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RESEARCH REPORT

Charcot-Marie-Tooth disease: frequency of genetic subtypes in a Southern Italy population

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Abstract The objective of this study is to assess the genetic distribution of Charcot-Marie-Tooth (CMT) disease in Campania, a region of Southern Italy. We analyzed a cohort of 197 index cases and reported the type and frequency of mutations for the whole CMT population and for each electrophysiological group (CMT1, CMT2, and hereditary neuropathy with susceptibility to pressure palsies [HNPP]) and for familial and isolated CMT cases. Genetic diagnosis was achieved in 148 patients (75.1%) with a higher success rate in HNPP and CMT1 than CMT2. Only four genes (*PMP22*, *GJB1*, *MPZ*, and *GDAP1*) accounted for 92% of all genetically confirmed CMT cases. In CMT1, *PMP22* duplication was the most common mutation while the second gene in order of frequency was *MPZ* in familial and *SH3TC2* in isolated cases. In CMT2, *GJB1* was the most frequent mutated gene and *GJB1* with *GDAP1* accounted for almost 3/4 of genetically defined CMT2 patients. The first gene in order of frequency was *GJB1* in familial and *GDAP1* in isolated cases. In HNPP, the majority of patients harbored the *PMP22* gene deletion. The novelty of our data is the relatively high frequency of *SH3TC2* and *GDAP1* mutations in demyelinating and axonal forms, respectively. These epidemiological data can help in panel design for our patients' population.

Key words: Charcot-Marie-Tooth disease, epidemiology, genetics, hereditary neuropathy

Introduction

Charcot-Marie-Tooth (CMT) disease, also known as Hereditary Sensory Motor Neuropathy, is the most common neurologic hereditary disorder with a prevalence of about 1:2500. CMT shows a great variability of inheritance (Autosomal Dominant/AD, Autosomal Recessive/AR, X-linked, and mitochondrial), age of onset, and clinical features. In most cases, it presents with progressive distal muscular atrophy and weakness, distal sensory loss, decrease or absence of deep tendon reflexes, and skeletal deformities as pes cavus *(Shy et al., 2005)*.

CMT is typically classified into two main groups based on upper limb nerve conduction study (NCS) and nerve pathology findings: demyelinating forms (CMT1 if AD, CMT4 if AR) show nerve conduction velocity (NCV) ≤38 m/s and pathologic evidence of nerve fiber demyelination; axonal forms (CMT2) instead have NCV >38 m/s and pathologic features of axonal degeneration and regeneration *(Harding and Thomas, 1980)*. Moreover, it is possible to identify a third group, called intermediate CMT, characterized by both myelin

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changes and axonal degeneration, and NCV between 25 and 45 m/s overlapping the values of CMT1 and CMT2 *(Nicholson and Myers, 2006)*. Additionally, CMT disease includes the hereditary neuropathy with susceptibility to pressure palsies (HNPP) that is typically characterized by slowing of nerve conduction velocity at the usual sites of entrapment *(Andersson et al., 2000)*.

Electrophysiological characterization plays a crucial role in addressing the genetic testing. However, molecular studies in the last years expanded the list of genes involved in the disease and 80 CMT-associated genes have now been discovered *(Timmerman et al., 2014)*. This broad genetic heterogeneity makes the diagnostic procedure difficult in clinical practice. Thus, epidemiological studies by evaluating the prevalence of different genetic CMT subtypes can help to design diagnostic flowchart to be used by clinicians in choosing genetic testing.

Three studies in German *(Gess et al., 2013)*, English *(Murphy et al., 2012)* and American *(Saporta et al., 2011)* populations have found that about 90% of patients with genetically confirmed diagnosis of CMT had a mutation in one of these four genes, *PMP22*, *GJB1*, *MPZ*, and *MFN2*. However, a more recent study developed in the Region of Valencia in Spain reported a higher frequency of *GDAP1* over *MFN2* gene *(Sivera et al., 2013)*. This difference raises the issue of the geographical area influence on CMT genotype distribution.

To our knowledge there are few and outdated *(Guzzetta et al., 1995; Mostacciuolo et al., 1995; Morocutti et al., 2002)* epidemiologic data on CMT in Italy and the aim of this study is to provide epidemiologic data from Campania, a region of Southern Italy on the Mediterranean Sea. Therefore, we report the genetic distribution in our cohort of CMT patients, for the main CMT phenotypes (CMT1, CMT2, and HNPP).

