Received: 17 February 2023 | Accepted: 8 May 2023

DOI: 10.1111/ene.15860

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Clinical spectrum and frequency of Charcot–Marie–Tooth disease in Italy: Data from the National CMT Registry

Chiara Pisciotta[1] | Alessandro Bertini[1] | Irene Tramacere[1] | Fiore Manganelli[2] | Gian Maria Fabrizi[3] | Angelo Schenone[4,5] | Stefano Tozza[2] | Tiziana Cavallaro[3] | Federica Taioli[3] | Moreno Ferrarini[3] | Marina Grandis[4,5] | Emilia Bellone[4,5] | Paola Mandich[4,5] | Stefano C. Previtali[6] | Yuri Falzone[6] | Isabella Allegri[7] | Luca Padua[8,9] | Costanza Pazzaglia[9] | Aldo Quattrone[10] | Paola Valentino[10] | Luca Gentile[11] | Massimo Russo[11] | Daniela Calabrese[1] | Isabella Moroni[1] | Emanuela Pagliano[1] | Paola Saveri[1] | Stefania Magri[1] | Silvia Baratta[1] | Franco Taroni[1] | Anna Mazzeo[11] | Lucio Santoro[2] | Giuseppe Vita[11] | Davide Pareyson[1] | for the Italian CMT Network

[1]Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

[2]Università Federico II di Napoli, Naples, Italy

[3]Università di Verona, Verona, Italy

[4]Università di Genova, Genoa, Italy

[5]IRCCS Ospedale Policlinico San Martino, Genoa, Italy

[6]IRCCS Ospedale San Raffaele, Milan, Italy

[7]U.O. Neurologia, A.O. di Parma, Parma, Italy

[8]Università Cattolica del Sacro Cuore, Rome, Italy

[9]Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

[10]Università Magna Graecia, Catanzaro, Italy

[11]Università di Messina, Messina, Italy

Correspondence
Davide Pareyson, Unit of Rare Neurological Diseases, Department of Clinical Neurosciences, Fondazione IRCCS Istituto Neurologico Carlo Besta, Via Celoria 11, 20133, Milan, Italy.
Email: davide.pareyson@istituto-besta.it

Funding information
Italian Ministry of Health (RRC).; Telethon-Italy Foundation grant GUP13006

Abstract

Background and purpose: Data are reported from the Italian CMT Registry.

Methods: The Italian CMT Registry is a dual registry where the patient registers and chooses a reference center where the attending clinician collects a minimal dataset of information and administers the Charcot–Marie–Tooth (CMT) Examination/Neuropathy Score. Entered data are encrypted.

Results: Overall, 1012 patients had registered (535 females) and 711 had received a genetic diagnosis. Demyelinating CMT (65.3%) was more common than axonal CMT2 (24.6%) and intermediate CMT (9.0%). The *PMP22* duplication was the most frequent mutation (45.2%), followed by variants in *GJB1* and *MPZ* (both ~10%) and *MFN2* (3.3%) genes. A relatively high mutation rate in some "rare" genes (*HSPB1* 1.6%, *NEFL* 1.5%, *SH3TC2* 1.5%) and the presence of multiple mutation clusters across Italy was observed. CMT4A was the most disabling type, followed by CMT4C and CMT1E. Disease progression rate differed depending on the CMT subtype. Foot deformities and walking difficulties were the main features. Shoe inserts and orthotic aids were used by almost one-half of all patients. Scoliosis was present in 20% of patients, especially in CMT4C. Recessive forms had more frequently walking delay, walking support need and wheelchair use. Hip dysplasia occurred in early-onset CMT.

Conclusions: The Italian CMT Registry has proven to be a powerful data source to collect information about epidemiology and genetic distribution, clinical features and disease progression of CMT in Italy and is a useful tool for recruiting patients in forthcoming clinical trials.

KEYWORDS
Charcot–Marie–Tooth disease, epidemiology, gene frequency, phenotype, registry

INTRODUCTION

Charcot–Marie–Tooth disease (CMT) encompasses a group of heterogeneous inherited peripheral neuropathies and is the most frequent genetic neuromuscular disorder with a pooled prevalence of 18:100,000 across distinct populations [1]. It is classified according to nerve conduction velocities and underlying pathology into demyelinating CMT (CMT1 if autosomal dominant [AD], CMT4 if autosomal recessive [AR]), axonal CMT2 (AD or AR) and intermediate CMT (I-CMT) (including the X-linked variety CMTX1 associated with *GJB1* mutations). Other related neuropathies are distal hereditary motor neuropathies (dHMN), hereditary neuropathy with liability to pressure palsies (HNPP) and hereditary sensory-autonomic neuropathies (HSAN). Further subdivision is based on causative genes or identified loci [2].

Different patients' series reporting gene mutation frequency have been published thus far, with somewhat similar profiles for the most frequent genes but also peculiarities related to regional differences and likely founder effects. The most relevant studies (Table S1) published so far concern CMT series in the USA [3], UK [4], Japan [5], Germany [6, 7], Spain [8], Italy [9, 10], Hungary [11], China [12] and in a large international series [13].

During the last few years, several registries have been developed for different neuromuscular disorders at a national and international level. Registries are important to gain epidemiological information, facilitate clinical trials planning and conduction, and define standards of care. In Italy, the alliance between several stakeholders allowed the creation and maintenance of the Registry for Neuromuscular Diseases (www.registronmd.it), including the National CMT Registry [14].

In this study data are reported from the Italian CMT Registry, where complete and reliable clinical and genetic information are collected, with the aim of giving an overview of CMT epidemiology across Italy and to report the clinical characteristics of the whole series and of the different CMT subtypes.

MATERIALS AND METHODS

The Italian CMT Registry (www.registronmd.it) has been developed [14] in collaboration with the "Associazione del Registro" (Registry Association) founded by Telethon-Italy and different patients' associations including ACMT-Rete. It is a dual registry where the patient registers herself/himself and chooses a reference center amongst nine spread all over Italy (Fondazione IRCCS Istituto Neurologico Carlo Besta of Milan [INB], IRCCS Ospedale San Raffaele of Milan, Universities of Genoa, Verona, Parma, Rome, Naples, Catanzaro and Messina) where the attending clinician, in an ad hoc visit, collects a minimal dataset of information and administers the clinical scale CMT Examination/Neuropathy Score (CMTES/CMTNS) [15]. The minimal dataset (slightly modified from Reilly et al. [16]) contains information on clinical, electrophysiological and genetic diagnosis, family history, disease onset, ability to walk, need for shoe inserts, ankle foot orthoses (AFOs), need of aids for walking, ability to walk, upper limb abilities, foot deformities; foot, hand and spine surgery; motor and sensory symptoms and signs such as decreased ability to feel, arthritic-like pain or burning in feet and hands; optic atrophy, hearing loss. Data are fully anonymized. All registry records are reviewed, and data are confirmed by local medical officers and validated by the registry curator. The Institutional Ethics Committee of INB (13 March 2013, no. 130/2013) and of each center approved the study. A written informed consent was obtained from all participants.

