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# Charcot-Marie-Tooth disease

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**Abstract** Charcot-Marie-Tooth (CMT) disease is the commonest inherited neuromuscular disorder affecting at least 1 in 2,500. Over the last two decades, there have been rapid advances in understanding the molecular basis for many forms of CMT with more than 30 causative genes now described. This has made obtaining an accurate genetic diagnosis possible but at times challenging for clinicians. This review aims to provide a simple, pragmatic approach to diagnosing CMT from a clinician's perspective.

*Key words:* Charcot-Marie-Tooth disease, genetics, neuropathy

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## Introduction

Charcot-Marie-Tooth (CMT) disease, also known as hereditary motor and sensory neuropathy (HMSN), encompasses a clinically and genetically heterogeneous group of disorders characterized by muscle wasting, weakness, and sensory loss usually most severe distally. The disease, first described in 1886, was named after the three clinicians who first reported it and is the commonest inherited neuromuscular disorder affecting at least 1 in 2,500 (Skre, 1974).

Progress in the understanding of CMT can be divided into two eras. The first era was the pre-genetic era from 1886 to 1991. This coincided with a very exciting time in the understanding of peripheral nerve diseases generally and from the CMT perspective is especially noteworthy for the development of techniques to study peripheral nerve neurophysiology and pathology. The identification and careful phenotyping of an increasing number of families allowed CMT to be classified into two main types: CMT1 (demyelinating) and CMT2 (axonal), using upper limb motor conduction velocities (MCVs) (median or ulnar nerve)

where type 1 is defined as MCVs < 38 m/s and type 2 as MCVs > 38 m/s (Thomas and Calne, 1974; Harding and Thomas, 1980) and this classification remains the cornerstone of modern diagnosis. The second era in the understanding of CMT began in 1991 with the identification of the 1.4-Mb duplication of chromosome 17 containing the peripheral myelin protein 22 (PMP22) gene as the cause of CMT1A (Lupski et al., 1991; Raeymaekers et al., 1991), making PMP22 the first causative gene for CMT to be identified. Since 1991, there have been rapid advances in understanding the molecular basis for many forms of CMT with more than 30 causative genes now identified (Table 1, Fig. 1), making an accurate genetic diagnosis possible in 70% of the patients (Pareyson and Marchesi, 2009). Achieving this diagnostic rate raises many challenges throughout the world. However, the progress in understanding the pathogenesis of CMT, with the subsequent move toward developing gene-specific therapies, is making an accurate genetic diagnosis critical (Reilly and Shy, 2009).

This role of clinicians in the diagnosis, management, and understanding of CMT is evolving. Clinicians were pivotal in the original identification and phenotyping of families that led to linkage and subsequent gene identification for many forms of CMT. Subsequently, clinicians are involved in diagnosis (diagnostic, predictive, antenatal, and pre-implantation), in managing patients, in helping understanding the pathogenesis

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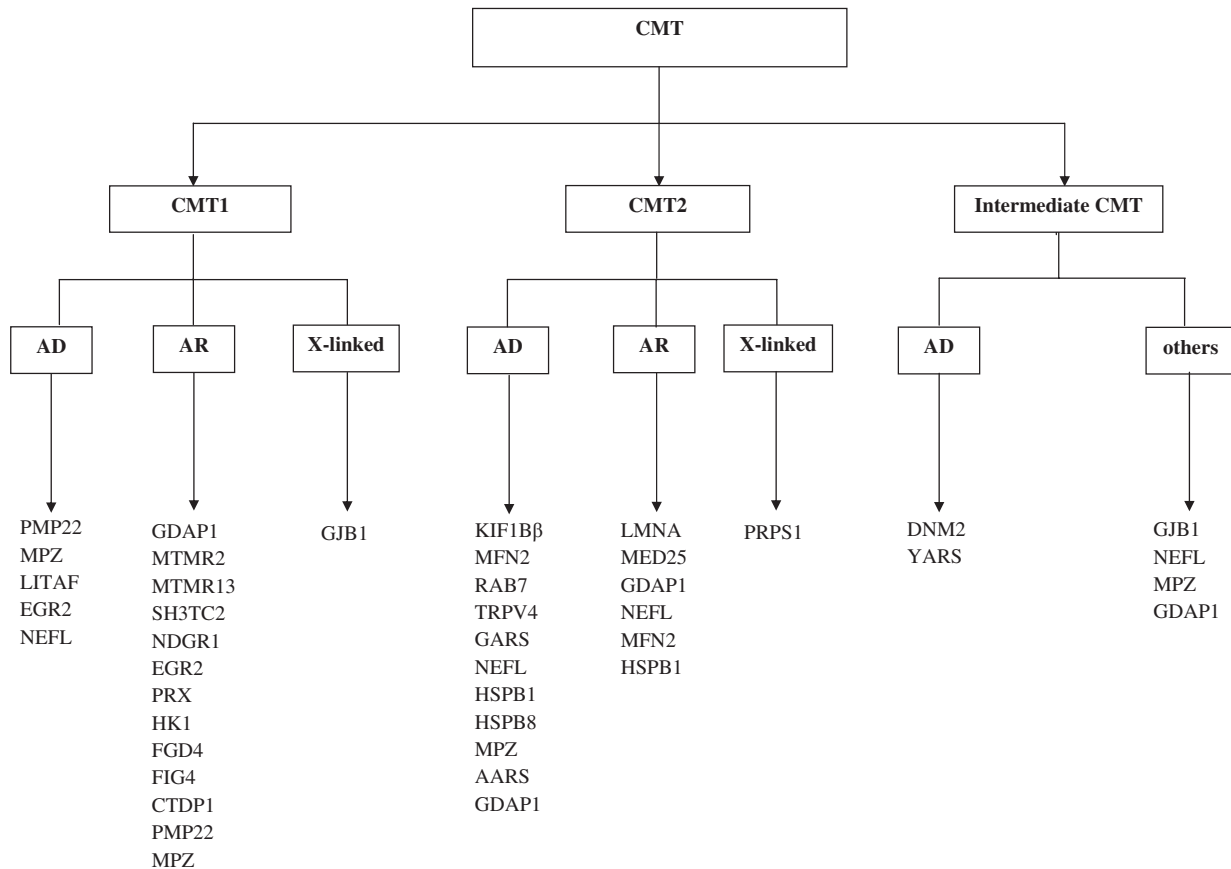
**Table 1.** Classification of Charcot-Marie-Tooth (CMT) disease.

