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ORIGINAL COMMUNICATION

Mutation update for myelin protein zero-related neuropathies and the increasing role of variants causing a late-onset phenotype

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Abstract

Mutations of myelin protein zero gene (*MPZ*) are found in 5% of Charcot–Marie–Tooth patients. In 2004, Shy et al. identified two main phenotypes associated with them: an early-onset subtype with mainly demyelinating features and a late-onset subgroup with prominent axonal impairment. We evaluated whether novel *MPZ* mutations described in literature during the last 14 years could still fit with this classification. We collected and revised reports of 69 novel *MPZ* mutations. Almost 90% of them could be alternatively classified as responsible for: (a) an early-onset phenotype, with first limitations starting before 3 years (2.5 ± 0.50 years), motor milestones delays, frequently severe course and upper limb MNCVs below 15 m/s; (b) late-onset neuropathy, with mean age of onset of 42.8 ± 1.5 years and mean upper limbs motor nerve conduction velocities (MNCVs) of 47.2 ± 1.4 m/s; (c) a phenotype more similar to typical CMT1A neuropathy, with onset during the 2nd decade, MNCV in the range of 15–30 m/s and slowly progressive course. The present work confirms that P0-related neuropathies may be separated into two main distinct phenotypes, while a third, relatively small, group comprehend patients carrying *MPZ* mutations and a childhood-onset disease, substantiating the subdivision into three groups proposed by Sanmaneechai et al. (Brain 138:3180–3192, 2015). Interestingly, during the last years, an increasing number of novel *MPZ* mutations causing a late-onset phenotype has been described, highlighting the clinical relevance of late-onset P0 neuropathies. Since the family history for neuropathy is often uncertain, due to the late disease onset, the number of patients carrying this genotype is probably underestimated.

Keywords Charcot–Marie–Tooth · Myelin protein zero · Phenotype classification · Genotype–phenotype correlation

Introduction

Charcot–Marie–Tooth disease (CMT), with a prevalence of 9.37–20.1/100.000 [1], is one of the most common hereditary disorders of the nervous system. The clinical hallmarks of the disease are distal weakness, muscle wasting

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and sensory loss; nevertheless, the clinical phenotype can be quite variable in terms of age of onset, disease progression and severity. Based on nerve conduction velocity, CMT can be distinguished into two main forms: demyelinating (CMT1), characterized by upper limb motor nerve conduction velocities (MNCVs) below 38 m/s, and axonal (CMT2), with preserved or mildly slowed nerve conduction velocities in the upper limbs (> 38 m/s). From a molecular point of view, CMT is a complex disorder, with more than 1000 putative mutations in 80 different disease-associated genes [2]. Mutations in myelin protein zero gene (*MPZ*), encoding for P0, are found in 4.1% of all CMT patients [3, 4], and were initially described as responsible for CMT1B; subsequently, mutations in this gene have been found also in cases of congenital hypomyelinating neuropathy/Dejerine Sottas disease and CMT2. To analyse the phenotypes associated with *MPZ* mutations, Shy et al. [5] evaluated patients seen in their clinic and re-evaluated clinical data from 64 cases of CMT1B reported in literature until 2004. They found that most patients could be classified as having either an early-onset or a late-onset neuropathy, the former presenting with onset of the disease during the 1st decade of life and with upper extremity MNCVs lower than 15 m/s, the latter with an age of onset over 20 years of age and with upper extremity MNCVs faster than 30 m/s. In a more recent work examining clinical severity of patients from Inherited Neuropathy Consortium [6], 47 *MPZ* mutations, of whom 15 were novel and 6 were described in literature after 2004, were classified as responsible for three phenotypes with onset in infancy, childhood and adulthood, respectively.

In the present study, we collected literature data related to novel *MPZ* mutations described between 2005 and 2018 to assess whether the distinction between early- and late-onset neuropathy can still be considered a landmark and to provide further insight into the disease mechanisms.

Methods

Literature evaluation

Reports about novel *MPZ* mutations described between 2005 and 2018 were collected from a search on PubMed and on the online database http://molgen-www.uia.ac.be/CMTMutations/. We used the following search terms: "myelin protein zero", "Charcot–Marie–Tooth disease", and "novel *MPZ* mutation". Reports of novel *MPZ* mutations not providing adequate clinical and neurophysiological data, i.e., a complete description of the clinical presentation and an upper limb neurophysiological study were excluded (Fig. 1). Mutations described by more than one author and associated with more than one phenotype were included in each of the described groups. *MPZ* mutations found in patients with a negative or not available family history were included if segregation analysis had been performed or if the mutation was absent in unrelated healthy controls. For each mutation, clinical (age of onset, number of affected family members, severity and additional clinical features) and neurophysiological data (upper and lower limbs motor conduction velocities and compound motor action potentials)

