heterogeneous, characterizing genetic basis of the disease for further management processes is essential. The affected patient in our study had muscle stiffness, lower limb weakness and hypotonia, so the results of clinical investigations were not sufficient to state a firm diagnosis. In order to identify a specific disorder, considering family tree and history of associated abnormalities among patient's relatives, the patient has been referred to exome sequencing analysis.

Exome sequencing of the patient revealed an alteration in the *MPZ* gene. The *MPZ* variant was a 4074 bp deletion which encompasses all 6 exons of the gene from exon 1 to the final nucleotide of exon 6. With respect to the fact that the deletion is large and cause lack of *MPZ*, assessment of pathogenicity and 3D protein structure modeling of the protein were not available in this case, but it was expected that the clinical manifestation were severe due to the loss of the encoded protein *MPZ*.

Considering various inheritance patterns of different CMT forms, co-segregation analysis of the patient's relatives by using specific primers have been done which revealed heterozygosity of parents, suggesting autosomal recessive form of CMT (Fig. 3).

Discussion

In this study we described clinical features of a CMT patient and reported a novel alteration in *MPZ* gene. To our knowledge, deletion of *MPZ* gene in a homozygous manner has not been reported in previous studies and here we describe first case with *MPZ* deletion.

In the CNS and PNS for axonal salutatory conduction, myelin is necessary. This structure wraps around specific axonal segments through a mechanism known as actin disassembly. each separate myelin unit in the PNS along an axon originates create the Schwann cell. Myelin in the PNS are highly enriched in multifunctional proteins such as MPZ, myelin basic protein (MBP) and peripheral myelin proteins 2 (P2), and PMP22 (Siems et al. 2020; Garbay et al. 2000; Raasakka and Kursula 2020).

MPZ is a type I transmembrane protein, highly expressed in peripheral nervous system (PNS) myelin, particularly compact myelin and has a 120-residue. The myelinating glia of the PNS or Schwann cells express this protein during their development until mature myelin

Table 1 Spacially Motor Nerve Conduction, Sensory Nerve Conduction, F Wave, and H Wave Studie

Motor nerve conduction								
Nerve and site		Latency	Amplitude	Segment	Latency difference	Distance	Conduction velocity	
Median. R	Wrist	NR ms	NR mV	Abductor pollicis brevis-Wrist	ms	mm	m/s	
	Elbow	NR ms	NR mV	Wrist-Elbow	ms	mm	m/s	
Ulnar. R	Wrist	ms	mV	Abductor digiti minimi (manus)-Wrist	ms	mm	m/s	
	Below elbow	ms	mV	Wrist- Below elbow	ms	mm	m/s	
Ulnar. L	Wrist	NR ms	NR mV	Abductor digiti minimi (manus)-Wrist	ms	mm	m/s	
	Below elbow	NR ms	NR mV	Wrist- Below elbow	ms	mm	m/s	
Median. L	Wrist	NR ms	NR mV	Abductor pollicis brevis-Wrist	ms	mm	m/s	
	Elbow	NR ms	NR mV	Wrist-Elbow	ms	mm	m/s	
Tibial. R	Ankle	NR ms	NR mV	Abductor halluces-Ankle	ms	mm	m/s	
	Popliteal fossa	NR ms	NR mV	Ankle- Popliteal fossa	ms	mm	m/s	
Peroneal. R	Ankle	NR ms	NR mV	Abductor pollicis brevis-Ankle	ms	mm	m/s	
	Fibula (head)	NR ms	NR mV	Ankle- Fibula (head)	ms	mm	m/s	
Tibial. L	Ankle	NR ms	NR mV	Abductor halluces-Ankle	ms	mm	m/s	
	Popliteal fossa	NR ms	NR mV	Ankle- Popliteal fossa	ms	mm	m/s	
Peroneal. L	Ankle	NR ms	NR mV	Extensor digitorum brevis-Ankle	ms	mm	m/s	
	Fibula (head)	NR ms	NR mV	Ankle- Fibula (head)	ms	mm	m/s	
Sensory nerve conduction								
Nerve and site		Onset latency	Peak latency	Amplitude	Segment	Latency difference	Distance	Conduction velocity
Median. R	Digit II (index finger)	NR ms	NR ms	NR μV	Wrist- Digit II (index finger)	ms	mm	m/s
Ulnar. R	Wrist	NR ms	NR ms	NR μV	Digit V (little finger)-Wrist	ms	mm	m/s
	Elbow	NR ms	NR ms	NR μV	Wrist-Elbow	ms	mm	m/s
Ulnar. R	Wrist	NR ms	NR ms	NR μV	Digit V (little finger)-Wrist	ms	mm	m/s

