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REVIEW

Advances in the molecular diagnosis of Charcot-Marie-Tooth disease

Paschalis Nicolaou, Kyproula Christodoulou

Paschalis Nicolaou, Kyproula Christodoulou, Neurogenetics Department, Cyprus Institute of Neurology and Genetics, 1683 Nicosia, Cyprus

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Correspondence to: Kyproula Christodoulou, PhD, Professor of the Cyprus School of Molecular Medicine, Head of the Neurogenetics Department, Cyprus Institute of Neurology and Genetics, 6 International Airport Av., P.O. Box 23462, 1683 Nicosia, Cyprus. roula@cing.ac.cy

Telephone: +357-22-392649 Fax: +357-22-392615
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Abstract

Charcot-Marie-Tooth (CMT) disease or hereditary motor and sensory neuropathy is the most common inherited neuromuscular disorder affecting at least 1 in 2500. CMT disease is pathologically and genetically heterogeneous and is characterized by a variable age of onset, slowly progressive weakness and muscle atrophy, starting in the lower limbs and subsequently affecting the upper extremities. Symptoms are usually slowly progressive, especially for the classic and late-onset phenotypes, but can be rather severe in early-onset forms. CMT is grouped into demyelinating, axonal and intermediate forms, based on electrophysiological and pathological findings. The demyelinating types are characterized by severely reduced motor nerve conduction velocities (MNCVs) and mainly by myelin abnormalities. The axonal types are characterized by normal or slightly reduced MNCVs and mainly axonal abnormalities. The intermediate types are characterized by MNCVs between 25 m/s and 45 m/s and they have features of both demyelination and axonopathy. Inheritance can be autosomal dominant, X-linked, or autosomal recessive. Mutations in more than 30 genes have been associated with the different forms of CMT, leading to major advancements in molecular diagnostics of the disease, as well as in the understanding of pathogenetic mechanisms. This editorial aims to provide an account that is practicable and efficient on the current molecular diagnostic procedures for CMT, in correlation with the clinical, pathological and electrophysiological findings. The most frequent causative mutations of CMT will also be outlined.

Key words: Charcot-Marie-Tooth disease; Charcot-Marie-Tooth; Neuropathy; Genetics; Molecular diagnosis

Core tip: Charcot-Marie-Tooth (CMT) disease is the most common neuromuscular disorder affecting at least 1 in 2500. CMT according to electrophysiological and pathological findings is categorised into demyelinating, axonal and intermediate forms and inheritance can be autosomal dominant, X-linked, or autosomal recessive. More than 30 causative genes have been identified. This editorial aims to present an efficient account of molecular diagnostic procedures for CMT, based on clinical, pathological and electrophysiological findings as well as summarize the most frequent causative mutations.

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INTRODUCTION

Charcot-Marie-Tooth (CMT) disease, also known as Charcot-Marie-Tooth neuropathy, hereditary motor and sensory neuropathy (HMSN) and Peroneal Muscular Atrophy was first described by Charcot *et al*[1] and Tooth[2] in 1886. CMT is the most common inherited neuromuscular disorder, with a prevalence of 17-40 per 100000 in-

dividuals[3,4]. Clinically, it is characterized by a variable age of onset and a variable phenotype. The main features of CMT comprise, a slowly progressive symmetric weakness and muscle atrophy of the peroneal and distal muscles of the lower limbs, sensory loss, foot deformities (pes cavus and hammer toes), and decreased or absent tendon reflexes. Hands and forearms are affected later in life. Bilateral pes cavus is almost invariably present with substantial variation in the level of sensory symptoms and signs[5]. According to electrophysiological and pathological findings CMT is classified into demyelinating, axonal and intermediate forms. The demyelinating types (CMT1 or HMSN I) are characterized by severely reduced motor nerve conduction velocities (MNCVs) (median nerve MNCV < 38 m/s) and mainly by myelin abnormalities on nerve biopsy including onion bulbs[6]. The axonal types (CMT2 or HMSN II) with primarily axonal degeneration are characterized by normal or slightly reduced motor nerve conduction velocities (median nerve MNCV > 38 m/s) but reduced amplitudes. Normal amplitudes are usually more than 4-6 μV, however this also differs between nerves[7-9]. Intermediate types include CMT patients that have features of both demyelination and axonopathy with median nerve MNCVs ranging from 25 to 45 m/s[10]. Inheritance in CMT can be autosomal dominant (AD)[11], X-linked[12,13], or autosomal recessive[14,15]. More than 50 loci and more than 30 CMT genes have thus far been identified (Table 1, http://neuromuscular.wustl.edu/time/hmsn.html).The majority of CMT patients worldwide have been characterized at the molecular genetic level. More than 70% of all CMT patients have mutations in one of four genes: *PMP22*, *GJB1*, *MPZ*, and *MFN2*. Approximately 25% of CMT patients are still pending molecular diagnosis, the great majority of them with CMT2[16]. Despite major advances in the identification of causative CMT genes, the related pathogenic mechanisms still remain to be clarified[17,18].

