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Charcot Marie Tooth (CMT) Subtypes and Genetic Testing Strategies

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Abstract

Background—Charcot Marie Tooth disease (CMT) affects one in 2500 people and is caused by mutations in more than 30 genes. Identifying the genetic cause of CMT is often necessary for family planning, natural history studies and for entry into clinical trials. However genetic testing can be both expensive and confusing to patients and physicians.

Methods—We analyzed data from 1024 of our patients to determine the percentage and features of each CMT subtype within this clinic population. We identified distinguishing clinical and physiological features of the subtypes that could be used to direct genetic testing for patients with CMT.

Findings—Of 1024 patients evaluated, 787 received CMT diagnoses. Five hundred twenty-seven patients with CMT (67%) received a genetic subtype, while 260 did not have a mutation identified. The most common CMT subtypes were CMT1A, CMT1X, HNPP, CMT1B, and CMT2A. All other subtypes accounted for less than 1% each. Eleven patients had more than one genetically identified subtype of CMT. Patients with genetically identified CMT were separable into specific groups based on age of onset and the degree of slowing of motor nerve conduction velocities.

Interpretation—Combining features of the phenotypic and physiology groups allowed us to identify patients who were highly likely to have specific subtypes of CMT. Based on these results, we propose a strategy of focused genetic testing for CMT illustrated in a series of flow diagrams created as testing guides.

Keywords

CMT; Charcot Marie Tooth disease; Autosomal Dominant; Autosomal Recessive

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INTRODUCTION

Charcot Marie Tooth disease (CMT) is the eponym for heritable peripheral neuropathy and is named for three investigators who described it in the late 1800s^{1, 2}. CMT affects ~1 in 2500 people³ and is the most common inherited neurological disorder. The majority of patients with CMT have autosomal dominant (AD) inheritance, although many will have forms with X-linked or autosomal recessive (AR) inheritance. Apparent sporadic cases occur, as dominantly inherited disorders may begin as a new mutation in a given patient. While the majority of CMT neuropathies are demyelinating, up to one third appear to be primary axonal disorders^{4, 5}. Most patients have a “classical” CMT phenotype characterized by onset in the first two decades of life, distal weakness, sensory loss, foot deformities (*pes cavus* and hammer toes), and absent ankle reflexes. However, many patients develop severe disability in infancy or early childhood (congenital hypomyelinating neuropathy and Dejerine-Sottas neuropathy), while others develop few if any symptoms of neuropathy until adulthood⁶.

Despite the clinical similarities among patients with CMT, it is clear that the disorder is genetically heterogeneous. AD demyelinating (CMT1), AD axonal (CMT2), AR (CMT4) and X-linked (CMTX) forms of CMT exist. At present, mutations in more than 30 genes have been identified that cause these various forms of inherited neuropathies, and more than 44 distinct loci have been identified

(<http://www.molgen.ua.ac.be/CMTMutations/Mutations/MutByGene.cfm>). The >30 CMT genes and their proteins constitute a human “microarray” of molecules that are necessary for the normal function of myelinated axons in the peripheral nervous system (PNS). When the genes and proteins are mutated they can also provide investigators with important insights into the pathogenesis of inherited neuropathies. However, this large number of CMT causing genes is often challenging for clinicians and patients. There is little information available to guide which gene to test and testing a patient for mutations in all commercially available CMT genes is not cost effective. Nevertheless, family planning and prognosis often require an accurate genetic diagnosis and current treatment trials depend on knowing the genetic cause of a patient’s CMT even if no cures are presently available. Currently we have evaluated > 1000 patients with CMT in our clinic, many of whom have had genetic testing. We elected to analyze the results of genetic testing performed on these patients to determine first whether we could analyze our phenotypic data to focus genetic testing for patients we evaluate in the future, and second, to ensure that our patient population was representative of those screened by various diagnostic laboratories. We have developed an algorithm based on clinical phenotypes, neurophysiology and prevalence that we propose as a guide to help focus genetic testing for various forms of CMT.