Statistical analysis

Participants' characteristics at baseline were described in terms of absolute numbers and percentages for categorical data and means with standard deviations (SDs) and range for continuous data. Comparisons of clinical characteristics amongst CMT subtypes were performed using the age-adjusted analysis of variance (ANOVA) or logistic models, as appropriate. Associations between age and CMTES amongst CMT subtypes were investigated through the Spearman correlation coefficient with the corresponding *p* value. A *p* value <0.05 was considered significant.

RESULTS

Data about the overall population are shown in Figure 1. In summary, between August 2012 and December 2020, 1012 patients had registered, 535 females (52.9%) and 477 males (47.1%), with mean

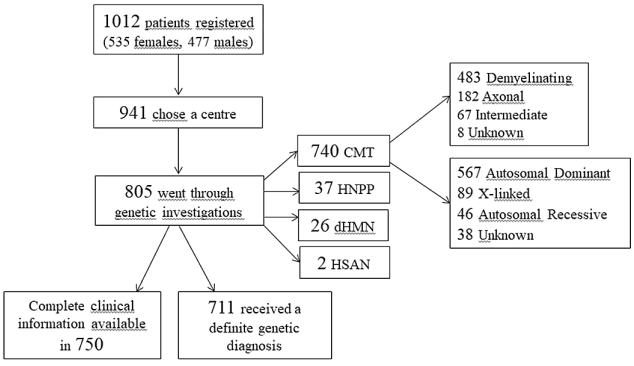

FIGURE 1 General information about the registry population. CMT, Charcot–Marie–Tooth disease; dHMN, distal hereditary motor neuropathy; HNPP, hereditary neuropathy with liability to pressure palsies; HSAN, hereditary sensory and autonomic neuropathy.

age 48.2 ± 16 years (range 1–91, 24 patients were <18 years); 941 had chosen a reference center, 805 went through genetic investigations and 711 had received a definite genetic diagnosis. The majority (n = 740; 91.9%) had CMT; 37 (4.6%) subjects had HNPP, 26 (3.2%) dHMN and there were two (0.2%) HSAN cases.

Amongst the 740 CMT patients, two-thirds had a demyelinating neuropathy (n = 483, 65.3%), one-quarter an axonal form (n = 182, 24.6%), 9.0% an intermediate type (n = 67; motor nerve conduction velocity of ulnar or median nerve 35–45 m/s and/or mutation(s) in I-CMT genes) and the nerve conduction pattern was unknown in the remaining eight patients; inheritance pattern was autosomal dominant in 567 (77.8%), autosomal recessive in 46 (6.2%), X-linked in 89 (12.0%) and unknown in 38 (5.1%) CMT patients. Autosomal dominant inheritance accounted for one-half of dHMN and HSAN cases.

Distribution of CMT subtypes and genotypes

A pathogenic mutation was found in 711 out of 805 investigated subjects, with an 88.3% diagnostic rate. The most prevalent mutated genes are reported in Table 1, whilst the less frequent genes are listed in Table S2. CMT1A (45.2%), CMTX1 (10.3%), CMT1B (5.0%), CMT2I/J (4.8%) and CMT2A (3.3%) were the most frequent CMT types. The most representative recessive CMT subtype was CMT4C (1.5%) followed by CMT4A (1.2%) and CMT2/dHMN-SORD (1.1%).

TABLE 1 The most frequently mutated genes amongst 805 CMT patients who underwent genetic investigation

Mutated genes	Number of patients (%)	CMT subtype related, *n* (%)
PMP22	408 (50.8%)	• CMT1A, 364 (45.2%) • HNPP, 37 (4.6%) • CMT1E, 7 (0.9%)
GJB1	83 (10.3%)	• CMTX1, 83 (10.3%) • Males, 46 (5.7%)/ females, 37 (4.6%)
MPZ	82 (10.2%)	• CMT1B, 40 (5.0%) • CMT2I/J, 39 (4.8%) • DI-CMTD, 3 (0.4%)
MFN2	27 (3.3%)	• CMT2A, 27 (3.3%)
GDAP1	17 (2.1%)	• CMT4A (recessive), 10 (1.2%) • CMT2K (dominant), 7 (0.9%)
HSPB1	13 (1.6%)	• CMT2F, 10 (1.2%) • dHMN2B, 3 (0.4%)
NEFL	12 (1.5%)	• CMT2E, 11 (1.4%) • CMT1F, 1 (0.1%)
SH3TC2	12 (1.5%)	• CMT4C, 12 (1.5%)
SORD	9 (1.1%)	• CMT2/dHMN SORD, 9 (1.1%)
Other genes	60 (7.5%)	
Unknown	82 (10.2%)	
Total	805	

Abbreviation: CMT, Charcot–Marie–Tooth disease.

The rate of genetic diagnosis was 96% in CMT1, 68% in CMT2, 82% in I-CMT and 57.7% in dHMN. The *PMP22* gene duplication was found in more than 75% of CMT1 cases, which is in keeping with the literature, whilst a relevant percentage of CMT2 cases with a genetic diagnosis was associated with either *MPZ* (20%) or *MFN2* (15%) genes. *GJB1* was the most frequently mutated gene (58%) in I-CMT.

Mutation clusters were identified in specific Italian areas (Figure 2). Amongst the 82 patients with *MPZ* mutations, 13/13 with the p.Pro70Ser amino acid change (associated with CMT2I) came from Lombardy, 8/10 with the p.Thr124Met (CMT2J) came from northern Italy (Veneto, Lombardy, Piemonte), 6/8 with the p.Ser44Phe (CMT2I/J) were from Sardinia, 6/6 with the p.Asp104ThrfsX13 came from Apulia and 12/14 with the p.Ser78Leu were Sicilian inhabitants or had Sicilian origin. Amongst 13 patients with a mutation in *HSPB1*, four were from Sicily and had the p.Arg136Leu variant. Finally, amongst CMTX1 patients, 5/5 patients with *GJB1* p.Thr191Phe193dupl came from Campania, 4/4 with the p.Arg164Leu variant and 3/3 carrying the p.Arg22Ter amino acid change were from Sicily. Most of these patients were apparently unrelated.

Clinical features

Complete clinical information was available for 750 patients. Table 2 describes the clinical features of the overall CMT population and Table 3 compares those of the most frequent CMT subtypes. In summary, the mean age of patients at the time of visit was 46.4 ± 15.7 years (range 2–91). The age was significantly higher in CMT2I/J (63.5 ± 12.6 years, range 35–85; $p < 0.001$) and CMT2F (61.7 ± 15.7 years, range 40–80; $p = 0.004$). In all, 529 (70.5%) patients had at least one affected relative alive, 171 cases were sporadic; for the remaining 50 patients, family history data were uncertain.