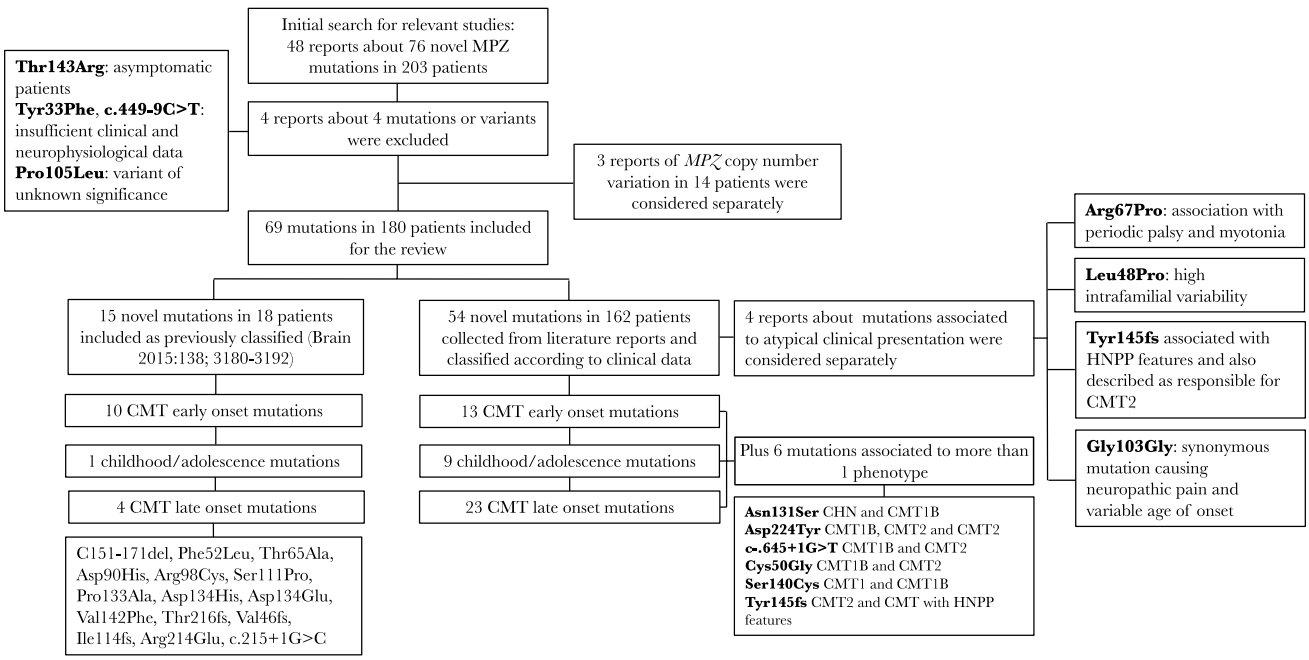

Fig. 1 Flowchart of the inclusion process for the review

were derived from the considered study for all the available patients. Mutations were classified as responsible for early-, childhood–adolescence- or late-onset neuropathy according to age of onset of the neuropathy (≤ 5 years, 6–20 years; ≥ 21 years), defined by the age at which the proband or another family member started to manifest clinical and/or neurophysiological signs; for each group, average values and standard error were calculated for the considered variables. The severity of the disease was classified based on CMTNS, when reported, or on clinical aspects described in the report.

Results

Between 2005 and 2018, 76 novel *MPZ* mutations in 203 patients have been reported in the literature [6–51] as responsible for Dejerine–Sottas disease, congenital hypomyelinating neuropathy, CMT1B or CMT2 neuropathies. We excluded three mutations described in five patients for insufficient clinical and neurophysiological data and one report about one variant of unknown significance (Figs. 1, 2; Supplementary Table 4); three reports [21, 29, 47] on *MPZ* copy number variation in 14 patients were considered separately (Supplementary Table 5). Reports about 69 novel *MPZ* mutations in 180 patients contained adequate clinical and neurophysiological data, thus allowing us to derive the phenotype, including a group of 15 novel *MPZ* mutations in 18 patients newly described in 2015 [6] and whose phenotype had already been classified has responsible for early-onset, CMT1B or late-onset neuropathy (Fig. 1).

Overall, 60 out of 69 mutations (87%) in 144 patients could be unambiguously classified, according to clinical and neurophysiological parameters, as responsible for an early-onset neuropathy (35 patients—24%; 23 mutations—38%), a late-onset neuropathy (74 patients—51%; 27 mutations—45%) or a childhood-onset phenotype (36 patients—25%; 10 mutations—17%). Six (9%) other mutations in 18 patients (10%) have been described in more than one report and associated by the authors to more than one phenotype and were therefore considered in each of the described groups; eventually, 3 further *MPZ* mutations (4%) in 14 patients (7%) were associated with an atypical phenotype [14, 20, 48] (Fig. 2).

From the descriptions of *MPZ* mutation in the literature, excluding those already classified in 2015 [6], we can derive as follows (Table 1, Fig. 3).

Twenty-six patients with 15 different novel mutations could be classified as having an early-onset neuropathy (Table 2). Among them, 17 patients with eight different mutations were described by the authors as having DSS, five patients with four different mutations were described as affected by CHN, and four patients with three different

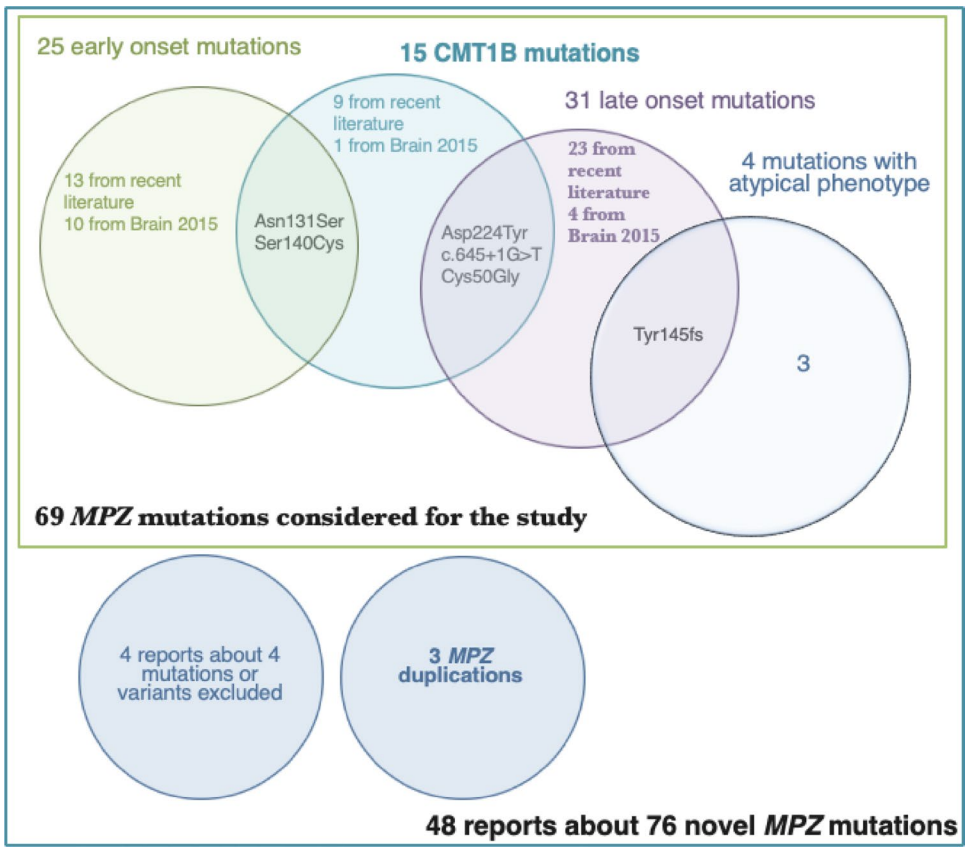

Fig. 2 Venn diagram showing mutations included and excluded from the review

Table 1 MPZ mutations phenotypes; literature review

	Early onset	Childhood/ adolescence	Late onset
Mutations (*N*)	15	14	27
Patients	26	44	76
Families	6 (40%)	9 (64%)	18 (66%)
Sporadic cases	9 (60%)	5 (36%)	9 (33%)
Age of onset (years)	2.5 ± 0.50	15.1 ± 1.1	42.8 ± 1.5
Pupillary abnormalities	Six patients with two mutations	0	One patient with one mutation
Hearing loss	Two patients with one mutation	0	Five patients with three mutations
Scoliosis	6 (24%)	0	0
CMTNS ≤ 10	3 (12%)	36 (82%)	59 (78%)
CMTNS 11–20	3 (12%)	8 (18%)	12 (16%)
CMTNS > 20	19 (76%)	0	5 (7%)
Mean UL mNCV (m/s)	7.4 ± 1.2	31.2 ± 2.6	47.2 ± 1.4
Mean UL CMAP (mV)	1.8 ± 0.4	6.6 ± 0.6	8.3 ± 0.7