Type	Gene	Specific phenotype
Autosomal dominant CMT1 (AD CMT1)		
CMT1A	<i>Dup 17p (PMP22)</i> <i>PMP22</i> (point mutation)	Classic CMT1 Classic CMT1/DSD/CHN
CMT1B	<i>MPZ</i>	CMT1/DSD/CHN/CMT2
CMT1C	<i>LITAF</i>	Classic CMT1
CMT1D	<i>EGR2</i>	Classic CMT1/DSD/CHN
CMT1F	<i>NEFL</i>	CMT2 but can have slow MCVs in CMT1 range +/- early-onset severe disease
Hereditary neuropathy with liability to pressure palsies (HNPPs)		
HNPP	<i>Del 17p (PMP22)</i> <i>PMP22</i> (point mutation)	Typical HNPP Typical HNPP
Autosomal recessive CMT1 (AR CMT1/CMT4)		
CMT4A	<i>GDAP1</i>	CMT1 or CMT2 usually early-onset and severe/vocal cord and diaphragm paralysis described/rare AD CMT2 families described
CMT4B1	<i>MTMR2</i>	Severe CMT1/facial/bulbar/focally folded myelin
CMT4B2	<i>MTMR13</i>	Severe CMT1/glaucoma/focally folded myelin
CMT4C	<i>SH3TC2</i>	Severe CMT1/scoliosis/cytoplasmic expansions
CMT4D (HMSNL)	<i>NDRG1</i>	Severe CMT1/gypsy/deafness/tongue atrophy
CMT4E	<i>EGR2</i>	CMT1/DSD/CHN phenotype
CMT4F	<i>PRX</i>	CMT1/more sensory/focally folded myelin
CMT4G (HMSN Russe)	<i>HK1</i>	Severe early-onset CMT1
CMT4H	<i>FGD4</i>	CMT1
CMT4J	<i>FIG4</i>	CMT1/predominantly motor/progressive
CCFDN	<i>CTDP1</i>	CMT1/gypsy/cataracts/dysmorphic features
AR CMT1	<i>PMP22</i> (point mutation)	Classic CMT1/DSD/CHN
AR CMT1	<i>MPZ</i>	CMT1/DSD/CHN/CMT2
Autosomal dominant CMT2 (AD CMT2)		
CMT2A1	<i>KIF1B<math>\beta</math></i>	Classic CMT2
CMT2A2	<i>MFN2</i>	CMT2/more progressive/optic atrophy
CMT2B	<i>RAB7</i>	CMT2 with predominant sensory involvement and sensory complications (similar phenotype to HSN1 secondary to SPTLC1 mutation)
CMT2C	<i>TRPV4</i>	CMT2 with vocal cord and respiratory involvement/congenital distal SMA/scapulo-peroneal syndrome
CMT2D	<i>GARS</i>	CMT2 with predominant hand wasting/weakness or dHMN-V
CMT2E	<i>NEFL</i>	CMT2 but can have slow MCVs in CMT1 range +/- early-onset severe disease
CMT2F	<i>HSPB1</i>	Classic CMT2 or dHMN-II
CMT2I	<i>MPZ</i>	Classic CMT2
CMT2J	<i>MPZ</i>	CMT2 with hearing loss and pupillary abnormalities
CMT2K	<i>GDAP1</i>	Late-onset CMT2
CMT2L	<i>HSPB8</i>	Classic CMT2 or dHMN-II
CMT2N	<i>AARS</i>	Classic CMT2
Autosomal recessive CMT2 (AR CMT2)		
CMT2B1	<i>LMNA</i>	CMT2 proximal involvement and rapid progression described/also causes muscular dystrophy/cardiomyopathy/lipodystrophy
CMT2B2	<i>MED25</i>	Classic CMT2
CMT2H	<i>GDAP1</i>	CMT2/pyramidal features

**Table 1.** Continued.

Type	Gene	Specific phenotype
X-linked CMT CMT 1X	<i>GJB1</i>	Males CMT1 (+/- patchy MCVs)/females CMT2
CMTX5	<i>PRPS1</i>	CMT2 and early-onset deafness/optic neuropathy
Dominant intermediate CMT (DI-CMT) DI-CMTB (CMT2M) DI-CMTC	<i>DNM2</i> <i>YARS</i>	Classic CMT Classic CMT

*AARS*, alanyl-tRNA synthetase; *AD*, autosomal dominant; *AR*, autosomal recessive; *CHN*, congenital hypomyelinating neuropathy; *CTDP1*, carboxy-terminal domain RNA polymerase II polypeptide A phosphatase subunit 1; *Del*, deletion; *dHMN*, distal hereditary motor neuropathy; *DI-CMT*, dominant intermediate Charcot-Marie-Tooth; *DNM2*, dynamin 2; *DSD*, Dejerine-Sottas disease; *Dup*, duplication; *EGR2*, early growth response 2; *FGD4*, actin filament-binding protein frabin; *FIG4*, FIG4 homolog *SAC1* lipid phosphatase domain containing; *GARS*, glycyl-tRNA synthetase; *GDAP1*, ganglioside-induced differentiation-associated protein 1; *GJB1*, gap-junction protein  $\beta$ -1; *HK1*, hexokinase 1; *HSPB1*, heat shock 27-kDa protein 1; *HSPB8*, heat shock 22-kDa protein 8; *KIF1B $\beta$* , kinesin family member 1B $\beta$ ; *LITAF*, lipopolysaccharide-induced tumor necrosis factor; *LMNA*, lamin A/C; *MCV*, motor conduction velocity; *MED25*, mediator complex subunit 25; *MFN2*, mitofusin 2; *MPZ*, myelin protein zero; *MTMR2*, myotubularin-related protein 2; *MTMR13*, myotubularin-related protein 13; *NDRG1*, N-myc downstream-regulated gene 1 protein; *NEFL*, neurofilament light chain polypeptide 68 kDa; *PMP22*, peripheral myelin protein 22; *PRPS1*, phosphoribosyl pyrophosphate synthetase 1; *PRX*, periaxin; *RAB7*, RAS-associated protein RAB7; *SH3TC2*, SH3 domain and tetratricopeptides repeats 2; *SMA*, spinal muscular atrophy; *SPTLC1*, serine palmitoyltransferase long-chain base subunit 1; *TRPV4*, transient receptor potential cation channel subfamily V member 4; *YARS*, tyrosyl-tRNA synthetase.