Patients and Methods

This is a descriptive study, based on examination of data from CMT patients evaluated from 1998 to 2013 in a tertiary care neuromuscular center at the University Federico II of Naples. Written informed consents were obtained for genetic analysis from all patients included in this study.

Patients were considered to have CMT if a sensorimotor neuropathy was present and the family history was positive for a similar condition. Patients without a positive family history (isolated) were considered to have CMT if their neurological and neurophysiological examination was typical for CMT and after excluding causes for an acquired neuropathy (toxic, metabolic, inflammatory, and infectious). Patients (index cases) were classified as demyelinating (CMT1) or axonal (CMT2) CMT, according to upper limb motor NCV. Accordingly, patients were classified as CMT1 if motor NCV was ≤38 m/s (except when the amplitude of compound muscle action potential was <0.5 mV) and as CMT2 if NCV was >38 m/s.

CMT1 patients were firstly tested for *PMP22* duplication of chromosome 17p11.2. When negative, patients were then tested for *GJB1* mutations (unless evidence of male to male transmission in the family), *PMP22* point mutations, or *MPZ* mutations. Patients with CMT1 were also screened for *EGR2*, *NEFL*, *GDAP1*, *LITAF*, *SH3TC2*, *FIG4*, or *CTDP1* mutations where appropriate.

CMT2 patients were, at first, tested for *GJB1* (unless male to male transmission in the family) mutations. Then, *MPZ*, *MFN2*, and *GDAP1* genes were screened for mutations. Further, CMT2 patients were tested for *NEFL*, *GARS*, *TRPV4*, *RAB7*, *HSPB1*, *HSPB8*, *SPTLC1*, *LMNAC*, or *HINT1* mutations where appropriate.

Patients with a medical history of transient palsies and/or sensory loss related to typical nerve compression points (pressure palsies), conduction blocks and/or slowing of NCV at the usual sites of entrapment, were considered for a clinical phenotype of HNPP. These patients were tested for deletions of chromosome 17p11.2 and if negative, patients were screened for point mutations in *PMP22*. In isolated cases in which a mutation was found, we analyzed also both parents (if available) confirming or excluding the *de novo* origin of the genetic defect.

We calculated the type and frequency of mutations for the whole CMT population and for each electrophysiological group (CMT1, CMT2, and HNPP). Moreover, within each electrophysiological group we calculated the type and frequency of genetic alterations for familial and isolated CMT cases and reported the number of *de novo* mutations.

Results

A total of 197 index cases, having clinical and electrophysiological features of CMT disease, were evaluated in our clinic over 15 years. All patients were from Campania. According to electrophysiological study, 109 patients (55.3%) were classified as CMT1, 55 patients (28%) as CMT2, and 33 patients (16.7%) as HNPP (Fig. 1). Genetic diagnosis was achieved in 148 patients (75.1%) with a success rate in descending order in HNPP (29/33: 87.8%), in demyelinating CMT (93/109: 85.3%), and in axonal CMT (26/55: 47.2%) (Fig. 1). Mutations in 12 different genes and 12 novel mutations were found (Table 1).