mutations received a diagnosis of CMT1. The mean age at onset was 2.5 ± 0.50 years (median 2 years; range 0–9), with eight cases where the neuropathy started within the 2nd year of life and seven patients presenting at birth as floppy babies. Family history was negative in the nine cases (60%) and six families (40%) with at least two affected members were described. A severe clinical course, defined by a CMTNS > 20 was associated with 13 mutations in 19 cases (76%); 2 mutations in 6 cases were responsible for a mild to severe neuropathy. The phenotype was complicated by the occurrence of kyphoscoliosis in six patients (24% of patients, 33% of all mutations). Cranial nerves involvement was reported for several patients with early-onset neuropathy. In particular, five patients carrying the His81Gln [13] mutation and one patient carrying the Ile30Thr mutation [19] showed Adie's pupils, while two patients carrying the Gly137Gly mutation [50] had sensory-neural hearing loss and ptosis as adjunctive features. Neurophysiology was consistent with a severe hypo- or demyelinating neuropathy with secondary axonal degeneration. All but three cases presented with MNCV of the median and ulnar nerves below 15 m/s, with mean MNCV of the median nerve of 7.4 ± 1.2 m/s; three patients showed absence of sensory and motor nerve responses both in upper and lower limbs. When obtainable, conduction velocities from lower limbs were similar to those obtained from the upper limbs. Compound muscle action potentials (CMAPs) and sensory nerve action potentials (SNAPs) were reduced, with mean CMAP = 1.8 ± 0.4 mV.

Seventy-six patients carrying 27 novel mutations could be classified as affected by a late-onset neuropathy (Table 3). In most cases, symptoms ensued after the 4th decade of life, and in several cases they started during the 6th or 7th decade (median 43 years; range 15–75; mean age of onset of 42.8 ± 1.5 years). Family history was negative in 33% of the cases. Emerging features of late-onset P0 neuropathy were consistent with a sensory-motor neuropathy with prominent involvement of lower limbs and causing a relatively low disability, with 56 patients (78%) having a slowly progressive, mild neuropathy (CMTNS < 10). Nevertheless, cases of rapidly progressive symptoms, appearing late in life but quickly conducting to severe disability and ambulation aid requirement have been described for Arg36Gly, Pro70Ser and His81Leu mutations [15, 27, 29]. Moreover, neuropathic pain was a prominent feature in several cases of late-onset P0 neuropathies, as in the case of Arg36Trp [11] and Arg36Gly [15]: in both cases, patients started to complain of spontaneous burning pain and tingling of hands and feet, and showed neurophysiologic features of an axonal sensory-motor neuropathy in all limbs. Additional clinical findings included slow or absent pupillary light reflexes in one patient carrying the Phe95Leu mutation [38], and sensory-neural hearing impairment in five patients harbouring the Phe95Leu, Pro105Thr or Arg106Cys mutations [23, 33, 37].

Electrophysiological analysis was consistent with an axonal neuropathy, with mean MNCV from ulnar nerve of 47.2 ± 1.4 m/s, and normal CMAP amplitudes from the upper limbs. Lower limbs neuronography, when recorded, was consistent with an axonal neuropathy (mean CMAP of common peroneal nerve = 2 ± 0.5 mV).

Forty-four patients with 14 different mutations presented a childhood–adolescence-onset phenotype that fits neither with an early- nor with a late-onset neuropathy, resembling rather CMT1A (Table 4). Usually patients showed a normal motor development and started to complain of sensory-motor symptoms during the 1st or 2nd decade of life, with a mean age of neuropathy onset of 15.1 ± 1.1 years (median 15 years; range 6–40). Nine cases were familiar (64%) and five sporadic (36%). The clinical course of disease within this group was mild in 82% of the cases, with a mean age of 39.1 ± 3.3 years at first neurological visit, usually 2 decades