CMT CLASSIFICATION

CMT is classified into the following 3 types, based on clinical and neurophysiological findings, the inheritance pattern and associated gene mutations.

CMT1 (HMSNI): Autosomal dominant demyelinating CMT

CMT1 is the most common type of CMT and is divided into different subtypes based on molecular genetic findings.

CMT1A is the most common subtype (70% of demyelinating CMT and 40% of all CMT patients)[16,19,20]. CMT1A is caused by the duplication of a 1.4 Mb region on chromosome 17p12 that contains the peripheral myelin protein 22 (*PMP22*) gene[16,21-24]. *De novo PMP22* duplication mutations occur in 6.5% of CMT1A patients. PMP22 protein is a hydrophobic 22 kDa glycoprotein that is expressed mainly in myelinating Schwann cells and plays an important role in myelination, proliferation and differentiation[25,26]. Overexpression of *PMP22* gene dosage reduces the proliferation of Schwann cells and may affect the intracellular degradation of membrane components[3,27]. The onset of clinical symptoms is in the first or second decade of life, usually in childhood, characterized by a typical CMT phenotype, and usually a mild disease progress. However, disease severity is variable, even in individuals of the same family. In many cases there is also

Table 1 Charcot-Marie-Tooth classifications

Type	Locus	Gene	OMIM	Ref.
CMT1: Dominant demyelinating				
CMT1A	17p12	*PMP22*	*601097	[21,22]
CMT1B	1q22	*MPZ*	*159440	[28]
CMT1C	16p13	*LITAF* (*SIMPLE*)	*603794	[171]
CMT1D	10q21.3	*EGR2*	*129009	[37]
CMT1E	17p12	*PMP22*	*601097	[21,22]
CMT1F	8p21	*NEFL*	*162280	[105]
CMT1	14q32	*FBLN5*	*604580	[47]
CMT2: Dominant axonal				
CMT2A	1p36.22	*MFN2*	*608507	[51,52]
CMT2B	3q21.3	*RAB7*	*602298	[55]
CMT2C	12q24.11	*TRPV4*	*605427	[61]
CMT2D	7p15	*GARS*	*600287	[64]
CMT2E	8p21	*NEFL*	*162280	[66]
CMT2F	7q11.23	*HSPB1* (*HSP27*)	*602195	[69]
CMT2G	12q12-13.3	*Unknown*		
CMT2H/2K	8q21.11	*GDAP1*	*606598	[76]
CMT 2I/2J	1q22	*MPZ*	*159440	[80,81]
CMT2L	12q24.3	*HSPB8* (*HSP22*)	*608014	[83]
CMT2M	19p13	*DNM2*	*602378	[84]
CMT2N	16q22.1	*AARS*	*601065	[89]
CMT2O	14q32.31	*DYNC1H1*	*600112	[93]
CMT2P	9q33	*LRSAM1*	*610933	[95,96]
CMT2Q	10p14	*DHTKD1*	*614984	[100]
DI-CMT: Dominant intermediate				
DI-CMTA	10q24.1-q25.1	*Unknown*		
DI-CMTB	19p13	*DNM2*	*602378	[84]
DI-CMTC	1p35.1	*YARS*	*603623	[106]
DI-CMTD	1q22	*MPZ*	*159440	[10]
DI-CMTE	14q32.33	*IFN2*	*610982	[107]
DI-CMTF	3q26.33	*GNB4*	*610863	[108]
CMT4: Recessive demyelinating				
CMT 4A	8q21.11	*GDAP1*	*606598	[78]
CMT 4B-1	11q22	*MTMR2*	*603557	[112]
CMT 4B-2	11p15	*MTMR13* (*SBF2*)	*607697	[117]
CMT 4C	5q23-33	*SH3TC2*	*608206	[119]
CMT 4D	8q24.3	*NDRG1*	*605262	[125]
CMT 4E	10q21.3	*EGR2*	*129010	[37]
CMT 4F	19q13.2	*PRX*	*605725	[43,129]
CMT 4G	10q23.2	*HK1*	*142600	[134]
CMT 4H	12p11.21	*FGD4*	*611104	[137,138]
CMT 4J	6q21	*FIG4*	*609390	[141]
AR-CMT2: Recessive axonal				
AR CMT 2A	1q22	*LMNA*	*150330	[144]
AR CMT 2B	19q13.3	*MED25* (*ACID1*)	*610197	[146]
AR-CMT 2C	8p21	*NEFL*	*162280	[66,150]
AR CMT2D	8q21.11	*GDAP1*	*606598	[76]
AR CMT2E	9q33	*LRSAM1*	*610933	[95,96]
CMTX: X-linked				
CMTX1	Xq13.1	*GJB1*	*304040	[153]
CMTX2	Xp22.2	*Unknown*		
CMTX3	Xq26.3-q27.1	*Unknown*		
CMTX4	Xq26.1	*AIFM1*	*300169	[161]
CMTX5	Xq22.3	*PRPS1*	*311850	[165]
CMTX6	Xp22.11	*PDK3*	*602526	[166]