METHODS

Characterization of CMT Subtypes

We included all patients evaluated at our CMT clinic between 1997 and 2009. Patients were considered to have CMT if they had a sensorimotor peripheral neuropathy and a family history of a similar condition. Patients without a family history of neuropathy were included if their medical history, neurophysiological testing, and neurological examination were typical for CMT1, CMT2, CMTX or CMT4. Patients were excluded if there were known diagnoses of acquired neuropathy including toxic (e.g. medication related neuropathies); metabolic (e.g. diabetic), immune mediated or inflammatory (AIDP or CIDP) polyneuropathies; neuropathy related to leukodystrophy, or congenital muscular dystrophy; and patients with severe general medical conditions. First or second degree relatives of genetically defined patients with a CMT phenotype were assumed to have the same

mutation. Patients without an identified genetic cause were classified based on nerve conduction velocities, physical examination, and family history.

Genetic Testing Hit Rates

Data was collected on patients for whom commercial genetic testing was ordered by Wayne State University between 2005 and 2009. Hit rates were defined as the number of positive results for a particular gene, out of the total number of times genetic testing was ordered for that gene. As our experience with different subtypes of CMT has grown we have incorporated phenotypic characteristics in our decision-making for genetic testing. Our criteria for which genes to test has evolved over the years and our “hit rates” should be interpreted with this in mind. Patients who had previously obtained positive genetic testing for their type of CMT were not included in the hit rate analysis but were included in our phenotypic analysis.

RESULTS

Distribution of CMT Subtypes

One thousand twenty-four patients were evaluated at our CMT clinic between 1997 and 2009, of which 787 were diagnosed with CMT. Of the 237 patients who did not have CMT, 118 were diagnosed with a different condition while 119 were determined to be an unaffected family member of a patient with CMT.

Five hundred twenty-seven of the 787 patients with CMT (67%) had or received a specific genetic diagnosis as a result of their visit, while in 260 patients with CMT no specific mutation was identified. The most prominent CMT subtypes identified in our clinic were CMT1A, CMT1X, HNPP, CMT1B, and CMT2A (Table 1). All other CMT subtypes accounted for less than 1% of all patients with genetically defined CMT each. Only 1.8% of patients with CMT1 were without a genetic diagnosis. These patients were defined as having a demyelinating phenotype and a dominant family history. Of patients with CMT2, 65.6% were without a genetic diagnosis. These patients were defined as having an axonal phenotype and a dominant family history (Table 2). The distribution of genetic subtypes identified in our clinic was similar to the distribution of patients identified by multiple laboratories that perform diagnostic testing for CMT (reviewed in ^{7, 8}). Comparing our results to those from these laboratories (their results follow in parentheses), we identified CMT1A in 82% (80%) of patients with clinically probable CMT1, as well as CMT1X in 10% (12%) and CMT1B in 6% (5%) of all patients with CMT. The practice parameter guideline cited just one study that identified *MFN2* mutations in 33% of all patients with CMT2 ⁹. However, multiple other studies have identified *MFN2* mutations in approximately 20% of their patients with CMT2 ¹⁰⁻¹², similar to the 21% that we found in our clinic population.

Diagnosing AR conditions was difficult because commercial testing is not available in the USA for all forms of AR CMT and research laboratories to test remaining forms are not readily available. However we were able to diagnose seven patients with AR CMT, accounting for 0.90% of all patients with CMT (Table 2). Additionally, we have 25 affected siblings without parents or other family members affected with CMT who are therefore likely to have AR inheritance for which we have no genetic diagnosis. If these patients were included in our analysis, up to 4% of our patients with CMT would have AR CMT. In addition, we have 77 patients without a family history who therefore are classified as having sporadic CMT, some of whom also may have an AR disorder.

We detected eleven patients with more than one subtype of CMT, as identified by genetic testing. These patients accounted for 1.4% of all patients with CMT (Table 3). Not all patients were tested for multiple mutations.

We were unable to identify a genetic cause in 33% of our patients with CMT. These patients were classified based on nerve conduction velocities, physical examination and family history (Table 4).

Genetic Testing Hit Rates and Methods for Targeted Testing

To determine our effectiveness in identifying the genetic causes of CMT we retrospectively calculated the percentage of times we correctly identified CMT causing mutations in commercially available CMT genes. These “hit rates” were highest in investigations for CMT1A or HNPP. Genetic testing for the duplication or deletion of *PMP22* was ordered 40 times, 32 of which yielded a positive result (80%), the highest hit rate for any genetic test. Of these 32 positive results, 26 (81%) were duplications of *PMP22* causing CMT1A, and 6 (19%) were deletions of *PMP22* causing HNPP (Table 5).