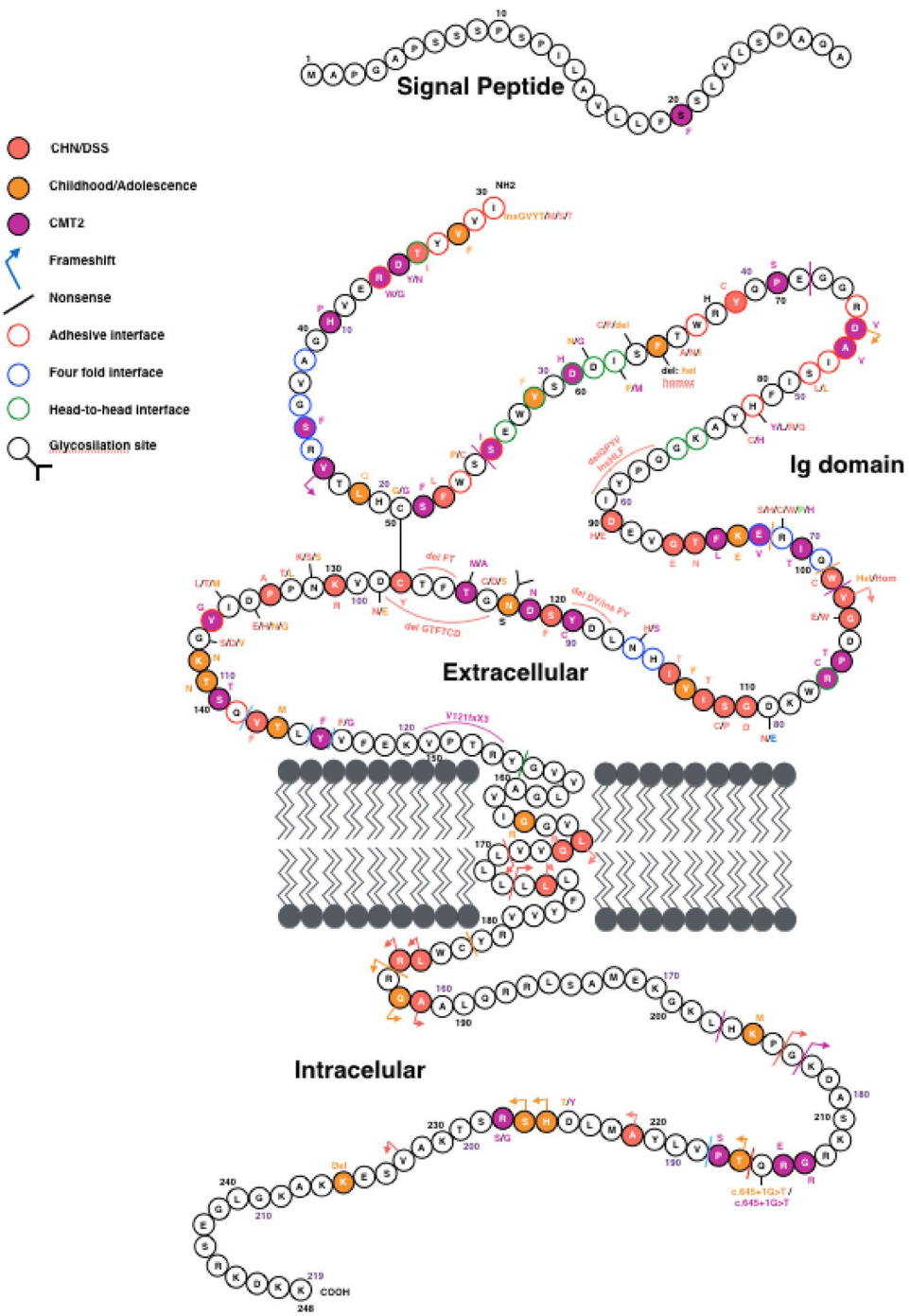

Fig. 3 Mutations in the MPZ gene associated with inherited neuropathies. Adhesive interface, fourfold interface and head-to-head interface, marked with colour to the border of circle, refer to amino acid residues deemed essential for *cis* and *trans* adhesion between adjacent myelin wraps. Both the numbering systems for MPZ mutations, including or not the 29 amino acid leader peptide cleaved before insertion in the myelin sheath, are reported. Mutations demonstrated by adding the letters that represent amino acid change, arrows that represent frameshift mutation and lines that represent nonsense mutation. Mutations causing early-onset phenotype are filled or noted with red colour, while those causing childhood-onset phenotype are in orange, and those causing late-onset phenotype are in purple (updated from Sanmaneechai et al. [6])

after first signs or symptoms' onset. Only eight patients with six mutations experienced a neuropathy of moderate severity (CMTNS 10–20). Cranial nerves involvement was never reported and patients had no additional features other than the polyneuropathy. Neurophysiological examination was consistent with a demyelinating polyneuropathy with MNCV approaching the so-called intermediate range, a mean ulnar nerve MNCV of 31.2 ± 2.6 m/s, and usually preserved upper limbs CMAP (6.6 ± 0.6 mV).

Eventually, four mutations were associated with a phenotype slightly different from the classical ones (Table 5): Gly103Gly synonymous mutation [14] has been described in two families with variable age of onset, neuropathic pain and predominant sensory involvement; Arg67Pro [20] has been described in a family with a compound genotype and phenotype of periodic palsy and myotonia, Leu48Pro [49] has been reported in two families with high intrafamilial variability in terms of age of onset, electrophysiological findings and

Table 2 Features of P0-related neuropathies—early-onset neuropathies

Mutation	Author diagnosis	Age of onset of first limitations	Age walked	Clinical course	NCV	CMAP	Pathology	Family history	Other clinical features	Author
Ile30Ser	CMT1	2 y	ND	Severe	*m* 4 m/s	*m* 0.8 mV	Not performed	1 pt	–	Miltenberger-Miltenyi et al. [35]
Ile30Thr	DSS	2–3 y	2.5–6 y	Severe (CMTNS 29–35)	*u* 0–9 m/s	*u* 0–1.5 mV	Not performed	AD 1F; 2 pt	Scoliosis, neuropathic pain, Adie's pupils	Floroskufi [19]
Thr65Asn	DSN/HMSN III	Infancy	> 18 months	Severe	*m* 4–12 m/s *u* 6–11 m/s *t* NE	*m* 1.8 mV *u* 1.7 mV *t* NE	Not performed	1pt de novo	Scoliosis	Brozkova et al. [10]
His81Gln	CMT1/DSS	1st dec (2–9 y)	–	Mild to severe (CMTNS 7–27)	*m* 6.2–14.9 m/s *u* 4.5–14.3 m/s *p* NE *t* NE	*m* 0.1–3.8 mV *u* 0.4–8.1 *p* NE *t* NE	Severe loss of MFs of all calibres; onion bulbs, regenerative clusters	AD 1F; 7 pt	Adie's pupils, tremor, ataxia	Choi et al. [13]
Gly103Trp	DSN/HMSN III	Infancy	> 18 months	Mild to Severe	*m* 17.6–22 m/s *u* 27–28.3 m/s *t* 0–6 m/s	*m* 2–5.8 mV *u* 7.5 mV *t* 0.1 mV	Not performed	1F, 2 pt	Scoliosis	Brozkova et al. [10]
Ser121Phe (Ser111Phe)	CHN	4 m	Never walked	Severe (unable to perform any voluntary movement)	*m* 2.9 m/s *u* 3.3 m/s *t* 3.6 m/s	*m* 0.56 mV *u* 0.99 mV *t* 0.143 mV	Severe loss of myelinated fibres; atypical onion bulbs	1 pt de novo	Respiratory insufficiency; CSF proteins: 87 mg/dl	Sevilla et al. [44]
Gly123Asp	DSS	2 y	–	Severe (CMTNS: 26)	*m* 6.7 m/s *u* 6.9 m/s *p* 9.2 m/s	*m* 4.0 mV *u* 2 mV *p* 0.7 mV	Not performed	1 pt de novo	Ataxia, kyphoscoliosis	Braathen et al. [9]
Asn131Ser[a]	CHN	2 y	2.5 y	Severe	*m* NE *u* NE *p* NE *t* NE	*m* NE *u* NE *p* NE *t* NE	Severe loss of myelinated fibres; onion bulb-like formations	1 pt de novo	–	McMillan et al. [34]
Pro132Thr	DSN/HMSN III	Early in infancy	>18 months	Severe	*m* NE *u* 3 m/s *t* NE	*m* NE *u* NE *t* NE	Not performed	1 pt de novo	Hypotonia	Brozkova et al. [10]
Ser140Cys (Ser111Cys)[a,b]	CMT1	1st dec	–	Severe	*m* 14.6 m/s *u* 12 m/s *p* 7.5 m/s	–	Not performed	AD 1F; 2 pt	–	Mandich et al. [32]