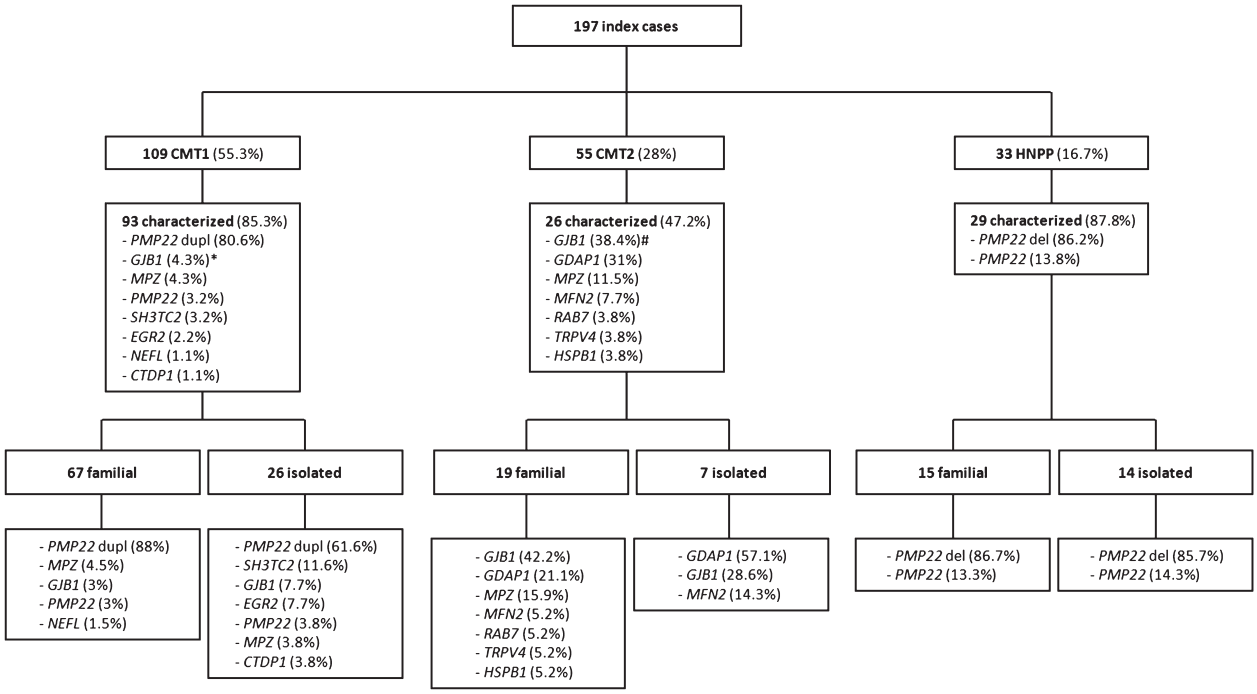

Figure 1. Genetic characterization of Charcot-Marie-Tooth (CMT) disease subtypes. * denotes 3 males and 1 female; # denotes 3 males and 7 females.

Patients with CMT1

In the 93 genetically diagnosed CMT1 probands, we detected *PMP22* duplication in 75, *GJB1* and *MPZ* mutations in 4, *PMP22* in 3, *SH3TC2* in 3, *EGR2* in 2, *NEFL* and *CTDP1* each in 1 patient. Six mutations were novel: p.Leu78Pro and p.Gln103X *(Pisciotta et al., 2009)* in *PMP22*, p.Tyr82Ser and p.Ser111Cys *(Mandich et al., 2009)* in *MPZ*, and p.Glu1005X and p.Tyr1107X in *SH3TC2* (Table 1). The majority of CMTX patients classified as having CMT1 were males (3/4: 75%).

Among the 93 genetically characterized CMT1 patients, 67 were familial and 26 isolated cases. In familial cases, *PMP22* duplication was found in 59 patients, *MPZ* mutations in 3, *GJB1* and *PMP22* in 2, and *NEFL* in 1 patient. In isolated cases, *PMP22* duplication was found in 16 patients, *SH3TC2* mutations in 3, *GJB1* and *EGR2* in 2 and, *PMP22*, *MPZ* and *CTDP1* each in 1 patient (Fig. 1). Five mutations were *de novo*: 1.5-Mb duplication in 17p11.2, p.Ser72Leu in *PMP22*, p.Tyr82Ser in *MPZ*, p.Arg381His in *EGR2*, and p.Ser26Leu in *GJB1*.

Patients with CMT2

In the 26 CMT2 probands with genetic diagnosis, we found *GJB1* mutations in 10 patients, *GDAP1* in 8, *MPZ* in 3, *MFN2* in 2 and, *RAB7*, *TRPV4*, and *HSPB1* each in 1 patient. Novel mutations were found in *GDAP1* (p.Arg120Gly; *Manganelli et al., 2012a*, p.Asp129His, and p.Glu145fs) and in *MPZ* (p.Asp109Glu) *(Santoro et al., 2004)* and *GJB1* (p.Gln99dup) genes (Table 1). The majority of CMTX patients classified as having CMT2 were females (7/10: 70%).

Among the 26 characterized CMT2 patients, 19 were familial and 7 isolated cases. In familial cases *GJB1* mutations were observed in 8 patients, *GDAP1* in 4, *MPZ* in 3, and *MFN2*, *RAB7*, *TRPV4*, and *HSPB1* each in 1 patient. In isolated cases, we found AR *GDAP1* mutations in 4 patients, *GJB1* in 2, and *MFN2* in 1 patient (Fig. 1). Two mutations were *de novo*: p.Trp3Gly in *GJB1* and p.Arg104Trp in *MFN2*.