MPZ sequencing was ordered 31 times, 9 of which yielded a positive result (29%). *GJB1* sequencing was ordered 25 times, 6 of which yielded a positive result (24%). *MFN2* testing was ordered 48 times, 6 of which yielded a positive result (13%). *PMP22* sequencing was ordered 18 times, 2 of which yielded a positive result (11%) (Table 5).

Phenotypic Associations

Most of our patients with CMT clustered into three broad phenotypic groups based on the age of symptom onset (Table 6). The first group we have characterized as the “classical phenotype”, based on the descriptions of Harding and Thomas^{4, 6}. Affected patients with a classical phenotype begin walking on time, usually by a year to 15 months of age, and develop weakness or sensory loss during the first two decades of life. Impairment slowly increases thereafter, and rarely do patients require ambulation aids beyond ankle foot orthotics (AFOs)^{13, 14}. Over 60% of our patients with CMT1A and 67.5% of males with CMT1X¹⁵ fell into this category whereas this phenotype was less common for patients with CMT1B (14.6%).

The second phenotype we defined as infantile onset in which patients do not begin walking until they are at least 15 months of age. These patients are often severely affected and are likely to require above the knee bracing, walkers or wheel-chairs for ambulation by 20 years of age. Over 35% of our patients with CMT1B fell into this category¹⁶.

The third phenotype was defined as adult onset, in which patients did not develop symptoms of CMT until adulthood, often not until approximately 40 years of age. An additional large group of patients with CMT1B (50%) and 56% of women with CMT1X fell into this category¹⁶.

Physiology Associations—We previously reported that specific genetic forms of CMT display characteristic patterns of motor nerve conduction velocities (MNCV) in their upper extremities¹⁷. For example, most patients with CMT1A have uniformly slowed MNCV between 20-25 m/s¹³, most patients with CMT1B have either very slow (≤ 15 m/s) or else nearly normal MNCV¹⁶, and most males with CMT1X have intermediately slow MNCV between 30 and 45 m/s¹⁵. We therefore investigated whether a careful grouping of MNCV in the upper limb would also prove useful in predicting which genes to screen for in patients with CMT. We separated our 787 patients with CMT into four groups: (1) those with normal MNCV (>45 m/sec); (2) those with mild or “intermediate slowing ($35 <$ and ≤ 45 m/sec); (3)

those with slow MNCV ($15 < \text{ and } \leq 35$ m/sec) and those with very slow MNCV (≤ 15 m/sec). We then investigated the number and percentage of genotypes identified within these groups. Patients with slow MNCV range were then sub-divided into those with velocities of $15 < \text{ and } \leq 25$ m/sec and $25 < \text{ and } \leq 35$ m/sec. Results confirmed that different CMT genotypes have characteristic MNCV patterns (Table 7). Over 76% of patients with CMT1A had MNCV in the slow range whereas only 23% were in the very slow group and no patient with CMT1A was in the intermediate or normal groups. Fifteen percent of patients with CMT1B were in the slow group while 21% of patients with CMT1B were in the very slow group and 64 % were in the intermediate or normal range. For males with CMT1X, 51% had MNCV of $15 < \text{ and } \leq 35$ m/sec. Most (81%) of these were in the $25 < \text{ and } \leq 35$ m/sec group. No woman with CMT1X had MNCV in the slow range, 18% had MNCV in the intermediate range and 82% had MNCV in the normal range. All patients with HNPP were in the intermediate or normal range as were those patients with CMT2A in whom CMAP amplitudes could be identified.

Phenotype combined with Physiology—Finally, we investigated whether combining phenotypic data with physiology further improved our ability to predict an accurate genetic diagnosis (Table 8). We found that virtually all patients (154/173, or 89%) with both MNCV in the $15 < \text{ and } \leq 35$ m/sec range and the onset of walking prior to 15 months of age had CMT1A. In addition, 89.5% (154/172) of patients with CMT1A who had MNCV in the $15 < \text{ and } \leq 35$ m/sec range began walking prior to 15 months of age. When slow MNCV were sub-divided, 96.9% (123/127) of patients who walked prior to 15 months of age and had MNCV between $15 < \text{ and } \leq 25$ m/sec had CMT1A. Onset of walking data was available for 53 patients with CMT1A and very slow MNCV (≤ 15 m/s). Sixty-eight percent (36/53) of patients in this group began walking before 15 months. Additionally, 17 patients in this group with CMT1A had delayed walking. All patients with CMT1B and very slow MNCV had delayed walking. However, because CMT1A is so common, there were still more patients with CMT1A (17) in this group than patients with early onset CMT1B (8).