Table 2 (continued)

Mutation	Author diagnosis	Age of onset of first limitations	Age walked	Clinical course	NCV	CMAP	Pathology	Family history	Other clinical features	Author
Gly137Gly	DSS	0–5 y	Delayed	Severe	*m* 5 m/S *u* 9 m/s *p* 5.5 m/s	*m* 1 mV *u* 0.2 mV *p* 0.15 mV	Loss of large myelinated fibres; onion bulbs	AD 1F; 2 pt	Ptosis, bilateral hypoacusia, scoliosis	Taioli et al. [50]
Leu184AlafsX51	CHN	At birth	Delayed	Severe	*m* 0–4 m/s *p* NE	*m* 0.8–3.3 m/S *p* NE	Absence of myelin sheaths	AD 1 F; 2 pt	–	Smit et al. [47]
Arg185AlafsX6	CMT1	1 y	ND	Severe	*m* 11 m/s	ND	Not performed	1 pt de novo	Macrocephalia	Miltenberger-Miltenyi et al. [35]
c.368_382delGCACGTTCACTTGTG	CHN	At birth	ND	Severe	Absent sensory and motor nerve responses in his upper and lower extremities	Absent sensory and motor nerve responses in his upper and lower extremities	Complete absence of myelination of both large or small fibres, despite intact axons	1 pt de novo	CSF proteins: 95 mg/dl	McMillan et al. [34]
c.618_619 insT	DSS	1st month of life	Delayed	Severe	*m* NE *u* 3 m/s *p* NE	*m* NE *u* 1.4 mV *p* NE	Not performed	1 pt de novo	CSF proteins: 3 g/ml; RMN: nerve and spinal roots enlargement	Zschüntzsch et al. [51]

Dec decade, *y* years, *m* median, *u* ulnar, *p* peroneal, *t* tibial, *s* sural, *NE* not evocable, *NR* not recorded, *AD* autosomal dominant, *F* family, *pt* patients

[a]Mutations described by more than one author

[b]Mutation also included in Brain 2015:138; 3180–3192

Table 3 Features of P0-related neuropathies—late-onset neuropathies

Mutation	Author diagnosis	Age of onset of first limitations	Age walked	Clinical course	NCV	cMAP	Pathology	Family history	Other clinical features	Author
Ser20Phe	CMT1B	60 y	ND	Slowly progressive	Normal median and ulnar conduction *p* NE *t* NE *s* 44 m/s	Normal median and ulnar conduction *t* NE *p* NE *s* 12 uV	Reduced thick myelinated fibres density, increased endoneurial connective tissue, absent demyelination	1 pt	Thigh and calf cramps after exercise and increased CK levels	Finsterer et al. [18]
Asp35Asn	CMT2	3rd to 7th dec	ND	CMTNS: 12–15	*m* 42–49 m/s *u* 52–60 m/S *p* 0–31 m/s *t* NE	*m* 4.4–7.5 mV *u* 5–7.7 mV *p* 0–0.4 *t* 0–0.5	Not performed	AD 2F; 3pt	–	Braathen et al. [9]
Arg36Trp[b]	CMT2	47 y	ND	–	*m* 45.6 m/s *u* 46.4–63.5 m/s *p* 28.9–41.9 m/s *t* 29.1–32.6 m/s	*m* 8 mV *u* 9.9–6.6 mV *p* 1.1–0.8 mV *t* 0.2–0.5 mV	Not performed	1F, 2 pt	Painful, acute onset, remitting CSF protein 60 mg%	Burns et al. [11]
Arg36Gly	CMT2	5th to 8th dec	–	Progressive unsteady gait	*t* 33.9–36.2 m/s *p* 35.2–40.7 m/S *s* 37.8–40.7 m/S	*t* 1–5.9 mV *p* 1.9–7.4 mV *s* 1.9–1.7 mV	Severe loss of myelinated fibres with sporadic axonal degeneration and regenerating clusters	AD 1F; 3 pt	Rapidly progressive clinical course	Dacci et al. [15]
Cys50Gly[a]	CMT1B	66 y	Normal	Mild	*m* 27.1 m/s *u* 29.2 m/s *p* NE *t* 19.5 m/s	*m* 9.9 mV *u* 12.05 mV *p* NE *t* 5.8 mV	Not performed	1 pt	Diffuse swelling and slight gadolinium enhancement of the cauda equina	Nishiyama et al. [36]
Ser54 fs	CMT1B	4th to 6th dec	Normal	Mild in the father, rapidly progressive in the son	*m* 24–37 m/s *u* 29–37 m/s	*m* 3.5–8.2 mV *u* 1.5–7.7 mV	Not performed	AD 1F; 2 pt	CSF protein 551 mg/L; benefit from PE	Chavada et al. [12]
Ser55Ile	CMTI	6th dec	–	Mildly progressive	*m* 37.3 m/s *u* 36.8 m/s *t* 25.6 m/s	*u* 8 mV *t* 0.7 mV	Not performed	AD 1F; 2 pt	–	Kleffner et al. [25]

Table 3 (continued)