Delayed motor milestones (walking after age 15 months) occurred in 83 (11%) patients and were significantly more frequent in CMT1B ($p = 0.006$). Gait difficulties, reported by three-quarters of the patients, ensued earlier in CMT4A ($p = 0.007$) and later in CMT2I/J ($p < 0.001$), CMT2F ($p = 0.009$) and CMTX1 females ($p = 0.010$).

Orthotic aids, including shoe inserts, were used by almost one-half of all patients, and AFOs were more frequently required by CMT2I/J ($p = 0.031$) and CMT4A ($p = 0.027$) patients, but the age of first use differed amongst the two groups, significantly earlier in CMT4A ($p < 0.001$) and later in CMT2I/J ($p < 0.001$). The need for walking support was higher for CMT4C ($p = 0.016$) and CMT4A ($p < 0.001$), as it was for a wheelchair in the latter group ($p < 0.001$).

Upper limb involvement, with difficulties with buttons and eating utensils, was reported by 55% and 15% of patients, respectively, with the highest percentages in CMT4A ($p = 0.023$ and $p < 0.001$) and CMT4C ($p = 0.024$ and $p = 0.049$). It was significantly higher also in CMTX1, both in males ($p = 0.001$ and $p = 0.012$) and females ($p = 0.035$ and $p = 0.012$).

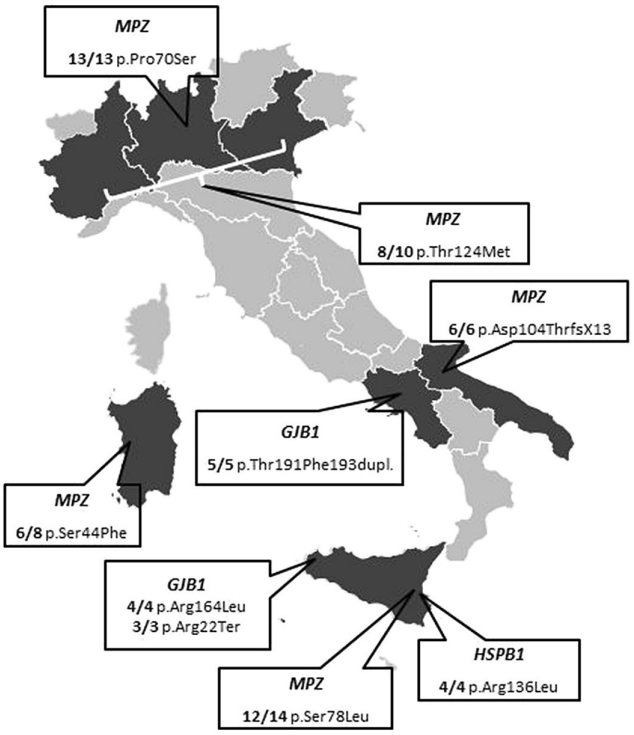

FIGURE 2 Distribution of the main genetic clusters.

Foot deformities were present in 634 (84.5%) patients with a significant lower prevalence in CMT4A ($p=0.010$) and late-onset CMT types (i.e., CMT2I/J, $p=0.012$, and CMT2F, $p=0.001$). A hundred and forty-nine patients (19.9%) underwent foot surgery, and its occurrence was significantly lower in CMT2I/J ($p=0.020$). Hand surgery was reported by only 25 patients (3.3%) with surgery for carpal tunnel syndrome being the most frequent procedure.

Scoliosis was found in 20% of the whole series and was particularly common and relevant amongst CMT4C patients (12/12 had scoliosis, treated in eight cases with bracing, in two with surgery). Hearing loss, partial in 100 subjects and complete in two patients, was especially frequent in CMT4C ($p=0.019$).

TABLE 2 Patients' clinical features ($n=750$)

Clinical features	*n* (%)	Mean age of occurrence ± standard deviation (range)
Delayed milestones (walked after 15 months)	83 (11.1%)	
Difficulty walking	557 (74.3%)	22.9 ± 17.7 (0–73)
Orthotic aids use	355 (47.3%)	33.1 ± 17.4 (2–72)
Shoe inserts	263 (35.1%)	
AFOs	140 (18.7%)	
Walking support need	81 (10.8%)	
Unilateral	54 (7.2%)	49.3 ± 18.2 (2–77)
Bilateral	25 (3.6%)	42.1 ± 20.6 (1–77)
Wheelchair use required	26 (3.5%)	
Intermittent	14 (1.9%)	37.3 ± 26.4 (1–78)
Regular	12 (1.6%)	32.2 ± 18.6 (12–62)
Difficulties with buttons	417 (55.6%)	
Difficulties with eating utensils	118 (15.7%)	
Burning/tingling in feet/hands	216 (28.8%)	
Decreased ability to feel	371 (49.5%)	
Arthritic-like pain	122 (16.3%)	
Foot deformities	634 (84.5%)	
Pes cavus	567 (75.6%)	
Pes planus	43 (5.7%)	
Foot surgery	149 (19.9%)	
Scoliosis	151 (20.1%)	
Surgery	9 (1.2%)	16.8 ± 4.4 (9–24)
Bracing	46 (6.1%)	10.9 ± 3.5 (2–20)
Hip dysplasia	16 (2.1%)	
Hearing loss	102 (13.6%)	

Abbreviation: AFOs, ankle foot orthoses.

Disease severity in cross-sectional analysis

The values of CMTES and CMTNS were available for 736 and 192 patients, respectively, and are reported in Table 4 for the main CMT subtypes.

The most severe type according to CMTES was CMT4A ($p<0.001$), followed by CMT4C ($p<0.001$) and CMT1E ($p=0.010$). In contrast, disease severity was lower in CMT2F associated with *HSPB1* mutations ($p=0.002$).

The association between age and disease severity was evaluated, assessed by the CMTES, in a cross-sectional analysis (Figure 3a–d). In CMT1A (Figure 3a), the analysis indicates mild-to-moderate progression over the years. Amongst patients with *MPZ* mutations (Figure 3b), onset occurred earlier in CMT1B than in CMT2I/J, but progression was much faster in the latter so that disease burden was the same by age 70. However, our series included CMT1B patients with nonsense mutations, typically with a milder phenotype compared to missense mutations. Regarding patients with *GDAP1* mutations, Figure 3c shows the different progression of CMT4A (AR), characterized by a very severe phenotype and rapid worsening with increasing age, compared with CMT2K (AD) which showed a slower course, even though not statistically significant. However, this difference in disease burden was significant on comparing the CMTES: the mean score was 17.4 in CMT4A and 8.8 in CMT2K ($p=0.002$). Figure 3d compares the ratio between age and disease severity in CMTX1 males and females and shows that the slope is steeper for males. Indeed, the age at onset of walking difficulties was significantly earlier in males (mean age 20.0 vs. 29.7; $p=0.020$) and the mean CMTES was higher in men, although the difference did not reach significance (10.2 vs. 8.9, $p=0.150$) and difficulties with walking were comparable (males 85.7% vs. females 84.8%).