Two-thirds of males with CMT1X began walking before 15 months and had MNCV in the $25 < \text{ and } \leq 45$ m/sec range. There was no obvious correlation between MNCV and the onset of walking with CMT1X. Patients with late onset CMT1B were likely to have MNCV in the >35 m/s range and not to develop symptoms until adulthood. No late onset patient with CMT1B had MNCV in the very slow range and only two had values in the slow range. No patient with CMT1B and intermediate or normal MNCV had delayed walking and no patient with CMT1A had MNCV in the intermediate or normal range. All patients with CMT2A who had detectable motor potentials in the arms had MNCV in the normal range and developed symptoms in infancy or childhood. Any patient with unobtainable potentials, including a number of patients with CMT2A, was not included in this table.

DISCUSSION

This analysis of over 1000 patients demonstrated that clinical and neurophysiologic information could be useful in focusing genetic testing for CMT. The characterization of common phenotypes for particular forms of CMT, these data can also be useful in determining whether a given patient is typical or unusual for a particular genotype. Recently, a practice parameter guideline was published simultaneously in *Neurology*, *Muscle and Nerve* and *PMR* that also addressed the issue of genetic testing for CMT^{8, 18, 19}. The guideline reviewed the literature from a number of diagnostic laboratories that performed genetic testing for patients with CMT. The practice parameter guideline proposed an algorithm based on the prevalence of particular genetic types of CMT in the literature, whether MNCV were < 38 m/s, and whether or not there was a family history of neuropathy^{8, 18, 19}. The algorithm was an important advance in how to focus genetic testing for CMT.

However, by incorporating phenotypic as well as more specific neurophysiologic data we now believe that we can further improve diagnostic yields of genetic testing for CMT. Based on our data we have developed a series of flow diagrams to direct future genetic testing performed in our clinic. While not every patient will fit perfectly into the major groups presented below, we believe that this grouping will permit us to efficiently arrive at a genetic diagnosis, when possible, for patients with genetic neuropathies. Only types of CMT for which we have received genetic testing results have been included in the flow diagram.. Some options are included in the text for future testing, though not in the diagrams. As people with more than one type of CMT are unusual, once a positive genetic test has been obtained, all testing stops unless the phenotype is atypical for the mutation in question.

Classical phenotype with slow MNCV (15 < and $\leq$ 35 m/sec s) (Figure 1)

The largest group of patients in our clinic began walking before 15 months of age and had slow MNCV in the upper extremities. Approximately 89% of this group had CMT1A and we propose to initially test ONLY for the CMT1A causing duplication in these patients. Screening for CMT1A should commence irrespective of whether there is a positive family history, as approximately 10% of CMT1A cases present with apparently *de novo* mutations²⁰. Additional testing will be pursued only if the patient does not have CMT1A. In this event, we propose first ascertaining whether there is a family history of male-to-male transmission (father and son affected), since CMT1X is the next most common form of CMT in this group based on results from our clinic. Only if this testing is negative or if there is male-to-male transmission in the pedigree should testing proceed for an unusual presentation of CMT1B, then CMT1E or other cause of dominantly inherited demyelinating neuropathy. In the absence of consanguinity, it is predicted that recessive forms of CMT will occur in at most 10% of our patients²¹. Therefore we propose to only test for AR forms when the family history clearly suggests this inheritance pattern (multiple affected siblings with no parent, child, or other family members affected) or when the dominant forms of demyelinating neuropathies have been excluded. In the rare cases with negative testing and a clear AD family history, we suggest next undertaking research testing to identify novel CMT causing genes.