Table 1 (continued)

Ulnar. L	Wrist	NR ms	NR ms	NR µV	Digit V (little finger)-Wrist	ms	mm	m/s
Median. L	Digit II (index finger)	NR ms	NR ms	NR µV	Wrist- Digit II (index finger)	ms	mm	m/s
Sural. R	Lower leg	NR ms	NR ms	NR µV	Ankle- Lower leg	ms	mm	m/s
Sural. L	Lower leg	NR ms	NR ms	NR µV	Ankle- Lower leg	ms	mm	m/s
F-wave studies				H-waves				
Nerve	M- Latency	F- Latency		Nerve		Latency	Amplitude (max)	
Median. R	1.7	0.0		Tibial. R	M-wave	ms	mV	
Ulnar. R		0.0			H-wave	ms	mV	
Ulnar.L		0.0		Tibial. L	M-wave	ms	mV	
Median.L		0.0			H-wave	ms	mV	
Tibial. R		0.0						
Peroneal. R		0.0						
Tibial. L		0.0						
Peroneal. L		0.0						

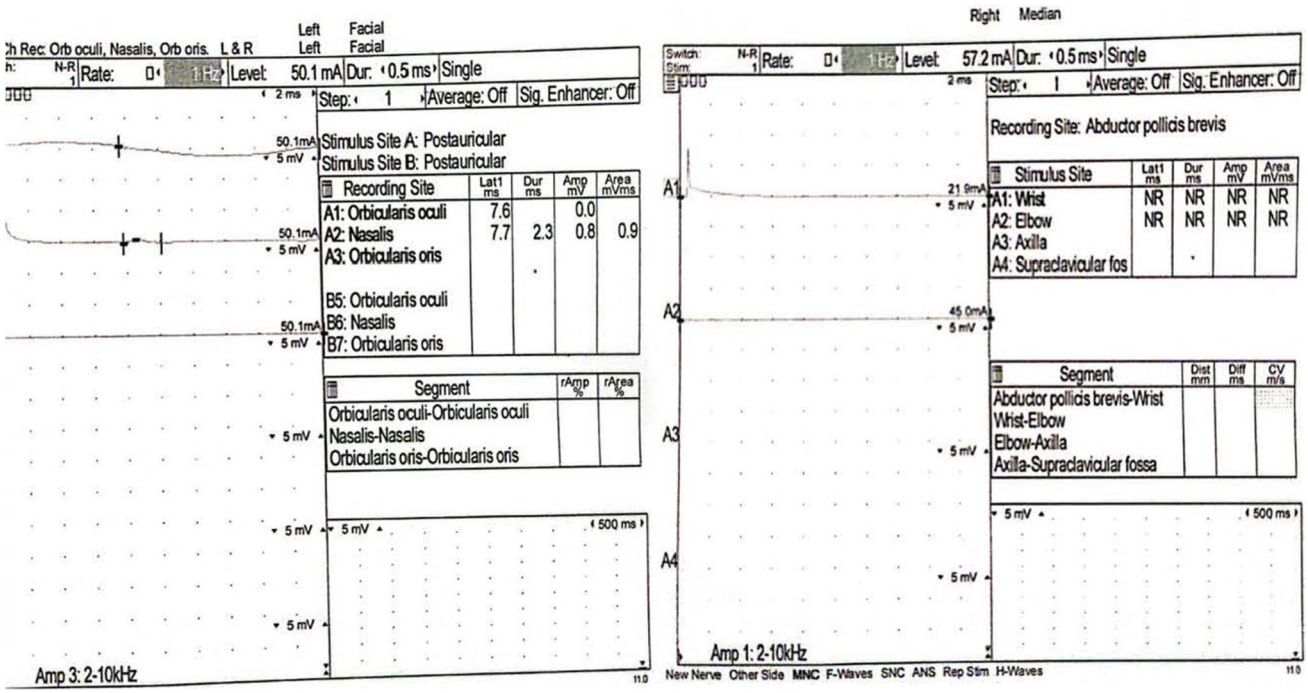

Fig. 2 Electrophysiological examination results of the proband, consistent with CMT-1