TABLE 3 Comparison of clinical features amongst the most frequent CMT subtypes.

Clinical features	CMT1A $n=332$	CMTX1 males $n=42$	CMTX1 females $n=33$	CMT1B $n=39$	CMT2I/2 J $n=38$	CMT2A $n=23$	CMT4C $n=12$	CMT4A $n=10$	CMT2K $n=7$
Delayed milestones (walked after 15 months)	33 (10%)	6 (14.3%)	1 (3%)	**9 (24.3%)**	0	2 (8.7%)	4 (33%)	2 (20%)	1 (14%)
Difficulty walking	237 (71.4%)	36 (85.7%)	28 (84.8%)	23 (62.2%)	28 (73.7%)	20 (87%)	12 (100%)	10 (100%)	7 (100%)
Onset age	21.5 ± 16.5 (1–70)	20 ± 11.1 (3–50)	**29.6 ± 13.3 (6–68)**	23.7 ± 15.2 (1–47)	**49 ± 14.6 (15–72)**	15.9 ± 13.6 (2–60)	12.3 ± 13.1 (1–35)	**3.5 ± 3.3 (1–12)**	23.4 ± 17.7 (2–46)
Orthotic aids use	149 (44.9%)	27 (64.3%)	17 (51.5%)	10 (27%)	**20 (52.6%)**	15 (65.2%)	9 (83%)	**8 (80%)**	4 (57%)
Onset age	31.1 ± 16.2 (4–62)	40.8 ± 14.4 (18–69)	36.8 ± 14.2 (16–62)	30.6 ± 13.5 (3–42)	**55 ± 7.6 (40–72)**	30.2 ± 21.7 (5–65)	28.6 ± 14.7 (7–45)	**3.4 ± 1.6 (2–6)**	30.7 ± 24.4 (3–49)
Shoe inserts	130 (39.2%)	20 (47.6%)	15 (45.5%)	7 (18.9%)	6 (15.8%)	13 (56.5%)	6 (50%)	1 (10%)	3 (43%)
AFOs	33 (10%)	11 (26.2%)	5 (15.2%)	6 (16.2%)	**16 (42.1%)**	6 (26.1%)	5 (42%)	**7 (70%)**	1 (14%)
Walking support need	22 (6.6%)	5 (11.9%)	2 (6.1%)	5 (12.8%)	7 (18.4%)	4 (17.4%)	**4 (33%)**	**6 (60%)**	0
Unilateral	18 (5.4%)	3 (7.1%)	2 (6.1%)	3 (8.1%)	5 (13.2%)	1 (4.3%)	2 (17%)	1 (10%)	0
Bilateral	5 (1.5%)	2 (4.8%)	0	2 (5%)	2 (5.2%)	3 (13%)	2 (17%)	5 (50%)	0
Wheelchair use	3 (0.9%)	1 (2.4%)	0	2 (5%)	1 (2.6%)	2 (8.7%)	1 (8%)	**6 (60%)**	1 (14%)
Intermittent	2 (0.6%)	1 (2.4%)	0	2 (5%)	1 (2.6%)	2 (8.7%)	0	0	0
Regular	1 (0.3%)	0	0	0	0	0	1 (8%)	6 (60%)	1 (14%)
Difficulties with buttons	175 (52.7%)	**33 (78.6%)**	**26 (78.8%)**	17 (45.9%)	12 (31.6%)	13 (56.5%)	**11 (92%)**	**9 (90%)**	4 (57%)
Difficulties with eating utensils	32 (9%)	**17 (40.5%)**	**9 (27.3%)**	6 (16.2%)	4 (10.5%)	4 (17.4%)	**3 (25%)**	**9 (90%)**	0
Burning/tingling in feet/hands	101 (30.4%)	5 (11.9%)	10 (30.3%)	15 (40.5%)	17 (44.7%)	5 (21.7%)	5 (42%)	2 (20%)	3 (43%)
Decreased ability to feel	154 (46.4%)	21 (50%)	19 (57.6%)	19 (51.4%)	28 (73.7%)	12 (52.2%)	9 (75%)	5 (50%)	4 (57%)
Arthritic-like pain	53 (15.9%)	6 (14.3%)	8 (24.2%)	4 (10.8%)	6 (15.8%)	6 (26.1%)	3 (25%)	1 (10%)	2 (29%)
Foot deformities	307 (92.2%)	41 (97.6%)	30 (90.9%)	30 (81.1%)	**27 (71.1%)**	19 (82.6%)	12 (100%)	**6 (60%)**	6 (86%)
Foot surgery	69 (20.1%)	7 (16.7%)	5 (15.2%)	6 (16.2%)	**1 (2.6%)**	8 (34.8%)	5 (42%)	4 (40%)	3 (43%)
Scoliosis	69 (20.8%)	3 (7.1%)	10 (30.3%)	4 (10.8%)	2 (5.2%)	4 (17.4%)	**12 (100%)**	2 (20%)	1 (14%)
Hip dysplasia	8 (2.4%)	0	0	1 (2.7%)	0	1 (4.3%)	1 (8%)	1 (10%)	0
Hearing loss	30 (9%)	10 (23.8%)	3 (9.1%)	5 (13.5%)	12 (31.6%)	3 (13%)	**6 (50%)**	0	1 (14%)

Abbreviations: AFOs, ankle foot orthoses; CMT, Charcot–Marie–Tooth disease.

Note: Significant results ($p < 0.05$) are in bold.

TABLE 4 CMTES and CMTNS values for the main CMT subtypes

CMT subtype	Mean age ± standard deviation (range)	No. of patients with CMTES score	CMTES score, mean ± standard deviation (range)	No. of patients with CMTNS score	CMTNS score, mean ± standard deviation (range)
CMT1A (*PMP22* dupl.)	46.8 ± 15.7 (2–84)	327	7.5 ± 4.3 (0–19)	83	13.9 ± 5.4 (1–27)
CMTX1 females (*GJB1*)	48.9 ± 13.3 (26–84)	35	8.9 ± 4.3 (1–18)	11	12.1 ± 4.3 (5–18)
CMTX1 males (*GJB1*)	47.6 ± 15.1 (17–78)	42	10.2 ± 4.6 (1–19)	14	15 ± 6.8 (3–25)
CMT2I/J (*MPZ* late onset)	63.5 ± 12.6 (35–85)	38	8.8 ± 5.3 (0–22)	10	12.4 ± 6.2 (2–21)
CMT1B (*MPZ*)	48.1 ± 13.1 (16–76)	37	7.9 ± 5.2 (0–20)	11	9.4 ± 5.6 (0–17)
CMT2A (*MFN2*)	45.1 ± 14.6 (9–79)	26	7.7 ± 6.1 (0–20)	5	8.4 ± 7.1 (2–20)
CMT2F (*HSPB1*)	61.7 ± 15.7 (40–80)	13	5.5 ± 3.9 (0–11)	4	9.5 ± 6.2 (3–17)
CMT2E/CMT1F (*NEFL*)	44.3 ± 12.7 (27–72)	12	8.1 ± 4.6 (2–16)	2	9.5 ± 3.5 (7–12)
CMT4C (*SH3TC2*)	40.9 ± 13.7 (19–61)	12	14.5 ± 6.4 (5–26)	3	18.3 ± 10.9 (12–31)
CMT4A (*GDAP1*-AR)	36.8 ± 14.9 (20–67)	10	17.4 ± 4.3 (12–26)	1	27
CMT2K (*GDAP1*-AD)	55.1 ± 19.2 (18–74)	7	8.8 ± 3.9 (3–13)	–	–
CMT1E (*PMP22* p.m.)	35.1 ± 14.3 (19–55)	7	14.1 ± 4.9 (6–21)	2	23.5 ± 2.1 (22–25)