Delayed walking with severely slow MNCV ($\leq$ 15 m/s) (Figure 2)

Many patients with severely slow MNCV did not begin walking independently until 15 months of age or later. Accordingly, we grouped patients with very slow MNCV and with delayed walking in the flow diagram shown in Figure 2. These patients were very likely to have CMT1A or CMT1B. Accordingly, we propose to begin testing for the *PMP22* duplication or mutations in the *MPZ* gene for all patients in this category. None of our patients with CMT1B and MNCV $\leq$ 15 m/s walked before 15 months of age. We thus propose to begin testing for only CMT1A for patients who have very slow nerve conductions and walked before 15 months of age. If this testing is negative, the next most common cause of CMT for this group is CMT1B in our clinic population. Because AD neuropathy is much more frequent than AR neuropathy in our clinic population, we again propose continuing with AD disorders, even if there is no obvious family history of CMT. If there is no *PMP22* duplication and if *MPZ* sequencing is normal we suggest sequencing *PMP22* (CMT1E), a less frequent cause of this presentation. Only if these tests are negative should testing proceed to CMT1C and CMT1D, very rare forms of CMT1 in our patient group. If testing for these is also negative, the presence or absence of an affected parent or child can be used to determine whether to next test for AR disorders or whether research testing for novel genes is more appropriate.

CMT with Intermediate MNCV 35 < and ≤45 m/sec) (Figure 3)

Patients with identified genetic causes of CMT who had intermediate MNCV had primarily CMT1X or CMT1B. For patients with intermediate MNCV, the first step is to determine whether the phenotype is classical or adult onset and then whether there is evidence of male-to-male transmission. For patients with no male-to-male transmission, intermediate conduction velocities, and a classical phenotype, the first test should be for *GJB1* mutations (CMT1X) (78% of our clinic population with this phenotype). If this testing is negative, testing should proceed to *MPZ* mutations. Alternatively, if there is male-to-male transmission, testing for CMT1B should occur first since the inheritance pattern would formally exclude CMT1X. If patients with intermediate MNCV first develop symptoms in adulthood, testing should begin with CMT1B, as this is most likely according to our results. As no patients with CMT1A had intermediate conduction velocities, testing for a *PMP22* duplication would not be warranted. If all testing is negative, the presence or absence of an affected parent or child can be used to determine whether to next test for rare or AR disorders or whether research testing for novel genes is more appropriate. Some rare genes for the dominant intermediate forms of CMT include *DNM2* (DI-CMTB) and *YARS* (DI-CMTC) mutations. These are not included on the flow diagram because there are no genetically confirmed cases of these in our clinic. However, it is possible that they will make up a clinically significant part of the CMT population in the future, and these flow charts can be altered to reflect that. Patients with HNPP were identified in the intermediate NCV group with childhood and adult onset of symptoms. This disorder was not included in Figure 3 (or Figure 4) because of its characteristic presentation of focal episodes of weakness or sensory loss and focal slowing of MNCV that distinguish it from other forms of CMT. These clinical and physiological findings should, by themselves, suggest testing for HNPP^{22, 23}.

Targeted testing for normal or unobtainable NCV (Figure 4)

Patients with CMT2A were frequently severely affected in infancy and childhood (Table 6) to the extent that their CMAP amplitudes and NCV were unobtainable by testing in the upper extremities (Tables 7, 8). Since patients with CMT2A form our largest group of patients with CMT2 (Feely, submitted) we propose to test patients with severe axonal neuropathies in childhood initially for mutations in *MFN2*, the cause of CMT2A. The other two common forms of CMT that presented with normal MNCV in the arms were CMT1X (particularly women), and CMT1B (Table 7). Testing for CMT1B and CMT1X would be reasonable for late onset patients with normal MNCV unless there was male-to-male transmission in the pedigree, in which case only CMT1B is appropriate. Testing for all other forms of CMT2 would be far less likely to be successful and would be reserved for those patients who were negative for CMT2A, CMT1X and CMT1B. In our clinic, we have four patients with mutations in *NEFL* causing CMT2E, five patients with a single (identical) mutation in *GDAP1* causing CMT2K, and three patients with mutations in *GARS* causing CMT2D. When performing the genetic testing, other potential causes of CMT2 including mutations in *NEFL* (CMT2E), *HSP22* (CMT2L) or *HSP27* (CMT2F) might then be considered. Patients with *RAB7* (CMT2B) and *SPTLC1* (HSN1) mutations have predominantly sensory phenotypes, and patients with *GARS* (CMT2D) or *BSCL2* (Silver syndrome) mutations often have relatively pure motor syndromes. Moreover, patients with CMT2D often note hand impairment prior to leg impairment that is unusual for patients with CMT. Thus in CMT2 we propose to use these specific phenotypes to direct additional genetic testing after initial negative testing. We also stress the need to perform nerve conduction studies on proximal nerves to exclude severe demyelinating neuropathies, when CMAP and SNAP potentials are unobtainable distally.