formation. *MPZ* protein has several sequence motifs and structural domains such as an N-terminal immunoglobulin (Ig)-like domain, a single transmembrane helix on the extracellular part, a transmembrane domain and cytoplasmic extension (P0ct) (Raasakka et al. 2019; Raasakka and Kursula 2020; Han et al. 2013).

The Ig-like domain of this protein is involved in formation of the myelin intraperiod line (IPL) (Eichberg 2002, Shy et al. 2004). In PNS myelin, homophilic intercalation of Ig-like domains brings two myelin membranes together and forms IPL which is a 5 nm narrow intramyelinic compartment (Filbin et al. 1990). This domain has been found

Table 2 Primers that have been used for co-segregation analysis

Primers	Sequence (5′3’)	Product length	Tm
Forward -1	CCTCTGTGTATGGGGTGGTA	387 bp	58
Reverse -1	GGGATTGCTGAGAGACACCT		
Forward -2	CTCGGTGACTGATGTGTGC	548 bp	58
Reverse -2	GCAGGTGAGGGGTAGGATTA		
Forward -1	CCTCTGTGTATGGGGTGGTA	631 bp	58
Reverse -2	GCAGGTGAGGGGTAGGATTA		

to interact with PMP22 and this interaction enables normal myelination maintenance (Hasse et al. 2004; Wrabetz et al. 2000). PMP22 is a membrane stacker but it cannot accomplish myelination in the absence of *MPZ* protein (Carenini et al. 1999). However, PMP22 is able to maintain a compact IPL when *MPZ* is missing suggesting that after myelin formation, *MPZ* is not immediately required for IPL stability. In Schwann cells, PMP22 is involved in the formation of lipid rafts and *MPZ* is linked to localization of rafts of certain lipid compositions. Pathogenic variations of Ig-like domain have been reported in CMT and Dejerine-Sottas syndrome (DSS) (Lee et al. 2014; Fasano et al. 2008).

Other than PMP22, MPZ in PNS along with MBP and peripheral P2 are involved in adhering apposing membrane leaflets together (Han et al. 2013; Inouye and Kirschner 2016), However, in the presence of mentioned proteins and absence of MPZ in mouse models, the myelination severely disrupted showing that these proteins cannot compensate lack of MPZ in peripheral myelin biogenesis (Raasakka and Kursula 2020).

P0ct domain contains 69 amino acids and has a central part (amino acids 180–199) encompassing immunodominant neuritogenic segment, but the potential function of this domain in membrane stacking has not been fully understood. However, most CMT-associated single nucleotide variants in P0ct are localized in this domain (de Sèze et al. 2016; Han et al. 2013). In a study, involvement of the P0ct in the maintenance of compact PNS myelin stability alongside with other cytosolic PNS myelin proteins has been proposed (Raasakka et al. 2019).

The presence of *MPZ* for PNS myelin is critical and this protein is considered as a conserved protein throughout vertebrates particularly in mammals. Variations in the *MPZ* gene cause almost 5% of all CMT cases in association with different forms of CMT including classical CMT1, severe DSS (CMT3B), DI-CMT, CMT2I and CMT2J with autosomal dominant inheritance (Lupski et al. 2010, Antonellis et al. 2010, Choi et al. 2011, Shy 2006, Nicolaou and Christodoulou 2013). Complete deletion of this protein has not been reported in previous studies. In model systems studies, lack of this protein has been described with deficiency in intramyelinic membrane stacking. The results showed that the presence of proteolipid protein (PLP) which is a transmembrane protein in CNS and a main contributor to intramyelinic membrane stacking did not rescue the formation of compact myelin in PNS in the absence of *MPZ* (Xu et al. 2000; Yin et al. 2006). However, this was not the case when PLP is replaced with *MPZ*. This replacement in the mouse CNS resulted in two consequences. First, IPL spacing is increased. Second, Schmidt-Lanterman incisures (SLIs) can be detected in CNS myelin, suggesting that *MPZ* is required for SLI formation (Yin et al. 2008; Yoshida and Colman 1996). Although *MPZ* has a fundamental role in PNS and its biogenesis, the patient presented here had mild CMT phenotypes similar to CMT2I and CMT2J. Several studies have defined pathogenic variants of this gene in association with early onset CMT especially CMT1B (usually first decade), yet our finding has shown that the absence of this protein is not associated with early presence of the