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CMT, Charcot–Marie–Tooth disease; CMTES, CMT Examination Score; CMTNS, CMT Neuropathy Score; dupl., duplication; p.m., point mutation.

DISCUSSION

The present study, based on the Italian CMT Registry, collects a wide range of clinical and genetic information and gives an overview of the disease across Italy. The nationwide study allowed the epidemiology of CMT disease to be characterized on the national territory. Previous Italian studies have been performed on smaller populations: in 2014 Manganelli et al. [9] published a study on 197 patients from southern Italy, whilst in 2017 Lorefice et al. [17] published a study on 119 Sardinian patients; the largest study on 585 patients was performed by Gemelli et al. in Genoa [10]. Moreover, the availability of clinical information from a large number of patients allowed the phenotype of the most common CMT forms to be profiled and compared.

Distribution of CMT subtypes and genotypes

It was found that in our cohort CMT1 was more common than the CMT2 and the I-CMT types (65.3%, 24.6% and 9.0%, respectively). These rates were comparable with those reported in large case series in the UK [4], USA [3] and Spain [8]. Overall, a high percentage (88.3%) of patients who underwent genetic investigation received a diagnosis, more than the 60%–70% observed in other large series from the USA [3], Europe [4, 8] and Asia [5]. The diagnostic yield for CMT1, CMT2 and I-CMT types separately was higher than that reported in previous studies. As in other reports, CMT1 had a higher genetic testing success rate than CMT2 (96% vs. 68%). Similar values were obtained in the study by Sivera et al. [8] (95% in CMT1 and 62.6% in CMT2), whilst in previous years the diagnostic hit rates were lower. This may be partly motivated by a selection bias as patients with a genetic diagnosis are more likely to be encouraged to participate in a registry.

The *PMP22* duplication was the most frequent mutation, found in 45.2% of patients, a rate similar to that found in the Spanish population [8]. *GJB1* and *MPZ* were the second most frequently mutated genes (about 10% for both), followed, with a much lower rate, by *MFN2* (3.3%) (Table 1). In our case series, the fifth most frequent gene was *GDAP1* (2.1%). These results are similar to those reported by Gemelli et al. [10]. Instead, in the studies by Manganelli et al. [9] and Sivera et al. [8] *GDAP1* was the third most frequently mutated gene, more common than *MFN2* and even *MPZ*.

The mutation of only four genes (*PMP22*, *GJB1*, *MPZ* and *MFN2*) accounted for 85% of all genetically confirmed CMT cases compared to 90%–92% of previous studies [3, 4, 6, 8]. A higher frequency of other genes such as *NEFL*, *SH3TC2* and *HSPB1* was observed, which altogether accounted for the 4.6% of all the genetic diagnosis compared to 1.8% found by Murphy et al. [4], 2.4% reported by Fridman et al. [13] and 2.5% observed by Manganelli et al. [9]; however, such differences might be related to the less widespread use of next generation sequencing techniques in previous years.

The higher frequency of some genes compared to previous studies was also motivated by the presence of multiple clusters across

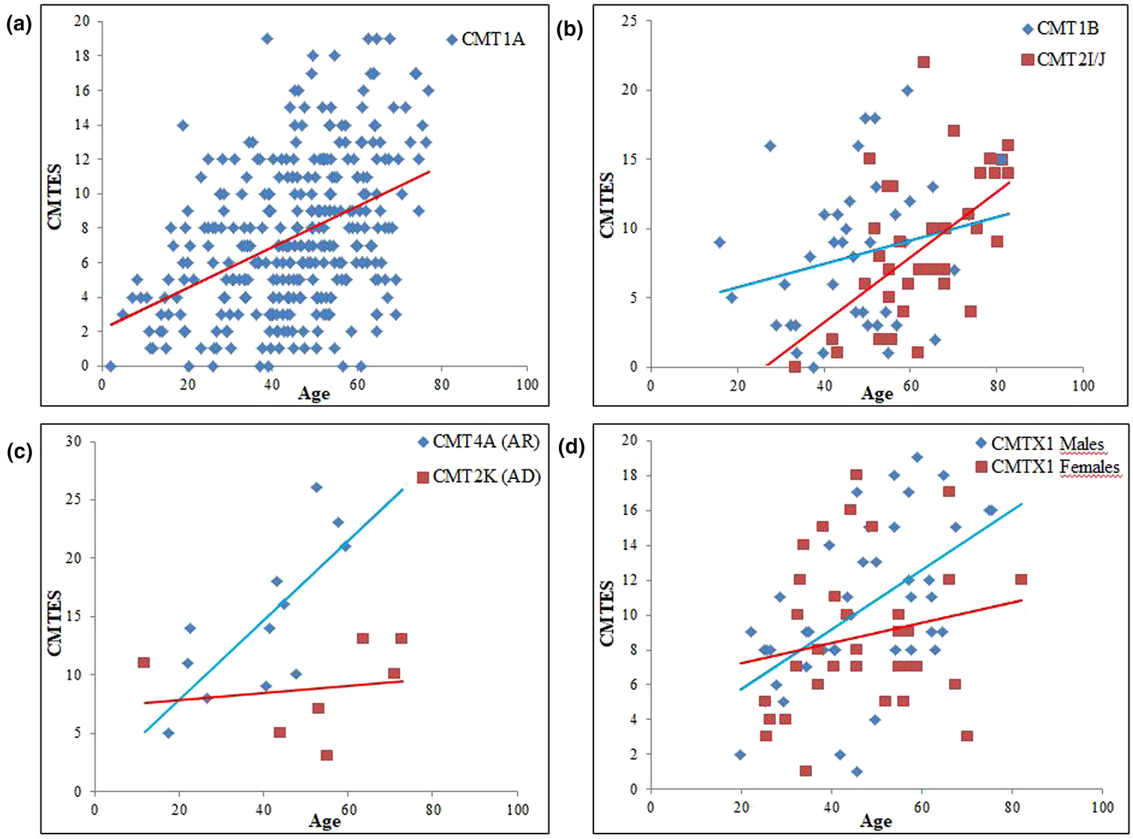

FIGURE 3 Correlations between CMTES and age in patients with different CMT subtypes. (a) CMT1A (*PMP22* duplication) ($R_s = 0.40$; $p < 0.001$). (b) CMT1B (*MPZ* early-onset) ($R_s = 0.28$; $p = 0.118$) and CMT2I/J (*MPZ* late-onset) ($R_s = 0.50$; $p = 0.001$). (c) CMT4A (*GDAP1* recessive, early-onset CMT) ($R_s = 0.6121$; $p = 0.0600$) and CMT2K (*GDAP1* dominant, late-onset CMT) ($R_s = 0.43$; $p = 0.33$). (d) CMTX1 (*GJB1*) males ($R_s = 0.57$; $p < 0.001$) and females ($R_s = 0.18$; $p = 0.287$).