OMIM: Online endelian inheritance in man; CMT: Charcot-Marie-Tooth; DI: Dominant intermediate; AR: Autosomal recessive.

nerve hypertrophy (25%) and in some hearing loss (5%)[3]. The MNCVs are reduced (< 38 m/s) in the early stages of the disease.

CMT1B is caused by mutations in the myelin protein zero (*MPZ* or *P0*) gene, located on chromosome 1q22-q23 and account for about 5% of CMT1 cases[3,16,28]. MPZ protein is a 28 kDa glycoprotein that is located in Schwann cells. This protein is necessary for normal myelin structure and function and is found in abundance in the myelin of peripheral nerve tissues and is completely absent from the myelin of the central nervous system[27,29]. CMT1B is characterized by an early onset (usually first decade) and most *MPZ* mutations cause a classical CMT1 phenotype, however, some mutations cause a more severe Dejerine-Sottas syndrome (DSS-CMT3B) or congenital hypomyelination neuropathy (CHN)[30,31]. Patients with an early onset have reduced MNCVs and patients with a late onset have normal or slightly reduced MNCVs[32].

CMT1C is caused by mutations in the lipopolysaccharide-induced tumor necrosis factor (*LITAF*)/small integral membrane protein of lysosome late endosome (*SIMPLE*) gene. The gene is located on chromosome 16p13.1-p12.3 and plays an important role in protein degradation[33]. *LITAF* mutations account for less than 1% of CMT patients[34]. The first clinical symptoms in patients with CMT1C appear in the second decade with a typical CMT1 phenotype and conduction velocities around 16-25 m/s[3,33,35,36].

CMT1D accounts for less than 1% of CMT patients and is caused by mutations in the early growth response element 2 (*EGR2*) gene, that is located on chromosome 10q21.3[37]. *EGR2* is a transcription factor that is involved in the regulation of myelin genes[38,39]. Most patients have very early onset CMT1 or the most severe DSS (DSS-EGR) or CHN phenotypes, however, patients with late onset and a milder phenotype have been described[37,40-43]. Patients with cranial nerve deficits, including diseases of the pulmonary system, respiratory failure, diplopia and vocal cord paresis have been reported[3,34]. Motor nerve conduction velocities are slightly to severely reduced (9-42 m/s)[3].

CMT1E is caused by point mutations in the *PMP22* gene[21-23]. Patients with *PMP22* point mutations have more severe symptoms than patients with CMT1A and usually have slower NCV[44]. Point mutations of *PMP22* may cause various other phenotypes such as HNPP, DSS (CMT3A) or CHN[45].