Patients with HNPP

In the 29 characterized HNPP probands, we found *PMP22* deletion in 25 patients and *PMP22* mutations in 4 patients. One of these mutations was novel (p.Trp39X) (Table 1). Among HNPP patients, 15 patients were familial and 14 isolated cases. In familial cases, we found *PMP22* deletion in 13 patients and *PMP22* mutation in 2 patients. In isolated cases, we found *PMP22* deletion in 12 patients and *PMP22* mutations in 2 patients (Fig. 1). One *PMP22* deletion was a *de novo* mutation.

Discussion

This study evaluates for the first time the frequency of genetic subtypes of CMT patients in a

Table 1. Details of gene alterations (without *PMP22* duplication and deletion).

CMT subtype	Gene	Mutation
CMT1A	*PMP22*	**p.Leu78Pro**
		p.Gln103X
Dejerine-Sottàs	*PMP22*	p.Ser72Leu
HNPP	*PMP22*	**p.Trp39X**
		p.Leu145fs
		p.Leu145fs
		p.Leu145fs
CMTX	*GJB1*	p.Trp3Gly
		p.Arg15Gln
		p.Ser26Leu
		p.Gln99dup
		p.Gln99dup
		p.Arg107Trp
		p.Phe153Ser
		p.Phe153Ser
		p.Phe153Ser
		p.Arg164Trp
		p.Arg183Cys
		p.Glu208Lys
		p.Thr191_Phe193dup
		p.Thr191_Phe193dup
CMT1B	*MPZ*	p.Ser78Leu
		p.Ser78Leu
		p.Tyr82Ser
		p.Ser111Cys
CMT2I/J	*MPZ*	**p.Asp109Glu**
		p.Thr124Met
		p.Thr124Met
CMT2K	*GDAP1*	p.Arg226Ser
		p.Arg120Gly
CMT4A/ARCMT2K	*GDAP1*	p.Met116Arg/p.Met116Arg
		p.Arg120Trp/p.Met116Arg
		p.Met116Arg/p.Met116Arg
		p.Met116Arg/**p.Glu145fs**
		p.Asp129His/p.Glu114fs
		p.Gln99X/Gln99X
CMT4C	*SH3TC2*	p.Arg954X/p.Arg1109X
		p.Arg954X/**p.Tyr1107X**
		p.Glu1005X/p.Arg1171Cys
CMT2A	*MFN2*	p.Arg94Gln
		p.Arg104Trp
CMT1D	*EGR2*	p.Arg381His
		p.Arg381His
CMT1F	*NEFL*	p.Pro22Ser
CMT2B	*RAB7*	p.Val162Met
CMT2C	*TRPV4*	p.Arg315Trp
CMT2F	*HSPB1*	p.Gly84Arg
CCFDN	*CTDP1*	p.Leu287fs

CMT, Charcot-Marie-Tooth; HNPP, hereditary neuropathy with susceptibility to pressure palsies. In bold are reported novel mutations identified by our group.

population from a tertiary care neuromuscular center in Campania, a region of Southern Italy. The detection mutation rate was 75.1% and only four genes (*PMP22*, *GJB1*, *GDAP1*, and *MPZ*) accounted for 92% of all genetically confirmed CMT cases (Table 2). This rate is broadly comparable with that previously described *(Saporta et al*., *2011*; *Murphy et al*., *2012*; *Gess et al*., *2013*; *Sivera et al*., *2013)* and, especially, our four most common genes correspond to those reported by Sivera *(Sivera et al*., *2013)*. Instead, the group of the four commonest genes includes *MFN2* rather than *GDAP1* in the studies of Gess *(Gess et al*., *2013)*, Murphy *(Murphy et al*., *2012)*, and Saporta *(Saporta et al*., *2011)* (Table 2).

In demyelinating patients, CMT1A duplication was by far the most common mutation detected both in familial and isolated cases whereas the second gene in order of frequency was *MPZ* (4.6%) in familial and *SH3TC2* (11.6%) in isolated cases.

The relatively high frequency of *SH3TC2* mutations that represents on the whole characterized CMT population the fifth gene in order of frequency (2%) was comparable with data reported by Murphy (1.6%) *(Murphy et al*., *2012)*. Actually, Sivera *(Sivera et al*., *2013)* also found a high prevalence of *SH3TC2* mutations but the result was biased by the presence of 26 Gypsy patients who harbored the *SH3TC2* founder mutation (p.Arg1109X) associated with the Gypsy population across Europe *(Gooding et al*., *2005*; *Claramunt et al*., *2007)*. All our CMT4C patients presented with early and severe scoliosis that represents the most common clinical sign. However, there was wide phenotypic variability. One patient (carrying the p.Arg1109X/p.Arg954X mutations) was wheelchair-bound, a second patient (carrying the p.Tyr1107X/p.Arg954X mutations) presented with marked contractures at upper limbs and the last one (carrying the p.Glu1005X/p.Arg1171Cys mutations) had a mild classical CMT phenotype.