**Figure 1.** Genetic classification of Charcot-Marie-Tooth (CMT).

of various types of CMT with genotype/phenotype studies and, more recently, in the development of outcome measures and the conducting of clinical trials.

As there is no specific treatment for any form of CMT to date, one of the main and increasingly

complex roles of the clinician is the accurate diagnosis of CMT. This review will outline the role of clinicians in CMT currently with a particular emphasis on a simple diagnostic approach to this complex group of disorders.

## Diagnosis of CMT

The approach to the diagnosis of CMT is evolving from a purely clinical approach in the past to a combined clinical/genetic approach currently. Despite the advances in the identification of many of the causative genes for CMT, the accurate diagnosis of CMT still requires a detailed knowledge of the clinical and genetic subtypes and their frequencies in different populations. With the exciting developments in disease-specific CHIPS, exome sequencing, and whole-genome sequencing, a simple, cheap, laboratory-based genetic diagnosis may well be available in the future, but currently genetic testing needs to be targeted and is not available in many parts of the world. There are also major differences in how genetic diagnoses are delivered in individual countries with varying test availability and costs. The most useful diagnostic tool for clinicians presently is a user-friendly combined clinical and genetic classification to be used as a basis for diagnosis.

## Classification

There is no universally accepted classification currently for CMT. Although many of the causative genes have been identified, a purely genetic classification is not yet possible or practical. In clinical practice, the main aim of a classification is to aid diagnosis and treatment. Current classifications (Table 1) combine the traditional neurophysiological classification, the causative genes, and the inheritance patterns, and although they are not entirely satisfactory they are more useful to clinicians in practice than solely genetic-based classifications. Table 1 only includes subtypes of CMT where the causative gene has been identified to keep it simple. CMT is traditionally classified into two types: CMT1 (demyelinating) and CMT2 (axonal), using upper limb MCVs (median or ulnar nerve) where type 1 is defined as MCVs < 38 m/s and type 2 as MCVs > 38 m/s (Reilly, 2007). Historically, CMT was also called HMSN, but CMT is the preferred term currently. HMSNI/HMSNII is identical to CMT1/CMT2, respectively. In the HMSN classification, severely affected children with the demyelinating form were classified as having HMSNIII (also called congenital hypomyelinating neuropathy [CHN] or Dejerine-Sottas disease [DSD]) and some current classifications refer to this group as CMT3. This group of early-onset diseases were originally predicted to be mainly autosomal recessive (AR) but as most of these patients actually have *de novo* autosomal dominant (AD) mutations in the genes that commonly cause AD CMT1 (*PMP22*, myelin protein zero [*MPZ*], and early growth response 2 [*EGR2*]), it seems simpler

to refer to these patients as having severe CMT1. Not everyone agrees with this and the terms CMT3, CHN, and DSD are still commonly used, but caution needs to be exercised in the use of these terms as they also include patients with AR inheritance. There are AR forms of both CMT1 and CMT2 and confusingly the AR forms of CMT1 are also called CMT4 and the much more rare AR CMT2 cases are generally referred to as AR CMT2. Some forms of CMT do not fit easily into type 1 or 2 using neurophysiological criteria and increasingly classifications use the term intermediate CMT referring to those patients with median or ulnar MCVs between 25 and 45 m/s. The classification of CMT as intermediate, whether in an individual or a family, can be a useful pointer toward a genetic diagnosis (see below). We prefer to keep things simple and use AD and AR CMT1, CMT2, and intermediate CMT as the basis for our classification as outlined in Table 1. Subtypes (CMT1A, CMT2A, etc.) are used to characterize specific genetic causes of each of the larger categories.

Regardless of what classification system a clinician chooses, it is important to be aware of the increasing complexities of phenotypes and inheritance patterns described with individual genes to avoid diagnostic errors. *MPZ* mutations were originally described to cause AD CMT1 (CMT1B) but are now recognized to cause AR CMT1, AD CMT2, and intermediate CMT as well (Ikegami et al., 1996; Shy et al., 2004). Similarly, neurofilament light chain (*NEFL*) mutations, originally described to cause AD CMT2, are now known to cause AD CMT1, intermediate CMT, and more recently AR CMT2 (Abe et al., 2009; Yum et al., 2009). Many other genes cause a similar diversity in phenotypes/inheritance patterns including *PMP22*, *EGR2*, mitofusin 2 (*MFN2*), ganglioside-induced differentiation-associated protein 1 (*GDAP1*), and heat shock 27 kDa protein 1 (*HSPB1*) (Fig. 1).

Finally, there is an emerging overlap of CMT with the hereditary sensory neuropathies (HSNs), also termed hereditary sensory and autonomic neuropathies [HSANs] and the distal hereditary motor neuropathies [dHMNs]. HSN describes forms of inherited neuropathies in which sensory (and in some types autonomic) involvement predominates and distal HMN describes purely motor forms. Examples of the overlap with CMT include HSN1 and CMT2B, which are clinically difficult to differentiate despite being caused by mutations in different genes (serine palmitoyltransferase long-chain base subunit 1 [*SPTLC1*] and RAS-associated protein RAB7 [*RAB7*], respectively) and between CMT2 and distal hereditary motor neuropathy (dHMN) in which four genes can cause either (glycyl-tRNA synthetase [*GARS*], *HSPB1*,

*HSPB8*, transient receptor potential cation channel subfamily V member 4 [*TRPV4*]).