While a detailed review of the pros and cons for testing is beyond the scope of this manuscript, we think it reasonable to provide some information about how we pursue

genetic testing²⁴. Clearly, not every patient with a genetic neuropathy wants or needs testing to identify the genetic cause of their disease. We believe that the ultimate decision to undergo genetic testing rests with the patient or the patient's parents if a symptomatic child is under 18 years of age. Reasons that patients give for obtaining testing include identifying the inheritance pattern of their CMT, making family planning decisions, and obtaining knowledge about the cause and natural history of their form of CMT. Natural history data is available for some forms of CMT such as CMT1A¹⁴ and CMT1X¹⁵, which can provide guidance for prognosis, recognizing that there can be phenotypic variability in these subtypes. Patients with other forms of CMT frequently choose to undergo genetic testing to contribute to the natural history data collection for other patients with the same subtype. There are also reasons why patients do not want genetic testing. These include the high costs of commercial testing and fears of discrimination in the workplace or in obtaining health insurance. Since there are currently no medications to reverse any form of CMT, many patients decide against testing since their therapies will not depend on the results. We maintain that is always the patient's decision whether or not to pursue genetic testing.

Once a genetic diagnosis has been made in a patient, other family members usually do not need genetic testing but can be identified by clinical evaluation with neurophysiology. We do not typically test patients for multiple genetic causes of CMT simultaneously, although we did identify 11 patients with multiple genetic causes of CMT. It is our current policy to only consider genetic testing clinically affected family members if their phenotype is atypical for the type of CMT in the family. In addition, we do not test asymptomatic minors with a family history of CMT, either by electrophysiology or genetic testing, due to the chance for increased psychological harm to the child²⁵. We do routinely perform limited nerve conduction studies, though not needle EMG, on symptomatic children with CMT. Since nerve conduction changes, including slowing, are often uniform and detectable in early childhood in CMT¹⁷, testing of a single nerve is often adequate to guide genetic testing or determine whether a **symptomatic** child is affected in a family with CMT.

In summary, patients with inherited neuropathies can serve as models of their own disease if their phenotypes are carefully analyzed and their genotypes characterized. Molecular mechanisms of demyelination, axonal loss and axo-glial interactions can thus be investigated and rational therapies can be developed, not only for CMT but for related neurodegenerative disorders. However genotyping of families is essential for this approach, is confusing to patients and physicians and is very expensive to undertake commercially or in research laboratories. We have developed what we believe is a focused approach to testing based on phenotype, physiology and prevalence that we hope will prove useful in our clinic and to others who care for patients with inherited neuropathies.

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Figure 1.

Flow diagram for genetically diagnosing CMT in patients with slow upper extremity MNCV.

This algorithm is designed to be a general guide and is not intended to encompass every potential clinical scenario nor all possible genetic etiologies. Dup= duplication; Seq=sequencing.

Figure 2.

Flow diagram for genetically diagnosing CMT in patients with very slow upper extremity MNCV.

This algorithm is designed to be a general guide and is not intended to encompass every potential clinical scenario nor all possible genetic etiologies. Dup= duplication; Seq=sequencing.

Figure 3.

Flow diagram for genetically diagnosing CMT in patients with intermediate upper extremity MNCV.

This algorithm is designed to be a general guide and is not intended to encompass every potential clinical scenario nor all possible genetic etiologies.

Figure 4.

Flow diagram for genetically diagnosing CMT in patients with axonal MNCV.. In most cases MNCV in upper extremities are >45 m/s. However in severe cases these potentials may be absent. In these cases it is important to test proximal nerves to ensure that the patient does not have a severe demyelinating neuropathy that can mimic axonal CMT. This algorithm is designed to be a general guide and is not intended to encompass every potential clinical scenario nor all possible genetic etiologies. This algorithm is designed to be a general guide and is not intended to encompass every potential clinical scenario nor all possible genetic etiologies.

Table 1

CMT subtype distribution

CMT Subtype	N	% of patients with genetically defined CMT (n=527)	% of all patients with CMT (n=787)
CMT1A	290	55.0%	36.9%
CMT1B	45	8.5%	5.7%
CMT1X	80	15.2%	10.2%
	Males	44	8.4%
	Females	36	6.8%
CMT2A	21	4.0%	2.7%
HNPP	48	9.1%	6.1%
Total	484	91.8%	61.5%

CMT = Charcot-Marie-Tooth disease; HNPP = Hereditary Neuropathy with liability to Pressure Palsies.