Mutation	Author diagnosis	Age of onset of first limitations	Age walked	Clinical course	NCV	cMAP	Pathology	Family history	Other clinical features	Author
Pro70Ser[b]	CMT2	5th to 6th dec	–	Moderate (CMTNS 10–18)	*m* 47–58 m/s *u* 50–53.7 m/s *p* 0–38.1 m/s *s* 33–44 m/s	*m* 6.5–17.8 mV *u* 13.3–16 mV *p* 0–0.3 *s* 0–0.57	Severe axonal neuropathy with wallerian-like degeneration and some clusters of regeneration	AD 2F; 5 pt and 1 sporadic case	–	Laurà et al. [27]
His81Leu	CMT2	5th to 6th dec	–	Severe (CMTNS: 24–25)	*m* 40–42 m/s	*m* 2–2.3 mV	Not performed	AD 1F; 3 pt	–	Liu et al. [29]
Tyr82His	CMT2	4th to 6th dec	ND	Mild	*m* 34–56 m/s *u* 48–59 m/s *p* NE–44 m/s	–	Loss of myelinated fibres, clusters of regenerating axons	AD 2F; 14 pt	–	Bienfait et al. [8]
Phe95Leu	CMT1B	4th to 7th dec	–	Slowly progressive or asymptomatic	*m* 41.1 m/s *u* 53 m/s *t* 25 m/s	*m* 9.6 mV *u* 11.6 mV *t* 0.3 mV	Not performed	AD 1F; 3 pt	Pupils abnormality; sensorineural hearing loss	O'Connor et al. [37]
Trp101Stop	CMTI	25 y proband (1st to 2nd to 4th dec)	–	Mild (CMTNS 6–8)	*m* 33–43 m/s *u* 36–50 m/s	*m* 5.6–10.2 mV *u* 2.2–7.7 mV	–	AD 1F; 6 pt	Neuropathic pain	Ramirez et al. [40]
Pro105Thr	CMT2	5th to 7th dec	–	Steppage gate	*m* 32.7–46.1 m/s *p* NE–30.2 m/s	*m* 6.9–8.0 mV *p* NE	Not performed	AD 1F; 4 pt	Sensory hearing loss; calf muscle hypertrophy; neuropathic pain	Kabzinska et al. [23]
Arg106Cys	CMT2	5th to 7th dec	Normal	Mild (CMTNS<10)	*m* 38–49 m/s *p* NE *s* NE	*m* 6.1–16 *p* NE *s* NE	Not performed	AD 2F; 4 pt	Sensory-neural hearing loss	Marttila et al. [33]
Asn116Ser	CMT1B	43 y	–	–	*m* 32 m/s *u* 34 m/s *p* 34 m/s *t* 32 m/s *s* NE	*m* 5 mV *u* 9.5 mV *t* 0.97 mV *s* NE	Not performed	1 pt de novo	–	Kleffner et al. [25]
Asp121Asn	CMT2	4th dec	–	Mild to moderate	*m* 46–55 m/s *u* 53 m/s *t* 33.3–37.9 m/s	*m* 3.7 mV *p* NE *t* 0.2–2.2 mV	Not performed	AD 1F; 6 pt	Sensory-neural hearing loss, pupils abnormalities	Duan et al. [16]

Table 3 (continued)

Mutation	Author diagnosis	Age of onset of first limitations	Age walked	Clinical course	NCV	cMAP	Pathology	Family history	Other clinical features	Author
Thr124Ala	CMT2	38 y	–	Mild	*t* 39 m/s *s* 42 m/s *u* 56 m/s	Reduced	Not performed	AD 1F: 3 pt		Mandich et al. [32]
Val136Gly	CMT1	45 y	–	Slowly progressive	*m* 34 m/s *p* 20 m/s	Decreased	Severe loss of myelinated fibres	1 pt Homozygous	Ataxia, tremor; MRI: multiple white matter lesions, with corpus callosum involvement	Reyes-Marin et al. [41]
V160fsX3 stop	CMT1B	3rd dec	Normal	Mild	*m* 36 m/s	Reduced	Not performed	AD 1F; 3 pt	–	Piazza et al. [38]
Leu144 fs	CMT1 presenting as acute remitting sensory neuropathy	44 y	Normal	Mild, remitting	*m* 30.6 m/s *u* 35.8 m/s	*m* 2.4 mV *u* 3.7 mV	Not performed	1 pt de novo	–	Simpson and Rajabally [46]
Tyr145 fs[a]	CMT2	40 y	–		*m* 38 m/s *t* 32.5 m/s *s* 30 m/s	Reduced	Not performed	1 pt de novo	Postural tremor of arms and legs	Mandich et al. [32]
Val146Gly	CMT1B	40 y	–	Mild	*m* 35.4 m/s *u* 43.9–45 m/s *t* 29.5–31.8 m/s	*m* 9.5 mV *u* 7.7 mV *t* 0.9–2.6 mV	Not performed	AD 1 F; 2 pt	–	Brozkova et al. [10]
Pro217Ser	CMT2I	27 y	–	–	*m* 53.8 m/s *p* 34.8 m/s *t* 28–31.3 m/s	*m* 11.4 mV *p* 5.8 mV *t* 6.5–5.3 mV	Not performed	1 pt de novo	–	Kleffner et al. [25]
Asp224Tyr[a]	CMT2/CMTI	43 y (proband)	–	Mild to moderate	*m* 34 m/s	*m* 12 mV	–	AD 1F; 3 pt	–	Miltenberger-Miltenyi et al. [35]
Asp224Tyr[a]	CMT2/CMTI	25–45 y	Normal	Mild to moderate	*m* 34–45 m/s *t* 35–43 m/s	*m* 3.8–12 mV *t* 2–11 mV	Mild axonal loss of myelinated fibres, groups of regenerating fibres	AD 1 F, 4 pt	Electrophysiological signs of inflammatory neuropathy	Schneider-Gold et al. [43]
Arg227Gly	CMT2	68 y	Normal	Mild	*m* 42.6 m/s *u* 43.1 m/s *t* 24.7 m/s	*m* 10.1 mV *u* 9.5 mV *t* 0.40 mV	Selective loss of large myelinated fibres; regenerating clusters; no onion bulbs	1 pt de novo	–	Shimizu et al. [45]

Table 3 (continued)

Mutation	Author diagnosis	Age of onset of first limitations	Age walked	Clinical course	NCV	cMAP	Pathology	Family history	Other clinical features	Author
c.645 + 1 G > T[a]	CMT1B	42 y	–	–	*p* 22.5 m/s *t* 28.8 m/s	*p* 1.5 mV *t* 2.4 mV	Not performed	1 pt de novo	–	Kleffner et al. [25]
c.614 + 2T > G[b]	CMT1B	3rd to 4th dec	Normal	Mild to moderate	*u* 38.8–42 m/s *p* 26.1–32.9 m/s	*u* 6.1–8 mV *p* 0.4–4.5 mV	Not performed	AD 1F; 4 pt	–	Sabet et al. [42]

Dec decade, *y* years, *m* median, *u* ulnar, *p* peroneal, *t* tibial, *s* sural, *NE* not evocable, *NR* not recorded, *AD* autosomal dominant, *F* family, *pt* patients

[a]Mutations described by more than one author

[b]Mutation also included in Brain 2015:138; 3180–3192

severity of the disease. Moreover, Tyr145 fs has been found by two different groups, in one case in a family with classical CMT2 phenotype [32], in the other [31] in three patients from one family with onset during the 4th decade of life and electrodiagnostic and pathologic findings of HNPP. In all the atypical cases, the identified mutation segregated with the disease in the families.