Overall in CMT2 group, *GJB1* was the most frequent mutated gene and *GJB1* with *GDAP1* mutations accounted for almost 3/4 of genetically defined CMT2 patients. Furthermore, the first gene in order of frequency was *GJB1* in familial and *GDAP1* in isolated cases.

CMTX is characterized by a great genetic variability as more than 300 mutations have been described in the *GJB1* gene, and it is noteworthy that we found 10 different mutations in 14 CMTX patients. Moreover, two of these mutations consisted of small insertions (p.Thr191_Phe193dup and p.Gln99dup) in the coding region of *GJB1* gene and to our knowledge few in-frame insertions in the *GJB1* gene have been identified so far (http://www.hgmd.org/).

Mutations in the *GDAP1* gene were found in 6 patients with autosomal recessive (AR) and 2 patients with autosomal dominant (AD) inheritance. In 4 of 6 AR patients the p.Met116Arg recurred, probably due to the described founder effect in Campania *(Di Maria et al*., *2004)*. Additionally, we detected two AD mutations (p.Arg226Ser and p.Arg120Gly) and one of them resulted in the substitution of a highly conserved

Table 2. Comparison of genetic distribution with other series.

	Frequency, % (number of patients)				
	Present study n = 197	Sivera et al. n = 404*	Gess et al. n = 589†	Murphy et al. n = 471‡	Saporta et al. n = 787
Characterized CMT					
Overall	75.1 (148)	81.9 (331)	57.5 (339)	63.0 (297)	67.0 (527)
CMT1	85.3 (93)	95 (229)	66.0 (233)	80.4 (193)	NA
CMT-I	NA	NA	NA	59.7 (37)	NA
CMT2	47.2 (26)	62.6 (102)	35.0 (53)	25.2 (29)	NA
HNPP	87.8 (29)	NA	64.0 (53)	67.3 (31)	NA
Genes					
PMP22#	**72.3 (107)**	**56.1 (186)**	**69.9 (237)**	**69.0 (205)**	**65.0 (343)**
GJB1	**9.5 (14)**	**16.9 (56)**	**13.8 (47)**	**15.4 (46)**	**15.1 (80)**
GDAP1	**5.4 (8)**	**12.7 (42)**	0	0.6 (2)	1.1 (6)
MPZ	**4.7 (7)**	**5.7 (19)**	**6.1 (21)**	**4.3 (13)**	**8.5 (45)**
SH3TC2	2.0 (3)	0.6 (2)	0	1.6 (5)	0.6 (3)
MFN2	1.3 (2)	1.2 (4)	**3.5 (12)**	**4 (12)**	**4 (21)**

CMT, Charcot-Marie-Tooth; HNPP, hereditary neuropathy with susceptibility to pressure palsies; NA, not applicable. Percentages and numbers reported in bold indicate the four most common genes in each series of patients.
*Caucasian cases only (excluded Gypsy cases).
†Patients with sufficient nerve conduction studies.
‡Patients attending inherited neuropathy clinic; CMT-I, CMT intermediate.
#*PMP22* duplication, deletion, and point mutations.

aminoacid at codon 120 that represents a mutational hotspot for dominant *GDAP1* forms *(Claramunt et al., 2005)*. As expected, patients with AR inheritance presented with a severe phenotype with important disability, whereas patients with AD *GDAP1* mutations showed milder phenotype and intrafamilial variability *(Manganelli et al., 2012a)*.

Patients carrying autosomal dominant *GDAP1* mutations are unequivocally classified as axonal CMT (CMT2K), while it is still controversial the electrophysiological classification of AR *GDAP1* forms in demyelinating (CMT4A) or axonal (AR-CMT2K) CMT. In fact, patients with demyelinating, intermediate or axonal nerve conduction studies have been reported. Moreover, pathological findings from sural nerve biopsies include both axonal degeneration and myelin abnormalities *(Baxter et al., 2002; Senderek et al., 2003; Sivera et al., 2013)*. In our study, NCS was consistent with axonal pathology as the only nerves with NCV in apparently demyelinating range were those in which compound motor action potential was severely reduced (<0.5 mV). Accordingly, all our *GDAP1* patients were classified on the basis of NCV as axonal CMT. This is in keeping with Sivera et al. *(Sivera et al., 2013)* that described 42 *GDAP1* patients and found that in these patients the neurophysiologic findings were unequivocally axonal.