Table 2

CMT1, 2 and 4 subtypes

CMT Types	N	% of patients by CMT type	% of patients with genetically defined CMT (n=527)	% of all patients with CMT (n=787)
CMT Type 1 group				
CMT1A	290	66.8%	55.0%	36.9%
CMT1B	45	10.4%	8.5%	5.7%
CMT1C	5	1.2%	1.0%	0.6%
CMT1D	1	0.2%	0.2%	0.1%
CMT1E	5	1.2%	1.0%	0.6%
CMT1X	80	18.4%	15.2%	10.2%
	Males	44	10.1%	5.6%
	Females	36	8.3%	4.6%
Total	426	98.2%	80.8%	54.1%
CMT1 Unknown	8	1.8%	-	1.0%
Total	434	-	-	55.2%
CMT Type 2 group				
CMT2A	21	21.9%	4.0%	2.7%
CMT2D	3	3.1%	0.6%	0.4%
CMT2E	4	4.2%	0.8%	0.5%
CMT2K	5	5.2%	1.0%	0.6%
Total	33	34.4%	6.3%	4.2%
CMT2 Unknown	63	65.6%	-	8.0%
Total	96	-	-	12.2%
CMT Type 4 group				
CMT4A	1	14.3%	0.2%	0.1%
CMT4C	3	42.9%	0.6%	0.4%
CMT4F	1	14.3%	0.2%	0.1%
CMT4J	2	28.6%	0.4%	0.3%
Total	7	-	1.4%	0.9%

CMT = Charcot-Marie-Tooth disease.

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Table 3

Patients with multiple CMT subtypes.

CMT Subtypes	N	Number of affected families	% of patients with genetically defined CMT (n=527)	% of all patients with CMT (n=787)
CMT1A/1E	5	2	1.0%	0.6%
CMT1E/1B	3	1	0.6%	0.4%
CMT1X/1B	2	2	0.4%	0.3%
CMT1A/1C	1	1	0.2%	0.1%
Total	11	6	2.1%	1.4%

CMT = Charcot-Marie-Tooth disease.

Table 4

Genetically undefined CMT.

Categorization	N	% of patients with genetically undefined CMT (N=260)	% of all patients with CMT (N=787)
Demyelinating Dominant Inheritance	8	3.1%	1.0%
Demyelinating Undetermined Inheritance	19	7.3%	2.4%
Axonal Dominant Inheritance	63	24.2%	8.0%
Axonal Undetermined Inheritance	61	23.5%	7.8%
Intermediate Dominant Inheritance	31	11.9%	4.0%
Intermediate Undetermined Inheritance	22	8.5%	2.8%
Hereditary Motor Neuropathies	7	2.7%	0.9%
Hereditary Sensory Neuropathies	17	6.5%	2.2%
Other	14	5.4%	1.8%

CMT = Charcot-Marie-Tooth disease.

Table 5

Genetic testing “hit” rates.

Genetic Test	Number of times ordered	Number of Hits	Hit Rate
<i>PMP22</i> Duplication/Deletion	40	32	80%
<i>PMP22</i> Sequencing	18	2	11%
<i>MPZ</i> Sequencing	31	9	29%
<i>GJB1</i> Sequencing	25	6	24%
<i>MFN2</i> Sequencing	51	7	14%

PMP22 = Peripheral myelin protein 22 gene; *MPZ* = Myelin protein zero gene; *GJB1* = Gap junction beta-1 gene; *MFN2*= Mitofusin-2 gene.