Italy. For example, in our series, the frequency of *MPZ* mutations, higher than previously reported outside Italy and close to the 7% rate in the series by Gemelli et al. [10], is explained by the presence of some clusters in different areas of the country (Figure 2). First, a notable cluster of 13 patients with the p.Pro70Ser mutation occurs in Lombardy. This cluster was previously described by Laurà et al. [18] and is related to a late-onset form of the disease with a relatively rapid progression that was observed in patients from Lombardy and Emilia. In Sardinia the most sizeable *MPZ* cluster carries the amino acid mutation p.Ser44Phe, described by Lorefice et al. [17], whilst in northern Italy some cases were found with the p.Thr124Met variant. In Apulia, a cluster of six apparently unrelated patients was discovered with the p.Asp104ThrfsX13 mutation, which is associated with a mild phenotype [19]. Finally, in Sicily a cluster of 12 patients was found with the p.Ser78Leu previously described by Mazzeo et al. [20]. Similarly, the higher prevalence of *HSPB1* mutations, as in the Spanish population [8] and in the series by Gemelli et al. [10], is due to a cluster in Sicily with the p.Arg136Leu amino acid change. Such information underlines the importance to ask patients about their geographical origin to properly address genetic testing.

Finally, the presence of nine patients (1.1%) carrying *SORD* mutations is highlighted, which is emerging as one of the most frequent causes of recessive/sporadic CMT2/dHMN [21].

Clinical features

In the literature there are relatively few data on detailed clinical features of CMT patients' series, usually reported in old papers and limited to the most frequent subtypes such as CMT1A and CMTX1. The last major study on CMT1A in which clinical features were also analyzed dates back to 2014 [22], whilst the paper by Fridman et al. focused on CMT1A disease progression [23]. In 2017 a work on a large series of CMTX1 patients, exploring the main clinical differences between males and females, was published by Panosyan et al. [24]. Feely et al. [25] and Pipis et al. [26] published studies on CMT2A in 2011 and 2020, respectively, whereas Fridman et al. [27] described CMT1B features and disease progression in a large cohort of patients in 2022. For the remaining subtypes of CMT the information is limited.

Foot deformities, especially pes cavus and hammertoes, are a main feature of CMT. Interestingly, the prevalence of pes cavus in CMT4A was significantly lower compared to the mean prevalence of the whole CMT population. Since pes cavus is a consequence of an imbalance of muscular forces, the lower prevalence in CMT4A patients might be linked to the high disease severity, involving both anterior and posterior compartments of the legs from an early age.

Walking difficulties are another typical feature of CMT. In recessive forms, such as CMT4A and CMT4C, but also in CMT1B, delay in walking was frequent, whilst in other CMT subtypes such as CMT2I/J walking difficulties began after the fourth decade.

Shoe inserts and orthotic aids were used by almost one-half of all patients. Patients with recessive CMT such as CMT4A and CMT4C started using orthotic aids as AFOs significantly earlier and often required walking support and even a wheelchair. However, it is interesting to note that the percentage of patients with CMT2I/J who used AFOs (albeit at an older age) was also high, confirming that, despite the late onset, the progression is quite rapid.

Upper limb involvement was more prevalent in CMT4A and CMT4C, highlighting the severity of these recessive subtypes.

Scoliosis was present in 20% of patients, whilst a previous study found a slightly lower prevalence (15%). Notably, as already reported [28], scoliosis prevalence in CMT4C was 100%.

A novel finding is the high prevalence of hip dysplasia in early-onset CMT such as CMT4A (10%), CMT4C (8%) and CMT2A (4.3%). The early onset of muscle weakness with delayed walking is probably a predisposing factor for the poor formation of the acetabular fossa.

The association between hearing loss and CMT has long been recognized and, interestingly, the rate of CMT-related deafness varies amongst CMT subtypes. It was found that more than 30% of patients with CMT2I/J showed hearing loss compared to 13% of patients with CMT1B (early-onset *MPZ* mutation). Remarkably, one-half of CMT4C displayed hearing loss, confirming that auditory neuropathy is a key feature of this subtype [28]. However, the absence or presence of hearing loss was evaluated at the time of the visit without taking note of the age of onset and this may have led to an overestimation of hearing loss in some subtypes of CMT as hearing loss in elderly patients occurs frequently and is likely to be unrelated to the neuropathy.

Disease severity and progression

Our work includes information about clinical outcome measures such as the CMTES/CMTNS for various subtypes of CMT, including uncommon forms, although the number of patients is low for some forms.

The mean CMTNS for CMT1A was similar to that reported by Pareyson et al. [29] (14.6) and Shy et al. [30] (13.7). Similarly, mean scores for CMTX1 were like those reported previously by Panosyan et al. [24], both for males (15 vs. 15) and females (12.1 vs. 11).

The scores for CMT1B and CMT2A, however, differed from prior studies. The mean CMTES for CMT1B (7.9) was lower than the 11.8 already reported [27]. The mean CMTNS for CMT2A (8.4) was much lower than the values of 21 and 15.3 reported previously [25, 26]. The higher variability of CMTNS in CMT1B and CMT2A amongst different studies is probably related, at least in part, to the type of mutation. Indeed, the phenotypes of both CMT1B and CMT2A are known to vary depending on the specific mutation. Previous reports on CMT1B have emphasized phenotypic differences between early (CMT1B) and adult (CMT2I/J) onset forms, both with different burdens of disease depending on the amino acid change [31]. Moreover, our CMT1B series includes six patients with the *MPZ* p.Asp104ThrfsX13 mutation (mean CMTES = 2) that is a null mutation causing *MPZ* haploinsufficiency associated with mild CMT1B. Several *MFN2* disease-causing mutations lead to an early-onset severe neuropathy for which patients become wheelchair users by young adulthood [25, 26]. Nonetheless, relatively few patients with severe CMT2A were observed, whilst others had mild phenotypes associated with pathogenic mutation according to ACMG criteria [32]. However, as the current study included few children it is possible that participants with the most severe CMT1B and CMT2A phenotypes were under-represented. Moreover, in predominantly motor types, such as CMT2A and CMT2F, the limited sensory involvement results in lower CMTES/CMTNS, and this is a limitation of the scale, which underrates pure/predominant motor CMT compared to sensory-motor forms.