### Approach to diagnosis

It may seem obvious but the first step toward making a diagnosis of CMT is to determine whether the patient has a genetic neuropathy. In some cases, this may be straightforward as when there is an affected parent and child making either AD or X-linked (if there is no definite male-to-male transmission) inheritance probable or when there are multiple affected siblings from a consanguineous marriage making AR inheritance likely. X-linked inheritance should always be kept in mind unless there is unequivocal evidence of male-to-male transmission, especially as families are often not large enough to confidently rule this out. In other patients, recognizing CMT can be more difficult. There may be no family history or families may be small and extensive family histories not available. Clinical features that may help the clinician decide whether the neuropathy is likely to be genetic include presentations in infancy, long, slow-disease progression, the presence of foot deformities and, in adults, the lack of positive sensory symptoms despite having clear sensory involvement. It is important not to rule out an inherited neuropathy if the clinical features raise the possibility even in the absence of a family history. These apparently sporadic patients are frequently encountered in practice and are usually found to have mutations in the common AD genes (including in some cases, *de novo* dominant mutations) and less commonly in the AR genes.

Once a clinical diagnosis of CMT is made and the patient has been classified by neurophysiology and inheritance (Table 1, Fig. 1), the approach to the genetic diagnosis is based to some extent on the ethnic background of the patient. In most UK/north European and US populations, about 90% of the cases of CMT are either AD- or X-linked, whereas in countries with a higher rate of consanguineous marriages, AR CMT accounts for about 40% of all CMT cases (*Dubourg et al., 2006*). The diagnostic approach will therefore vary in specific countries and in specific ethnic groups. In all populations, CMT1 is consistently reported to be more common than CMT2 but as more than 60% of the genes have yet to be identified for CMT2, the true prevalence of CMT2 is unknown.

### Autosomal dominant CMT1

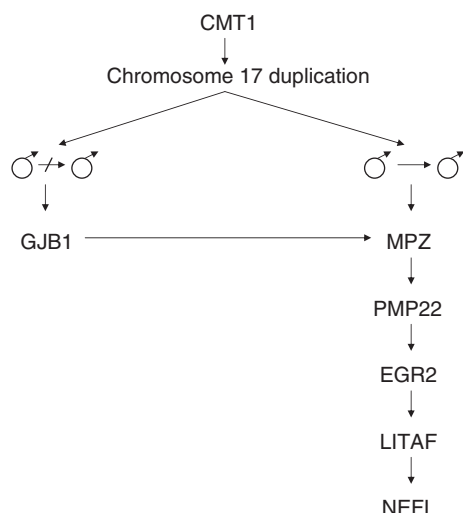
AD CMT1 is the most common form of CMT seen in most populations. Patients usually present with a “classical CMT phenotype” characterized by lower limb motor symptoms (difficulty walking/foot deformity) beginning in the first two decades accompanied



**Figure 2.** Classical Charcot-Marie-Tooth (CMT). (A) The legs of a patient with “classical” CMT, showing distal wasting with pes cavus and clawed toes. (B) Close-up of a foot showing pes cavus and clawed toes in a patient with CMT1A.

by distal atrophy, weakness and sensory loss, hyporeflexia, and frequent foot deformity (e.g., pes cavus) (Fig. 2). It is often easier to ascertain the decade of onset rather than the year of onset as the symptoms in the first two decades of life may be non-specific (e.g., poor at sports, last in races, clumsiness, difficulty fitting shoes). Patients with this phenotype usually have normal life spans, frequently need ankle-foot orthotics (AFOs), and rarely require wheelchairs for routine ambulation. The “classical CMT phenotype” is length-dependent with the upper limbs involved later than the lower limbs. It is very common for the patients not to complain of hand weakness that is detectable on examination unless asked specific questions. Median and ulnar MCVs are below 38 m/s and the sensory action potentials (SAPs) are either reduced or absent. Nerve biopsies are rarely performed now but when done, show de- and re-myelination with onion bulb formation.

The approach to the genetic diagnosis of AD CMT1 requires an appreciation of the frequency with which a



**Figure 3.** Algorithm for autosomal dominant (AD) and X-linked Charcot-Marie-Tooth disease type 1 (CMT1).

particular gene causes AD CMT1 (Table 1, Fig. 3). As a general rule, most AD CMT1 patients have a “classical CMT phenotype” and the approach to the genetic diagnosis is therefore based on the frequency of the underlying genetic causes. “Classic CMT phenotypes” and MCVs less than 38 m/s (commonly around 20 m/s) are strongly suggestive of CMT1A, caused by a 1.4-Mb duplication on 17p11.2 containing the *PMP22* gene (Lupski et al., 1991; Raeymaekers et al., 1991). The lack of family history does not exclude CMT1A, as sporadic cases occur in about 10% of the CMT1A cases. In European populations, CMT1A accounts for 70% of all CMT1 cases (Nelis et al., 1996) but this frequency may be less in populations with a high rate of consanguinity, where AR CMT1 cases may be more common. Mutations in the *PMP22* gene can also cause CMT1, but are also associated with a wider spectrum of phenotypes including classical CMT1A, more severe CMT1, and also certain mutations can cause hereditary neuropathy with liability to pressure palsies (HNPP) (see below).

CMT1B, the second commonest cause of AD CMT1, is caused by mutations in the *MPZ* gene comprising about 10% of AD CMT1. Patients can present with the classical CMT1 phenotype but are more likely to have either a more severe early-onset form of CMT with MCV < 10 m/s or a late-onset form of CMT with median MCVs in the intermediate/axonal range (Shy et al., 2004).

Mutations in lipopolysaccharide-induced tumor necrosis factor (*LITAF*) and *EGR2* are rare (<1% each) causes of AD CMT1 (Warner et al., 1998; Street et al., 2003). *LITAF* patients frequently resemble those with CMT1A, whereas *EGR2* patients usually present with a more severe CMT1 phenotype. Mutations in

*NEFL* were originally described as a cause of CMT2 (Mersivanova et al., 2000), but as some patients have MCVs in the demyelinating range, *NEFL* mutations also need to be considered in patients with AD CMT1 (Sevilla and Vilchez, 2004).