In addition to the classical small intragenic mutations, cases of *MPZ* copy number variation have recently been described (Supplementary Table 5). Hoyer [21] first described a family carrying an extra copy of the *MPZ* gene from exon 1 to exon 6, associated with a demyelinating neuropathy with onset within the 1st decade of life and slowly progressive course, while Maeda [30] described a family carrying *MPZ* triplication, affected by a demyelinating sensory-motor neuropathy with pupillary abnormalities and high intrafamilial heterogeneity in terms of age of onset and disease severity. Recently, Speevak [48] reported another case of *MPZ* duplication in a child affected by motor hypodemyelinating neuropathy with onset during the 1st year of life and a copy number variation of a region including *MPZ* and succinate dehydrogenase complex subunit C (*SDHC*) genes.

Six patients among all those included in our study, six carrying late-onset variants (Arg36Trp, Cys50Gly, Ser54 fs, Asp224Tyr, Arg36Gly, Val136Gly) [11, 12, 15, 36, 41, 43] initially received a diagnosis of inflammatory neuropathy, given an acute/subacute fluctuating clinical course eventually associated with pain as a prominent feature, markedly increased CSF protein concentration, and diffuse hypertrophy and slight gadolinium enhancement of the cauda equina roots at MRI. Moreover, co-occurrence with multiple sclerosis or asymptomatic CNS myelin abnormalities has been described for the Asp224Tyr [17] and Val136Gly [41] mutations, respectively.

Discussion

In this study, we aimed to define the spectrum of *MPZ*-associated phenotypes [5, 6] collecting and reviewing literature data regarding novel *MPZ* mutations described during the last 14 years (2005–2018), to better characterize the clinical features associated with them.

We identified 76 novel *MPZ* mutations associated with CMT in the recent literature. We excluded one VUS and other three mutations (5%) from the current work because of inadequate clinical data and considered separately three *MPZ* copy number variations (5%). Four mutations resulted in an atypical phenotype and six were described by more than one author as responsible for distinct phenotypes. The remaining 60 mutations, including 15 newly reported in a recent paper [6] analysing the clinical records of patients

Table 4 Features of P0-related neuropathies—CMT1B neuropathies

Mutation	Author diagnosis	Age of onset of first limitations	Age walked	Clinical course	NCV	CMAP	Pathology	Family history	Other clinical features	Author
Leu48Gln	CMT1B	2nd dec	Normal or delayed	Mild	*m* 29–35 m/s *u* 32–41 m/s *s* 27–40 m/s or NR	*m* 5.1–11.4 mV	Not performed	AD 2F; 3 + 7 pt	–	Brozkova et al. [10]
Cys50Gly[a]	CMT1	6 y	ND	–	*m* 16 m/s	*m* 6 mV	Not performed	1 pt	–	Miltenberger-Miltenyi et al. [35]
Glu97 fs	CMT1B	2nd dec	Instable walk	Mild	*m* 31–42 m/s *u* 37–42 m/s *s* 36–37 m/s	*m* 1.4–9.3 mV	Not performed	AD 1F; 5 pt	–	Brozkova et al. [10]
Gln100X	CMT1	Childhood	–	–	*m* 29 m/s	*m* 2 mV	Not performed	AD 1 F, 5 pt	–	Miltenberger-Miltenyi et al. [35]
Gly123Ser	CMT1B	2nd dec	Normal	Slowly progressive	*m* 15.7–19.6 m/s	ND	Severe loss of myelinated fibres, some onion bulb formation with clusters of regenerative fibres, and a large endoneurial area	AD 1 F, 9 pt	–	Lee et al. [28]
Asn131Ser[a]	CMT1B	Childhood	Normal	–	*m* 16.3 m/s	*m* 0.1 mV	Severe loss of myelinated fibres	1 pt de novo	Upper limbs predominant weakness with initial symptoms of entrapment neuropathy	Iida et al. [22]
Ile135Met	CMT1	Childhood	Normal	Mild	*m* 12.9 m/s *u* 13.6 m/s *t* NE *s* NE	*m* 1.4 mV *u* 4.8 mV *t* NE *s* NE	Not performed	AD 1 F; 2 pt	–	Lin et al. [26]
Gly137Val	CMT1B	10 y	–	Slowly progressive, CMTNS 15	NE	NE	Severe loss of myelinated fibres, onion bulbs	1 pt		Prada et al. [39]
Ser140Cys[a]	CMT1B	2nd dec (10–19 y)	–	CMTNS: 3–19	*m* 17–21.3 m/s	*m* 10.6–14.5 mV	–	AD 1 F; 2 pt	–	Liu et al. [29]

Table 4 (continued)

Mutation	Author diagnosis	Age of onset of first limitations	Age walked	Clinical course	NCV	CMAP	Pathology	Family history	Other clinical features	Author
Gln187ProfsX63	CMT1	Childhood	Normal	Moderate	*m* 13.6 m/s *u* 15.1 m/s *t* NE *s* NE	*m* 3.8 mV *u* 3.6 mV *t* NE *s* NE	Not performed	1 pt de novo	–	Lin et al. [26]
Lys214Met (Lys-204Met)	DI-CMT	2nd dec (14–17 y)	–	Very mild	*m* 35.3–41.6 m/s *p* 25.8–36.9 m/s	*m* 1.6–8.8 mV *p* 2–4.3 mV	Not performed	AD 1F; 9 pt	Calf hypertrophy in 3 pt	Banchs et al. [7]
Asp224Tyr[a]	CMT1B	2nd dec	Normal	Mild to moderate	*m* 17–44 m/s *u* 20–50 m/s *p* 16–42 m/s	*m* 4.9–12 mV *p* 0.9–6 mV	Chronic demyelinating process with complex onion bulbs and abnormally thickened myelin sheaths	1F, 4 pt; Proband homozygous	Multiple sclerosis in the proband	Fabrizi et al. [17]
c.645 + 1G > T[a]	CMT1B	12 y	Normal	Mild	*m* 32.6 m/s *t* 22.7 m/s *s* 31 m/s	*m* 8.4 mV *t* 1.3 mV *s* 2.58 uV	Not performed	1 pt de novo	–	Brozkova et al. [10]
c.674_675insA (His225Glnfs*10)	CMT1	2nd dec	Normal	Mild to moderate	*m* 15.3–23.9 m/s *u* 11.9–14.9 m/s *p* NE–21.2 m/s *s* NE	*m* 4–4.5 mV *u* 3–6.7 mV *p* NE–2.5 mV	Not performed	AD 1 F; 5 pt	–	He et al. [68]

Dec decade, *y* years, *m* median, *u* ulnar, *p* peroneal, *t* tibial, *s* sural, *NE* not evocable, *NR* not recorded, *AD* autosomal dominant, *F* family, *pt* patients

[a]Mutations described by more than one author

Table 5 Features of P0-related neuropathies—*MPZ* mutations with atypical phenotype