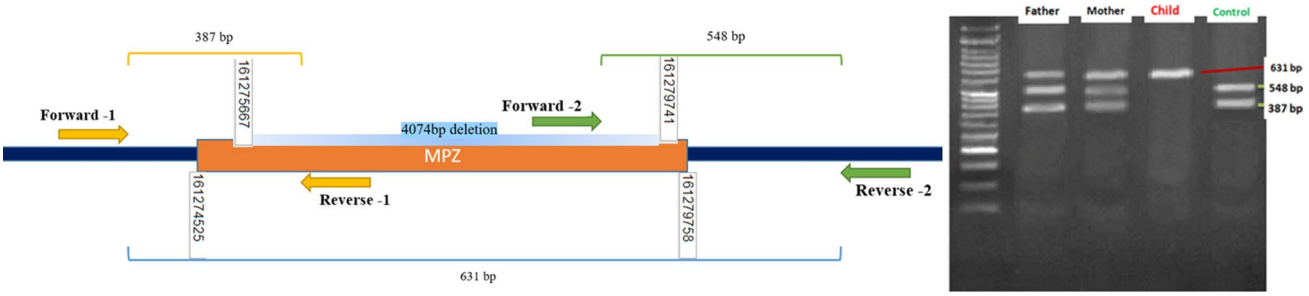

Fig. 3 Co-segregation results. Considering the deletion area three pairs of primers were designed which in control group result in two bands with 387 bp and 548 bp length (two pairs of primers in two sides of break points). In effected individual due to the deletion only one band with length of 631 bp was produced while heterozygous people-the proband’s parents- have three different bands including three depicted bands in the picture

CMT features. Taken together, our findings suggest that there might be another protein other than *MPZ* which compensates lack of *MPZ* and attenuates severe phenotypic effects of *MPZ* missing.

Conclusion

In conclusion, biogenesis of PNS myelin and its assembly have several etiological pathways and multiple proteins are involved in the processes. *MPZ* is one of the fundamental parts of the process and its pathogenic alterations have been described in association with CMT condition. Although all MPZ variants associated with CMT follow AR form of inheritance and some of them result in early onset CMT, we here described first CMT case with homozygote deletion of *MPZ* with late onset and mild phenotype. Our findings suggest that there should be another protein with compensatory role in the lack of *MPZ* which attenuates severe phenotypic features of CMT. However, functional studies and different modeling investigations are essential to confirm our findings. Furthermore, diverse biomolecular examinations are needed to identify the proposed protein associated with PNS myelin formation and its maintenance.

Abbreviations *MPZ*: Myelin protein zero; CMT: Charcot-Marie-Tooth; AD: Autosomal dominant; AR: Autosomal recessive; PNS: Exome sequencing, peripheral nervous system; HSMN: Hereditary sensory and motor neuropathy; NCV: Nerve conduction velocity; PMP22: Peripheral myelin protein 22 gene; MBP: Myelin basic protein; P2: Peripheral myelin proteins 2; IPL: Intraperiod line; DSS: Dejerine-Sottas syndrome; PLP: Proteolipid protein; SLIs: Schmidt-Lanterman incisures

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Authors' contributions MT, HH and SGF wrote the draft and revised it. JG and MR perfumed the data collection and designed the tables and figures. BMH, MS and AN contributed in data collection and analyzing the data All authors contributed equally and fully aware of submission.

Data availability The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participant All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent forms were obtained from all study participants. The study protocol was approved by the ethical committee of Shahid Beheshti University of Medical Sciences. All methods were performed in accordance with the relevant guidelines and regulations.

Consent of publication Not applicable.

Competing interest The authors declare they have no conflict of interest.

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