### Hereditary neuropathy with liability to pressure palsies

HNPP is an AD condition usually caused by a deletion of the same 1.4-Mb portion of chromosome 17 that is duplicated in CMT1A (Chance et al., 1993). Nonsense or frameshift mutations that truncate *PMP22* and effectively cause a loss of function of one copy of *PMP22* can also rarely cause HNPP. There is usually no difficulty distinguishing these patients from CMT patients as they typically present with transient, recurrent episodes of focal weakness or sensory loss, usually precipitated by pressure, in the distribution of individual nerves or plexus (Li et al., 2004). Peripheral nerves which are susceptible to pressure along their routes are most commonly involved (e.g., common peroneal nerve at fibular head, ulnar nerve at elbow). Nerve conduction studies often show focal areas of slowing around sites subject to compression (Li et al., 2002). Patients with isolated pressure palsies such as carpal tunnel syndromes should not be screened for HNPP as to date all patients shown to have the genetic abnormality have widespread nerve conduction abnormalities even if they have only one nerve involved clinically.

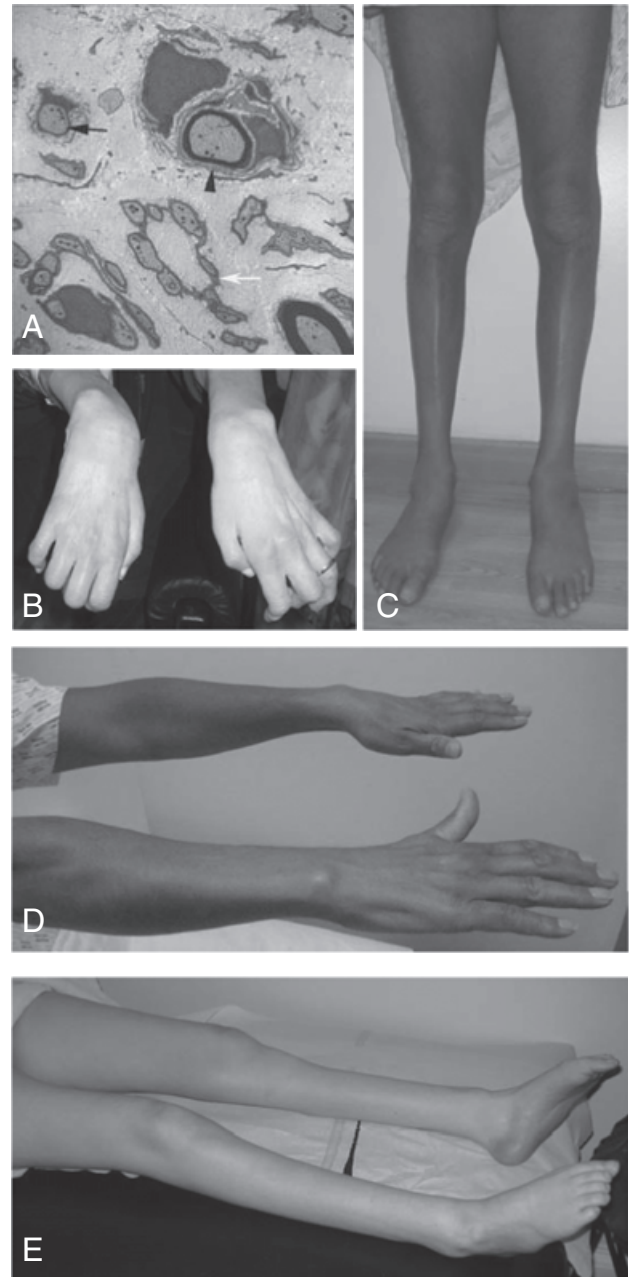
### Autosomal recessive CMT1 (AR CMT1/CMT4)

In most populations, AR CMT is less common than AD CMT with the exception of communities with a high rate of consanguinity. As explained earlier, AR CMT1 is commonly termed CMT4. To date, 13 genes have been identified that cause CMT4 (including 3 genes – *PMP22*, *MPZ*, and *EGR2* – that also cause AD CMT1) (Table 1). No one algorithm is suitable for the evaluation of CMT4 as both clinical features and ethnic background need to be carefully considered in selecting genes to screen (Reilly, 2007). In general, CMT4 cases have early onset and are more severe than typical patients with AD CMT1. Weakness often progresses to involve proximal muscles and may result in early loss of ambulation. Unlike most cases of AD CMT1, nerve biopsies can be a useful addition in phenotyping certain cases because specific features make a particular genetic diagnosis more likely (see below). Although there are many causative genes for CMT4, most are rare and will not be described extensively here. Table 1 shows how certain clinical features and ethnic background may help direct genetic diagnosis. Particular points to consider in patients with CMT4 include the following:

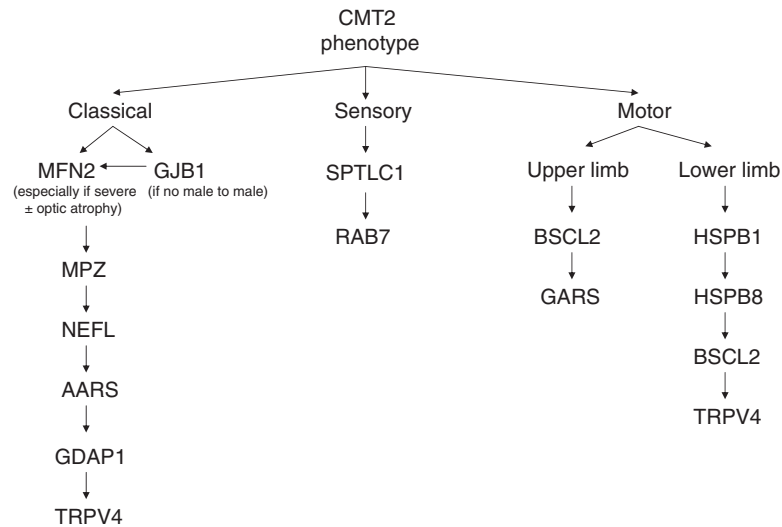
- Using MCVs to identify demyelination may occasionally be difficult in CMT4, because motor and sensory amplitudes are often unobtainable at routine recording sites as the patients are too severely affected. Studying nerves innervating proximal muscles (e.g., axillary, musculocutaneous, facial) may help. Nerve biopsies are sometimes done in these circumstances to help clarify the type of CMT.
- Nerve biopsies showing focally folded myelin are very helpful diagnostically as they are characteristic of CMT4B1 (myotubularin-related protein 2 [*MTMR2*]) and CMT4B2 (myotubularin-related protein 13 [*MTMR13*]), but focally folded myelin can also be seen with *MPZ* (Gabreels-Festen et al., 1996), periaxin (Guilbot et al., 2001), and actin filament-binding protein frabin (*FGD4*) mutations (De Sandre-Giovannoli et al., 2005).
- Severe and early scoliosis may be seen with CMT4C due to mutations in the SH3 domain and tetratricopeptides repeats 2 (*SH3TC2*) gene. Characteristic nerve biopsy features including basal membrane onion bulbs and multiple cytoplasmic processes of the Schwann cells ensheathing unmyelinated axons are also seen with *SH3TC2* mutations (Fig. 4A) (Gabreels-Festen et al., 1999; Houlden et al., 2009a). Recent articles suggest that this form of CMT4 is emerging as the commonest form of AR CMT in many populations (Houlden et al., 2009b).
- Three forms of AR CMT are largely confined to patients of Balkan gypsy origin. CMT4D secondary to N-myc downstream-regulated gene 1 protein (*NDRG1*) mutations is the best known of these and is characterized by a demyelinating neuropathy with a high prevalence of deafness. Tongue atrophy can also be seen. CCFDN (congenital cataract, facial dysmorphism, and neuropathy syndrome) secondary to carboxy-terminal domain RNA polymerase II polypeptide A phosphatase subunit 1 (*CTDP1*) mutations is also found in gypsies. The gene for a third form of AR CMT1 in Balkan gypsies (CMT4G/HMSN Russe) has recently been identified as the hexokinase 1 (*HK1*) gene (Hantke et al., 2009).
- CMT4F secondary to periaxin mutations should always be considered in patients with predominant sensory involvement.

### Autosomal dominant CMT2

In all the published series of CMT to date, CMT1 is more frequent than CMT2 but as genes have only been identified for about 40% of the CMT2 cases, the true prevalence of CMT2 remains unknown. In particular, AD CMT2 can be difficult to distinguish from an idiopathic axonal neuropathy especially in older patients presenting with a neuropathy which



**Figure 4.** Charcot-Marie-Tooth (CMT) phenotypes. (A) Sural nerve biopsy from a patient with CMT4C, due to a homozygous *SH3TC2* mutation, shows occasional demyelinated fibers (black arrow) and basal laminal onion bulbs (arrowhead). The most characteristic finding is abnormal Remak fibers in which the Schwann cells form very attenuated processes (white arrow). These abnormalities are difficult to appreciate by light microscopy, and so electron microscopy is necessary for diagnosis. (B) Severe wasting and weakness of distal arm and hand muscles in a patient with CMT2A due to a heterozygous *mitofusin 2* (*MFN2*) mutation. (C) Proximal and distal leg wasting and (D) wasting of distal forearms and intrinsic hand muscles in a patient with CMT2F due to a heterozygous mutation in heat shock 27-kDa protein 1 (*HSPB1*) (*HSP27*). (E) Marked proximal and distal leg wasting in a patient with CMT2A due to a heterozygous *MFN2* mutation.



**Figure 5.** Algorithm for autosomal dominant axonal Charcot-Marie-Tooth disease type 2 (AD CMT2).

is mild, long-standing, and with no family history or family members available to examine. Eleven causative genes for AD CMT2 have been identified (Table 1) accounting for about 40% of all the AD CMT2 cases. Unlike AD CMT1, there is no equivalent of the chromosome 17 duplication to account for most cases. CMT2A secondary to *MFN2* mutations is the commonest cause of AD CMT2 but it is not appropriate to screen this gene in all AD CMT2 cases as, unlike in AD CMT1 where genetic testing is based on the frequency of the causative genes, in AD CMT2 genetic testing should be strongly guided by the phenotype. AD CMT2 can be subdivided into three distinct phenotypes to help this process (Fig. 5).

In the first, and most common phenotype, patients present with the “classical CMT phenotype,” which is indistinguishable clinically from the classical AD CMT1 phenotype until MCVs are done confirming an axonal neuropathy. Later ages of onset may be seen in AD CMT2. Nerve biopsies are rarely helpful diagnostically and therefore rarely indicated, but if done show an axonal neuropathy usually without any specific diagnostic features. Five genes (*MFN2*, *MPZ*, *NEFL*, alanyl-tRNA-synthetase [*AARS*], *GDAP1*) have been described as causing the “classical CMT phenotype,” but there remains a large group of patients with this phenotype in whom a genetic diagnosis has not been possible to date. Mutations in *MFN2* cause CMT2A (Zuchner et al., 2004), which represents about 20% of all AD CMT2 cases. Although the “classical CMT phenotype” can be seen with *MFN2* mutations, patients with *MFN2* mutations more commonly present with a more severe phenotype that may cause significant impairment in childhood (Figs. 4B and 4E) (Verhoeven et al., 2006). As about 20% of

*MFN2* mutations are *de novo* in most series and many mutations are novel, this gene can cause diagnostic difficulties particularly in determining whether an observed change is pathogenic. Occasional CMT2A patients also have optic atrophy (HMSN VI in previous classifications [Zuchner et al., 2006]). Brisk reflexes and minor white matter changes on brain magnetic resonance imaging (MRI) are also described (Chung et al., 2006; 2010). Overt central nervous system (CNS) disease is seen more rarely (Boaretto et al., 2010). Mutations in *MPZ* and *NEFL* can also cause the “classical CMT phenotype” as mentioned above. A new tRNA-synthetase gene, *AARS* has recently been identified to cause the “classical CMT phenotype” but the frequency of this gene has yet to be determined (Latour et al., 2010). *GDAP1*, which usually causes AR CMT1 or CMT2, can rarely cause AD CMT2 (Chung et al., 2008). It should be kept in mind that patients with gap junction protein  $\beta 1$  (*GJB1*) mutations (especially females) can appear to have AD inheritance and can be mistakenly thought to have AD CMT2. The lack of male-to-male transmission should always raise the possibility of X-linked inheritance and prompt a screen for *GJB1* mutations when clinically appropriate.