Table 6

CMT based on age of onset

CMT subtypes	Childhood onset		Adult onset		Subtotal ^a	Subclinical ^b	Unknown	Total
	Walk-age onset ≥ 15 months	Walk-age onset < 15 months	3rd decade of life	4th decade of life				
CMT1A	40 (16.2%) ^c	149 (60.3%)	18 (7.3%)	15 (6.1%)	247	11	32	290
CMT1B	15 (35.7%)	6 (14.3%)	2 (4.8%)	3 (7.1%)	42	1	2	45
CMT1X	7 (10.8%)	36 (55.4%)	9 (13.8%)	4 (6.2%)	65	8	7	80
Males	5 (12.5%)	27 (67.5%)	4 (10.0%)	3 (7.5%)	40	-	4	44
Females	2 (8.0%)	9 (36.0%)	5 (20.0%)	1 (4.0%)	25	8	3	36
CMT2A	3 (15.0%)	16 ^d (80.0%)	1 (5.0%)	-	20	-	1	21
HNPP	2 (4.2%)	25 (52.1%)	8 (16.7%)	11 (22.9%)	48	-	-	48

CMT = Charcot Marie Tooth disease; HNPP = Hereditary Neuropathy with liability to Pressure Palsies.

^aSubtotal: The sum of all symptomatic cases with known developmental history.

^bSubclinical: No functional complaints at the time of the evaluation, but may have peripheral neuropathy based on physiology and absent deep tendon reflexes.

^cThe percentages shown in this table were calculated using the subtotal value for each CMT subtype.

^dAll patients with CMT2A have more severe phenotypes compared to the other patients with childhood onset who walked < 15 months.

Table 7

CMT based on ulnar MNCV.

CMT subtypes	Ulnar MNCV ^a					NR ^b	Not tested ^c	Total
	Very slow ≤ 15	15 < and ≤ 25	Slow 25 < and ≤ 35	Intermediate 35 < and ≤ 45	Normal > 45			
CMT1A	61 (23.4%) ^e	162 (62.1%)	38 (14.6%)	-	-	12	17	290
CMT1B	8 (20.5%)	4 (10.3%)	2 (5.1%)	11 (28.2%)	14 (35.9%)	2	4	45
CMT1X	-	4 (5.3%)	17 (22.7%)	19 (25.3%)	35 (46.7%)	1	4	80
Males	-	4 (9.8%)	17 (41.5%)	13 (31.71%)	7 (17.1%)	1	2	44
Females	-	-	-	6 (17.7%)	28 (82.4%)	-	2	36
CMT2A	-	-	-	-	8 (100%)	8	5	21
HNPP	-	-	-	7 (14.9%)	40 (85.1%)	0	1	48

CMT = Charcot Marie Tooth disease; HNPP = Hereditary Neuropathy with liability to Pressure Palsies.

^aMNCV unit: meter/second.

^bNR: Not recordable.

^cNot tested cases: Exam refused.

^dSubtotal: All tested cases with obtainable responses.

^eAll percentages in the table were calculated using the subtotal value for each CMT subtype.

Table 8

CMT subtypes based on age of onset and physiology

Ulnar MNCV ^a	CMT subtypes	Walk-age onset ≥ 15 months	Childhood onset Walk-age onset < 15 months	Adult onset ^b	N
Very slow					
≤ 15	Subtotal		25	30	61
	CMT1A		17	30	53
	CMT1B		8	-	8
Slow					
15 < and ≤ 25	Subtotal		16	95	143
	CMT1A		14	93	137
	CMT1B		1	-	2
	CMT1X		1	2	4
	Males		1	2	4
	Females		-	-	-
25 < and ≤ 35	Subtotal		6	29	52
	CMT1A		4	16	35
	CMT1B		-	1	2
	CMT1X		2	12	15
	Males		2	12	15
	Females		-	-	-
Intermediate					

Ulnar MNCV ^a	CMT subtypes	Childhood onset	Adult onset ^b	N
	Walk-age onset ≥ 15 months	Walk-age onset < 15 months		
35 < and ≤ 45	Subtotal	1	24	36
	CMT1B	-	4	10
	CMT1X	1	14	19
	Males	1	10	13
	Females	-	4	6
	HNPP	-	6	7
	Normal			
> 45	Subtotal	6	33	85
	CMT1B	-	1	14
	CMT1X	2	8	25
	Males	-	3	6
	Females	2	5	19
	CMT2A	2	5 ^c	8
	HNPP	2	19	38

CMT = Charcot Marie Tooth disease; HNPP = Hereditary Neuropathy with liability to Pressure Palsies.

^aMNCV unit: meters/second.

^bAdult onset: If symptoms onset was ≥ 3rd decade of life.

^cAll patients with CMT2A have more severe phenotypes compared to the other patients with childhood onset that began walking before 15 months of age. Patients with unobtainable CMAP (compound muscle action potential) amplitudes in the upper extremities were not included in this table.