The progression of the disease was different depending on the CMT subtype. Disease progression rate was recently studied in a large series of CMT1A [23] and CMT1B [27] patients by Fridman et al. and CMT2A subjects by Pipis et al. [26]. The CMTES scores were correlated with age in a cross-sectional analysis, providing data about the severity of the disease at different ages and giving an indirect measure of the disease course. When comparing age-related disease severity in different CMT types with mutations in the same gene, it was observed that CMT2I/J had a more rapid course than CMT1B (*MPZ*), AR-CMT4A (*GDAP1*) had earlier onset and more severe course than AD-CMT2K, and disease onset occurred significantly earlier in CMTX1 men who were also slightly more affected than CMTX1 women (*GJB1*).

CONCLUSIONS

The Italian CMT Registry is a model for the study of CMT and rare diseases in general. It has proven to be a powerful data source to collect information about epidemiology and genetic distribution, clinical features and disease progression in CMT in Italy.

The registry, however, has limitations too and cannot be considered fully representative of the Italian CMT population, as less than 5% of it was recruited and there are enrollment biases. Participation occurs on a voluntary basis: patients are more likely to register if they are already engaged in patients' community and have instruments to become aware of the registry; the most severely affected patients are more likely to attend tertiary centres, which are more often involved in the registry; clinicians may be more prone to encourage registration of patients with genetically defined CMT.

AUTHOR CONTRIBUTIONS

Chiara Pisciotta: Writing – original draft; data curation; investigation; validation. **Alessandro Bertini:** Writing – original draft; formal analysis. **Irene Tramacere:** Formal analysis; validation. **Fiore Manganelli:** Data

curation; validation; investigation. **Gian Maria Fabrizi:** Validation; data curation; investigation. **Angelo Schenone:** Validation; data curation; investigation. **Stefano Tozza:** Data curation; validation; investigation. **Tiziana Cavallaro:** Validation; data curation; investigation. **Federica Taioli:** Validation; data curation. **Moreno Ferrarini:** Validation; data curation. **Marina Grandis:** Validation; data curation; investigation. **Emilia Bellone:** Validation; data curation; investigation. **Paola Mandich:** Validation; data curation; investigation. **Isabella Allegri:** Validation; data curation; investigation. **Luca Padua:** Data curation; validation; investigation. **Costanza Pazzaglia:** Investigation; data curation; validation. **Aldo Quattrone:** Validation; investigation. **Paola Valentino:** Data curation; validation; investigation. **Luca Gentile:** Validation; data curation; investigation. **Massimo Russo:** Investigation; validation; data curation. **Daniela Calabrese:** Data curation; validation. **Isabella Moroni:** Investigation; validation; data curation. **Emanuela Pagliano:** Investigation; validation; data curation. **Paola Saveri:** Validation; data curation. **Stefania Magri:** Validation; data curation. **Silvia Baratta:** Validation; data curation. **Franco Taroni:** Validation; data curation. **Anna Mazzeo:** Validation; data curation; investigation. **Lucio Santoro:** Validation; data curation; investigation. **Giuseppe Vita:** Validation; data curation; investigation. **Davide Pareyson:** Conceptualization; investigation; funding acquisition; writing – original draft; validation; methodology; data curation; supervision.

ACKNOWLEDGEMENTS

The authors are gratefully indebted to all the patients and their families and the controls for their active participation in the study and to ACMT-Rete, Associazione del Registro and Telethon-Italy Foundation for supporting the research and the Registry. The other members of the Italian CMT Network listed in Appendix S1 are also thanked. Open access funding provided by BIBLIOSAN.

CPi, PS, SM, FT and DP are members of the Inherited Neuropathy Consortium RDCRN.

CPi, FM, AS, MG, SCP, YF, LP, IM, PS, SM, FT, AM and DP are members of the European Reference Network for Rare Neuromuscular Diseases (ERN EURO-NMD).

FUNDING INFORMATION

This work was funded by Telethon-Italy Foundation grant GUP13006 and partially supported by the Italian Ministry of Health (RRC).

CONFLICT OF INTEREST STATEMENT

GMF acknowledges donations from Pfizer to support research activities of his Research Unit, financial support from Akcea, Kedrion, Pfizer for participation in national and international meetings and from Ackcea, Alnylam and Pharnext for participation in Advisory Boards. MG acknowledges donations from Sanofi Genzyme to support research activities of her Research Unit, financial support from Alnylam and Sanofi Genzyme for participation in national and international meetings, participation in an Advisory Board of Pfizer, speaker honorarium from Sanofi Genzyme. AM acknowledges financial support from Pfizer, Alnylam and Akcea for participation in national and international meetings, participation in Advisory Boards of Pfizer, Alnylam and Akcea. GV acknowledges donations from Pfizer and PTC to support research activities and participation in Advisory Boards of Pfizer, Alnylam, Akcea and Pharnext. DP acknowledges financial support from Alnylam and Kedrion for participation in international meetings, participation in Advisory Boards of Inflectis, Alnylam, Akcea, Arvinas, Augustine Tx, DTx, speaker honorarium from Alnylam. CPi, AB, IT, FM, AS, ST, TC, FT, MF, EB, PM, SCP, YF, IA, LP, CPa, AQ, PV, LG, MR, DC, IM, EP, PS, SM, SB, FT, LS report no disclosure.

DATA AVAILABILITY STATEMENT

Data relevant to the study are included in the article or uploaded as online supplemental information. Data supporting study results are deposited in an ad hoc repository and are available to be shared anonymously by the Principal Investigator (DP) on request from any qualified investigator.