The second AD CMT2 phenotype is CMT2 with major sensory involvement. Unlike the classical CMT phenotype, which presents with motor problems, these patients present with lack of sensation and complications of sensory loss including ulcerations, osteomyelitis, and amputations (Auer-Grumbach et al., 2003). Motor involvement is often present but usually much later and to a lesser degree than the sensory involvement (Reilly and Shy, 2009). It has been argued that this phenotype should be more accurately called HSN (HSAN) and indeed of the two genes that have

been described to cause this phenotype (*SPTLC1* and *RAB7*), patients with *SPTLC1* mutations are classified as having HSN1 (HSAN1) (Bejaoui et al., 2001; Dawkins et al., 2001). Many of these patients, particularly males, develop significant motor involvement and hence the overlap with CMT2 (Houlden et al., 2006). Patients with the second causative gene for this phenotype, *RAB7*, are traditionally classified as having CMT2B (Verhoeven et al., 2003) and are difficult to distinguish from those with *SPTLC1* mutations, although unusually for hereditary neuropathy patients the patients with *SPTLC1* mutations often have neuropathic pain (Houlden et al., 2006). These two genes should be considered in patients presenting with prominent sensory features but there remain families with this phenotype who do not have mutations in either of these two genes (Klein et al., 2005).

The third AD CMT2 phenotype is CMT2 with major motor involvement. The four genes (*GARS*, heat shock 27-kDa protein 1 [*HSPB1*], heat shock 22-kDa protein 8 [*HSPB8*], *TRPV4*) described to cause this phenotype can also cause various forms of pure HMN, that is distal HMN. Mutations in *GARS* cause CMT2D (Antonellis et al., 2003). Unlike the “classical CMT phenotype,” where patients present with lower limb involvement first, patients with CMT2D present with atrophy and weakness of the small muscles of the hand (this can be unilateral and misdiagnosed as thoracic outlet syndrome) with much later involvement of the distal lower limb muscles. Some patients have no sensory involvement and have been classified as dHMN type V, an allelic condition. The dHMN V phenotype has subsequently been shown to be more commonly due to mutations in the *BSCL2* gene (Rohkamm et al., 2007), which usually causes Silver syndrome (spastic legs and distal amyotrophy of the upper limbs) but can present (in 33% of the cases) with just amyotrophy of the upper limbs (Auer-Grumbach et al., 2005). Therefore, in patients presenting with AD CMT2/dHMN and predominant involvement of the small hand muscles, *BSCL2* and *GARS* should be screened first. Further genes will undoubtedly also cause this phenotype as there are patients who do not have mutations in these two genes. The small heat-shock protein genes *HSPB1* (*HSP27*) and *HSPB8* (*HSP22*) are rare causes of AD CMT2 (Figs. 4C and 4D), which is length dependent but with minimal sensory involvement (these two genes also cause a purely motor phenotype, dHMN type II; reviewed in Irobi et al., 2006). A homozygous mutation in *HSPB1* has also recently been described to cause AR CMT2 (Houlden et al., 2008). Recently, mutations in *TRPV4* have been described as causing three different motor predominant inherited neuropathies including CMT2C (CMT2 with vocal cord paralysis), scapulo-peroneal

spinal muscle atrophy, and congenital distal spinal muscle atrophy. Subsequently, mutations in *TRPV4* were identified in eight index cases with varying clinical features from a series of 145 patients with inherited neuropathies, confirming this wide range of phenotypes seen with this gene (Zimon et al., 2010).

### Autosomal recessive CMT2

AR CMT2 is very rare compared to AD CMT2. Three causative genes have been identified (lamin A/C [*LMNA*], mediator complex subunit 25 [*MED25*], and *GDAP1*) (Table 1). Patients with mutations in *LMNA* are classified as CMT2B1 (De Sandre-Giovannoli et al., 2002) and present in the second decade with a severe CMT phenotype including proximal muscle involvement although some have a milder phenotype. *LMNA* mutations have been associated with a wide spectrum of other phenotypes including Emery-Dreifuss muscular dystrophy, cardiomyopathy, and Dunnigan-type familial partial lipodystrophy. A mutation in the *MED25* gene has been described as causing a mild form of AR CMT2 in a Costa Rican family (Leal et al., 2009). *GDAP1* mutations cause a wide range of phenotypes including AR CMT1 and 2 and AD CMT2. Vocal cord paralysis is frequently seen with mutations in this gene.

### X-linked CMT

Genes have been identified for two forms of X-linked CMT, CMTX1 and CMTX5 (Table 1).

CMTX1, an X-linked dominant disorder, secondary to mutations in the *GJB1* gene encoding connexin 32 (Cx32), is the second commonest form of CMT (Bergoffen et al., 1993). As expected in an X-linked disorder, males are usually more severely affected than females. Males usually present in the first two decades of life and although they have a length-dependent neuropathy, they more commonly show some asymmetry such as different degrees of ankle dorsiflexion weakness compared to the “classical CMT phenotype” seen with CMT1A. A diagnostically useful pointer to CMTX1 is more severe involvement of the abductor pollicis brevis compared to the first dorsal intersosseus seen in many patients (Kuntzer et al., 2003). The phenotype in females, while usually less severe than that seen in males, varies more and includes asymptomatic patients who only have signs. This is postulated to be due to random X-inactivation. Nerve conduction are commonly slower in males (demyelinating CMT1 range) than females, who are usually in the axonal CMT2 range, but in both the MCVs are often in the intermediate range (25–40 m/s) (Lewis and Shy, 1999). Occasional CMTX1 patients have asymmetric MCVs reminiscent of CIDP which can cause diagnostic confusion (Michell et al., 2009). Although oligodendrocytes

also express Cx32, the CNS is rarely involved symptomatically but patients may have mild asymptomatic involvement (e.g., extensor plantars, mild deafness, abnormal brainstem-evoked potentials) (Kleopa et al., 2002). However, occasionally transient severe CNS involvement characterized by ataxia and dysarthria has been described (Paulson et al., 2002). Novel *GJB1* mutations are frequent with more than 300 causative mutations having been described to date (available at <http://www.molgen.ua.ac.be/CMTMutations/default.cfm>). Mutations are predicted to cause a loss of function and hence, unlike distinct *PMP22* and *MPZ* mutations, virtually all males with *GJB1* mutations have similar age-related phenotypes (Shy et al., 2007). The predicted loss of function due to mutations is diagnostically very useful as (as expected) all exonic amino acid changing mutations described to date, with one exception, are pathogenic. The recently described exception is a mutation in one of the few non-conserved amino acids between mouse and human *GJB1* (Brozkova et al., 2010).