Mutation	Author diagnosis	Age of onset of first limitations	Age of walk	Disease course	NCV	CMAPs	Pathology	Family history	Other clinical findings	Author
Arg67Pro	CMT1	35 y (51)	ND	ND	*m* 28 m/s	ND	–	AD 1 F, 13 pt	Periodic palsy, myotonia	Hisama [20]
Leu48Pro	CMT1B	0–41 y	–	Highly variable	*m* 19.3–43 m/s *p* 20.5–32 m/s	*m* 3.68–7.5 mV *p* 1.9–8.4 mV	Decrease of large and small myelinated fibres, thin myelin sheath or concentric and eccentric thickenings. Cluster of regenerating fibres	AD 1 F, 7 pt	High intrafamilial variability in terms of age of onset and ENG findings	Szabo et al. [49]
Gly103Gly	CMT1B	2nd dec	Normal	Mild	*m* 33–42 m/s *t* 19–33 m/s	*m* 5–12 mV *t* 3.2–5.4 mV	Not performed	AD 2F; 3 + 3 pt	Neuropathic pain	Corrado et al. [14]
Tyr145 fs	HNPP	30–45 y	Normal	Mild	*m* 39–53 m/s *u* 33–48 m/s *p* 30–45 m/s	*m* 4.6–6.5 mV *u* 3.9–6.1 mV *p* 1.5–4.7 mV	Presence of tomacula	AD 1 F, 4 pt	Electrodiagnostic and pathologic features of HNPP	Magot et al. [31]

Dec decade, *y* years, *m* median, *u* ulnar, *p* peroneal, *t* tibial, *s* sural, *NE* not evocable, *NR* not recorded, *AD* autosomal dominant, *F* family, *pt* patients

carrying *MPZ* mutations recruited by the Inherited Neuropathy Consortium in a natural history study, corresponded to either early demyelinating, a childhood demyelinating or the late axonal phenotype.

In more detail, one quarter of the cases presented an early-onset phenotype, manifesting during motor development and characterized by very slow MNCV, while one half of the patients with novel *MPZ* mutations had an adult-onset axonal neuropathy with normal or minimally impaired MNCV. Interestingly, another quarter of the cases evaluated in this study had a distinct phenotype, presenting with motor and sensory symptoms usually during the 2nd decade of life and showing a slowly progressive course, with MNCV in the lower limit of the intermediate range. Such a phenotype, definable as childhood–adolescence onset, has been also highlighted, with a similar percentage, by Sanmaneechai et al. [6].

Myelin protein zero is the most abundant protein of the peripheral compact myelin, where it maintains the cohesion between adjacent myelin wraps through homophilic interactions [52]. As P0 is a prominent myelin protein, the mechanisms whereby MPZ mutations act in the generation of disorders alternatively affecting myelin or axons remain to be elucidated.

In the last years, different pathomechanisms for *MPZ* mutations have been dissected, particularly for mutations causing an early-onset neuropathy, ranging from endoplasmic reticulum retention and activation of the canonical unfolded protein response [53–56] to altered trafficking of the protein to non-myelin plasma membranes and altered radial axonal sorting during the early phases of myelination [57]. Other proposed mechanisms include the disruption of the intercellular adhesion properties with a structural packing defect [53] and mis-glycosylation of P0 with either loss of the native glycosylation site, the Asp122, frequently associated to a late-onset axonal neuropathy, or the gain of a new glycol site, resulting in an hyperglycosylated P0 variant, observed for mutations causing a severe demyelinating neuropathy [54, 58].

Advances have been achieved by the evidence that P0 not only localises in the compact myelin but also at the paranode and node of Ranvier, where it interacts with neurofascin 155 (NF155) and neurofascin 186 (NF186), participating in the maintenance of the nodal structure [59] and that Asp6Tyr, Asp32Gly, and His52Tyr mutations, responsible for late-onset CMT, display homophilic adhesion properties comparable to wild-type P0, but are unable to interact with components of the paranodal and nodal complexes.

CMT2 accounts for 30% of all CMT patients [60]. From our results, in the last decade, there was an increasing amount of novel *MPZ* mutations associated with late-onset axonal neuropathies rather than early-onset hypo- or demyelinating neuropathies. If we consider that while severe early-onset P0 variants often occur de novo and remain limited to a restricted number of cases, late-onset mutations are frequently familial and involve a larger number of subjects and recessive transmission, usually more common in severe early-onset diseases, has been described as associated with a late-onset phenotype in a patient carrying Val136Gly mutation, located in the same residue of Val136Glu but associated with heterozygous DSS and the prevalence of late-onset *MPZ* mutations, which has long been underestimated, is likely to be higher than expected, as growing awareness is increasing diagnostic rate and patients without overt family history may still be misdiagnosed.

Our data also include cases with presenting or superimposed features of an acquired inflammatory neuropathy. Given that the association between hereditary and inflammatory neuropathies is not yet clarified, and that neurophysiological and laboratory findings once considered typical for acquired inflammatory neuropathies have been described in various forms of CMT, genetic causes, including *MPZ* mutations, should be considered in the workup of patients with features of inflammatory neuropathy, especially if not all diagnostic criteria for inflammatory neuropathies are fulfilled and clinical response to immunosuppressive treatment is poor.

Molecular diagnosis of CMT can be achieved in 60–80% of cases [3, 56, 60, 61]. While up to 98% [56] of patients affected by CMT1 eventually receive a molecular diagnosis, this is still frequently challenging for patients suffering from late-onset CMT2, with the rate of diagnosis ranging between 25 and 63% using a gene-by-gene approach.

During the last years, the landscape of mutations responsible for CMT2 has expanded, ranging between the more common *GJB1* heterozygous mutations and autosomal dominant *GDAP1* mutations, and the incorporation of next-generation sequencing in the diagnostic practice has allowed the discovery of novel CMT genes, especially causing late-onset CMT2 [62], including *HARS* [63], *MARS* [64], *MME* [65] MORC2 [66] and NEFH [67].

The increasing amount of new genes associated with CMT2 and by the fact that other genetically determined neuropathies such as transthyretin-related amyloidosis, a systemic disease with involvement of peripheral nerves, can also manifest after the 6th decade, it is conceivable that an increasing number of late-onset neuropathies, previously misdiagnosed as acquired or age related, have a genetic cause.

In conclusion, our data, focusing on P0-related neuropathies heterogeneity, confirms the existence of three distinct phenotypes deriving from *MPZ* mutations, and highlights the clinical relevance of late-onset P0 neuropathies as well as the need to increase our knowledge about their underlying molecular mechanisms.

Compliance with ethical standards

Conflicts of interest None of the authors have any conflict of interest regarding this work.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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