CMT series from Northern Europe *(Murphy et al., 2012; Gess et al., 2013)* and the United States *(Saporta et al., 2011)* report lower frequencies of *GDAP1* mutations than our own. Vice versa in those series, *MFN2* has been identified as a common gene in axonal CMT, while *MFN2* mutations were rarely found in our study (7.7% of CMT2).

The relatively higher frequency of *GDAP1* over *MFN2* mutations is closer to data from the Spanish population, pointing out a possible influence of geographical area (Mediterranean area) in genetic distribution. However, a high frequency of *MFN2* mutations has been recently reported in a cohort of Italian CMT2 patients *(Bergamin et al., 2014)*. In this cohort, apart from two patients coming from Southern Italy, the origin of the other CMT2A patients was not reported. Thus, as all our patients came from a well-defined geographical area, we might still support the hypothesis of a possible geographical influence. However, we cannot exclude that there might be some bias beyond regional difference. Indeed, given the high frequency of *de novo MFN2* mutations and the wide clinical variability *(Bombelli et al., 2014)*, some patients possibly harboring *MFN2* mutations may not have been suspected of having CMT disease and therefore were not being directed to our reference center for hereditary neuropathies.

In our cohort of patients we also identified a very rare form of CMT. Among demyelinating patients we found families carrying mutations in *NEFL* (CMT1F), *EGR2* (CMT1D), and *CTDP1* (CCFDN) genes. Diagnosis of CCFDN was suspected based upon peculiar clinical features (congenital cataract, facial dysmorphism, and demyelinating neuropathy) and Balcan gypsy origin of family *(Manganelli et al., 2013)*. Likewise, among axonal patients the finding of ulcero-mutilating neuropathy and vocal cord paralysis led to identify mutations in *RAB7* (CMT2B) and *TRPV4* (CMT2C) genes, respectively *(Santoro et al., 2002; Manganelli et al., 2012b)*.

From our data it emerges that in demyelinating forms the diagnosis is achieved in most cases, whereas in axonal forms more than half of the patients remain without a molecular definition despite extensive genetic screening. Accordingly, it can be assumed that several other genes are still unknown, even though it could be argued that not all known CMT genes were tested in our cohort. However, 80 genes cause CMT and so it is costly and time consuming to test all known genes in every patient negative for the most common genes. Therefore the high number of diagnostic failures requires a new genetic approach as next-generation sequencing (NGS). On the other hand, the high rate of diagnostic genetic success in HNPP, achieved by only testing *PMP22* gene, argues a limited molecular genetic heterogeneity underlying HNPP.

Although our results are comparable to those from larger CMT series, one limitation of this study could be the smaller number of patients sampled, but they all belong to a well-defined geographical area and it is not our intent to extend these results to all South Italy.

Another limitation could be that we have not considered, in calculating the distribution of gene alterations, the intermediate CMT as a distinct electrophysiological category. This may have influenced our high frequency of *GJB1* mutations in CMT2. Indeed, the majority of our CMTX index cases were classified as having axonal CMT according to upper limb motor NCV, but more than 60% of these families would be classified as having intermediate forms of CMT disease. However, we think that when the aim is the geographical distribution of CMT genes the distinct cut-off criterion of 38 m/s, leading to two main electrophysiological categories, is more efficacious and practical. Additionally, it is conceivable that the high rate of *GJB1* mutations in CMT2 group may also depend on the high number of females (as index cases) that, as expected, have more frequently NCV in axonal range.

In conclusion, a rational diagnostic procedure in evaluating a patient with CMT phenotype, in order to optimize cost and time, and to increase the chance of diagnostic genetic achievement, should take into account the electrophysiological characterization, the family history and, if already known, the genetic distribution in a defined geographical area. Therefore, the epidemiological data we present here can help in panel design for our patients' population. The novelty of our data is the relatively high frequency of *SH3TC2* and *GDAP1* mutations in demyelinating and axonal forms, respectively. Additional studies concerning genetic distribution are needed to evaluate whether this is only a local feature or it can be expanded to the whole Southern Italy and compared with other regions of the Mediterranean area.

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