CMTX5, an X-linked recessive disorder also referred to as the Rosenberg-Chutorian syndrome, due to mutations in the phosphoribosylpyrophosphate synthetase 1 (*PRPS1*), is a very rare axonal form of CMT characterized by a severe neuropathy with deafness and optic atrophy (Kim et al., 2007).

### Dominant intermediate CMT

Certain forms of AD CMT characteristically present with MCVs in the intermediate range (25–45 m/s) and have been called dominant intermediate CMT (DI-CMT). These include dominant intermediate DI-CMTB caused by dynamin 2 (*DNM2*) mutations (Zuchner et al., 2005) and DI-CMTC caused by glycyl-tRNA synthetase (*YARS*) mutations (Jordanova et al., 2006). Clinicians need to be aware that, as discussed earlier, patients with mutations in a variety of other genes with different modes of inheritance, including *GJB1*, *NEFL*, *MPZ*, and *GDAP1*, can also present with intermediate MCVs. The usefulness of classifying patients as having intermediate CMT is debated.

### Diagnostic algorithms

Diagnostic algorithms for AD and X-linked CMT1 and for AD CMT2 are given in Figs. 3 and 5, respectively. The algorithms are guidelines only and each patient will need individual assessment. In AR CMT cases, algorithms are not as useful as it is better to accurately phenotype each patient. The availability of tests varies in each country and this will limit the extent to which testing can be performed in an individual patient. It is a challenge for practicing clinicians to keep up to date with the rapidly expanding field and it may be more appropriate once the common

genes have been screened to seek an opinion from a clinician with expertise in the genetic neuropathies before further extensive and expensive genetic testing.

A few useful “clinical practice points” to keep in mind include the following:

- Diagnosing AD CMT1 is largely based on the frequencies of causative genes, whereas the diagnosis of AD CMT2 is largely based on the phenotype.
- In patients with early-onset CMT and normal parents, always consider *de novo* dominant inheritance as well as AR inheritance.
- Be aware of the emerging group of genes that can cause either distal HMN or motor predominant CMT2 (*GARS*, *HSPB1*, *HSPB8*, *TRPV4*).
- Be aware of the emerging overlap between certain forms of HSN and CMT2 (*HSN1* and *CMT2B*).
- Intermediate conduction velocities can help by suggesting *GJB1*, *MPZ*, *NEFL*, *GDAP1*, *DNM2*, or *YARS* mutations.

### Diagnostic challenges

There are many diagnostic challenges associated with CMT. Not least of these is the relatively restricted number of genes available for routine diagnostic testing in many countries, despite the rapidly expanding number of genes being identified. For many patients, this may make achieving a genetic diagnosis more difficult. In the future with new generation sequencing techniques this is predicted to be less of a problem.

Currently, there is also a nihilistic attitude toward genetic testing among some practitioners, as there is no specific therapy available to date for any type of CMT. Although this is understandable to a certain extent, the benefits to patients of an accurate genetic diagnosis need to be stressed. These include more accurate prognosis and the availability of predictive, antenatal, and pre-implantation diagnosis. A major benefit of a genetic diagnosis in the “sporadic” patient includes limiting invasive tests (e.g., nerve biopsies) and trials of treatments with potentially serious side effects (e.g., immunosuppressants).

Further diagnostic challenges are seen increasingly in the laboratory. The prediction of whether a novel amino acid changing mutation in an exon is pathogenic can pose difficulties. Segregation of the mutation with the disease in the family, the absence of the mutation in an adequate number of controls, conservation of the mutated base among diverse species, and the use of predictive computer programs are all very useful, but not infallible, in predicting pathogenicity. Functional gene-specific tests of pathogenicity clearly need to be developed. Predicting pathogenicity becomes even

more difficult with splice site, intron, and promoter changes and this is predicted to be even more of a problem when more extensive genome sequencing is more readily available.

## Other Roles for Clinicians in the Management of CMT

Although the clinician's role in the diagnosis of CMT in patients is very important, there are many other established and new roles for clinicians in treating patients with CMT. Disease-specific therapies are not yet available for CMT, but physicians have treated and continue to treat CMT patients symptomatically with physiotherapy, rehabilitation therapy, orthotics, orthopedic intervention, pain management, and fatigue management. CMT is lifelong, needing different types and levels of support throughout the disease course.

Clinicians also remain very important in driving research into CMT forward. This role includes continuing to identify families to aid the identification of new genes and performing genotype/phenotype studies to help understand the pathogenesis of known genes. Disease-specific therapies are already beginning to be investigated in the common form of CMT (ascorbic acid in CMT1A) and other potential therapies are being investigated in animal models. Thus, the need for well-performed natural history studies and the search for reliable, validated, and responsive outcome measures and biomarkers for clinical trials, and eventually for monitoring treatment, in CMT become even more important. MRI and skin biopsies looking at the dermal myelinated nerve fibers are just two tools currently being studied. The role of clinicians in the management of CMT is consequently evolving rapidly.

## Conclusion

This is an exciting and challenging time for clinicians managing patients with CMT. In the two decades since the first causative gene was identified for CMT there has been an explosion in the identification of causative genes. Most patients can now get an accurate genetic diagnosis. The emergence and trialing of potential novel therapies for CMT marks the beginning of a new era. Most new therapies are likely to be gene specific, making an accurate genetic diagnosis even more important for patients. The major challenge for clinicians currently is the development of reliable outcome measures and the search for reliable biomarkers to monitor treatment in CMT, which especially in the common form,

CMT1A, is a slowly progressive disease particularly in adults.

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