ORCID

Chiara Pisciotta https://orcid.org/0000-0002-3850-076X
Fiore Manganelli https://orcid.org/0000-0002-1442-9604
Stefano Tozza https://orcid.org/0000-0002-9672-4577
Stefano C. Previtali https://orcid.org/0000-0003-2546-4357
Luca Padua https://orcid.org/0000-0003-2570-9326
Davide Pareyson https://orcid.org/0000-0001-6854-765X

REFERENCES

1. Ma M, Li Y, Dai S, et al. A meta-analysis on the prevalence of Charcot–Marie–Tooth disease and related inherited peripheral neuropathies. *J Neurol*. 2023;270:2468-2482.
2. Rossor AM, Polke JM, Houlden H, Reilly MM. Clinical implications of genetic advances in Charcot–Marie–Tooth disease. *Nat Rev Neurol*. 2013;9:562-571.
3. Saporta AS, Sottile SL, Miller LJ, Feely SM, Siskind CE, Shy ME. Charcot–Marie–Tooth disease subtypes and genetic testing strategies. *Ann Neurol*. 2011;69:22-33.
4. Murphy SM, Laura M, Fawcett K, et al. Charcot–Marie–Tooth disease: frequency of genetic subtypes and guidelines for genetic testing. *J Neurol Neurosurg Psychiatry*. 2012;83:706-710.
5. Yoshimura A, Yuan JH, Hashiguchi A, et al. Genetic profile and onset features of 1005 patients with Charcot–Marie–Tooth disease in Japan. *J Neurol Neurosurg Psychiatry*. 2019;90:195-202.
6. Gess B, Schirmacher A, Boentert M, Young P. Charcot–Marie–Tooth disease: frequency of genetic subtypes in a German neuromuscular center population. *Neuromuscul Disord*. 2013;23:647-651.
7. Rudnik-Schöneborn S, Tölle D, Senderek J, et al. Diagnostic algorithms in Charcot–Marie–Tooth neuropathies: experiences from a German genetic laboratory on the basis of 1206 index patients. *Clin Genet*. 2016;89:34-43.
8. Sivera R, Sevilla T, Vílchez JJ, et al. Charcot–Marie–Tooth disease: genetic and clinical spectrum in a Spanish clinical series. *Neurology*. 2013;81:1617-1625.
9. Manganelli F, Tozza S, Pisciotta C, et al. Charcot–Marie–Tooth disease: frequency of genetic subtypes in a southern Italy population. *J Peripher Nerv Syst*. 2014;19:292-298.
10. Gemelli C, Geroldi A, Massucco S, et al. Genetic workup for Charcot–Marie–Tooth neuropathy: a retrospective single-site experience covering 15 years. *Life (Basel)*. 2022;12:402.
11. Milley GM, Varga ET, Grosz Z, et al. Genotypic and phenotypic spectrum of the most common causative genes of Charcot–Marie–Tooth disease in Hungarian patients. *Neuromuscul Disord*. 2018;28:38-43.

12. Chen CX, Dong HL, Wei Q, et al. Genetic spectrum and clinical profiles in a southeast Chinese cohort of Charcot–Marie–Tooth disease. *Clin Genet*. 2019;96:439-448.
13. Fridman V, Bundy B, Reilly MM, et al. CMT subtypes and disease burden in patients enrolled in the Inherited Neuropathies Consortium natural history study: a cross-sectional analysis. *J Neurol Neurosurg Psychiatry*. 2015;86:873-878.
14. Ambrosini A, Calabrese D, Avato FM, et al. The Italian Neuromuscular Registry: a coordinated platform where patient organizations and clinicians collaborate for data collection and multiple usage. *Orphanet J Rare Dis*. 2018;13:176.
15. Murphy SM, Herrmann DN, McDermott MP, et al. Reliability of the CMT neuropathy score (second version) in Charcot–Marie–Tooth disease. *J Peripher Nerv Syst*. 2011;16:191-198.
16. Reilly MM, Shy ME, Muntoni F, Pareyson D. 168th ENMC international workshop: outcome measures and clinical trials in Charcot–Marie–Tooth disease (CMT). *Neuromuscul Disord*. 2010;20:839-846.
17. Lorefice L, Murru MR, Coghe G, et al. Charcot–Marie–Tooth disease: genetic subtypes in the Sardinian population. *Neurol Sci*. 2017;38:1019-1025.
18. Laurà M, Milani M, Morbin M, et al. Rapid progression of late onset axonal Charcot–Marie–Tooth disease associated with a novel MPZ mutation in the extracellular domain. *J Neurol Neurosurg Psychiatry*. 2007;78:1263-1266.
19. De Angelis MV, Di Muzio A, Capasso M, et al. Segmental conduction abnormalities and myelin thickenings in Val102/fs null mutation of *MPZ* gene. *Neurology*. 2004;63:2180-2183.
20. Mazzeo A, Muglia M, Rodolico C, et al. Charcot–Marie–Tooth disease type 1B: marked phenotypic variation of the Ser78Leu mutation in five Italian families. *Acta Neurol Scand*. 2008;118:328-332.
21. Cortese A, Zhu Y, Rebelo AP, et al. Biallelic mutations in SORD cause a common and potentially treatable hereditary neuropathy with implications for diabetes. *Nat Genet*. 2020;52:473-481.
22. Colomban C, Micallef J, Lefebvre MN, et al. Clinical spectrum and gender differences in a large cohort of Charcot–Marie–Tooth type 1A patients. *J Neurol Sci*. 2014;336:155-160.
23. Fridman V, Sillau S, Acsadi G, et al. A longitudinal study of CMT1A using Rasch analysis based CMT neuropathy and examination scores. *Neurology*. 2020;94:e884-e896.
24. Panosyan FB, Laura M, Rossor AM, et al. Cross-sectional analysis of a large cohort with X-linked Charcot–Marie–Tooth disease (CMTX1). *Neurology*. 2017;89:927-935.
25. Feely SM, Laura M, Siskind CE, et al. MFN2 mutations cause severe phenotypes in most patients with CMT2A. *Neurology*. 2011;76:1690-1696.
26. Pipis M, Feely SME, Polke JM, et al. Natural history of Charcot–Marie–Tooth disease type 2A: a large international multicentre study. *Brain*. 2020;143:3589-3602.
27. Fridman V, Sillau S, Bockhorst J, et al. Disease progression in Charcot–Marie–Tooth disease related to MPZ mutations: a longitudinal study. *Ann Neurol*. 2023;93:563-576.
28. Piscosquito G, Saveri P, Magri S, et al. Screening for SH3TC2 gene mutations in a series of demyelinating recessive Charcot–Marie–Tooth disease (CMT4). *J Peripher Nerv Syst*. 2016;21:142-149.
29. Pareyson D, Reilly MM, Schenone A, et al. Ascorbic acid in Charcot–Marie–Tooth disease type 1A (CMT-TRIAAL and CMT-TRAUK): a double-blind randomised trial. *Lancet Neurol*. 2011;10:320-328.
30. Shy ME, Chen L, Swan ER, et al. Neuropathy progression in Charcot–Marie–Tooth disease type 1A. *Neurology*. 2008;70:378-383.
31. Shy ME, Jáni A, Krajewski K, et al. Phenotypic clustering in MPZ mutations. *Brain*. 2004;127:371-384.
32. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17:405-424.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Pisciotta C, Bertini A, Tramacere I, et al. Clinical spectrum and frequency of Charcot–Marie–Tooth disease in Italy: Data from the National CMT Registry. *Eur J Neurol*. 2023;30:2461-2470. doi:10.1111/ene.15860

Novo Nordisk science presented in conjunction with the Alzheimer's Association International Conference® 2023

Amsterdam, The Netherlands
July 16 – 20

New perspectives on the evolution of the treatment landscape and future opportunities in Alzheimer's Disease

Learn more

novo nordisk®