CMT1F is caused by mutations in the neurofilament light chain (*NEFL*) gene located on chromosome 8q21. The encoded protein plays a role in intracellular transport of axons and dendrites[46]. The first symptoms of the disease appear in the first decade of life and are usually severe, with severely reduced MNCVs (15-38 m/s)[3]. *NEFL* mutations also cause CMT2E and CMT4C2.

CMT1G has been recently described and is caused by mutations in the fibulin-5 (*FBLN5*) gene on chromosome 14q32[47]. *FBLN5* is located in an extracellular matrix and is a calcium-binding glycoprotein that plays an important role in elastic fiber assembly and in endothelial cell adhesion[48]. The age of onset, the phenotype and the MNCVs of the disease vary[47].

CMT2 (HMSNII): Autosomal dominant axonal CMT

CMT2 accounts for 20% of all CMT patients and is characterized by normal or slightly reduced MNCVs[16,35].

CMT2A is the most common form of CMT2 and accounts for 20% of CMT2 patients[49,50]. It is caused by mutations in the mitofusin 2 (*MFN2*) gene, located on chromosome 1q36.22. A mutation in the kinesin motor protein 1B (*KIF1B*) gene has been reported in a Japanese family, but mutations in the *KIF1B* have not thus far been confirmed in any other family[51]. MFN2 is a large dynamin-like GTPase protein that plays an important role in the fusion of mitochondria. When this protein is modified as a result of gene mutations, it leads to an insufficient protein transfer between mitochondria and the axons of peripheral nerves[3]. Most patients (80%) have an early onset of symptoms (< 10 years old) with a severe phenotype and usually become wheelchair bound by 20 years of age. The remaining 20% of patients have a later onset of symptoms (10-50 years old) and a milder phenotype[52]. CMT2A patients with optic atrophy, hearing loss, cerebral white matter abnormalities and diabetes mellitus have been described[16,49,50,53,54]. Motor nerve conduction velocities are typically normal, however, the amplitudes are slightly to severely reduced or absent[54].

CMT2B is caused by mutations in the RAS-associated GTP-binding protein (*RAB7*) gene located on chromosome 3q21.3[55]. RAB7 is a GTPase protein that localizes to late endosomes and lysosomes and is involved in the regulation of late endocytic traffic[56,57]. Clinical symptoms appear between the second and fourth decades and include typical CMT phenotype and mild to moderate sensory loss, that often leads to foot ulcerations and subsequently infections and amputations[58,59]. MNCVs are normal to slightly reduced with usually reduced amplitude.

CMT2C is caused by mutations in the transient receptor potential vanilloid 4 (*TRPV4*) gene located on chromosome 12q24.11[60,61]. The TRPV4 protein is a cation channel (Ca^{2+} channel) that activates pathways leading to the regulation of systemic osmotic pressure[62]. CMT2C is characterized by weakness of proximal muscles, vocal cord, diaphragmatic paresis and occasionally a fatal outcome. Some other features have been reported including sensorineural hearing loss, raspy voice, bladder urgency and incontinence[7,61,62]. The age of onset is between the second and fifth decades of life and MNCVs are normal (> 50 m/s)[61,62].

CMT2D is caused by mutations in the glycyl-tRNA synthetase (*GARS*) gene located on chromosome 7p15[63,64]. The encoded protein plays an important role in translation processes and *GARS* gene mutations affect protein synthesis, which is important for the normal function of the motor nerve[3]. The first symptoms appear between first and forth decade and primarily affect the upper extremities and then to a lesser extent the

lower extremities[64,65]. MNCVs are normal.

CMT2E is caused by mutations in the *NEFL* gene[66]. *NEFL* mutations also cause CMT1F and CMT4C2[66,67]. CMT2E is clinically similar to CMT1F, although typically it is less severe, with normal or slightly reduced MNCVs.

CMT2F is caused by mutations in the heat shock protein B1 (*HSPB1*, also known as *HSP27*) gene located on chromosome 7q11.23[68,69]. The HSPB1 protein protects the structure of other proteins (bind and prevent misfolding and aggregation of nascent proteins) and also interacts with the NEFL protein and protects motor neurons[57,70]. Symptoms progression is slow and they begin with symmetrical weakness of the lower extremities resulting in foot drop, foot deformities, and sensory dysfunctions and then progresses slowly to the upper extremities[71]. The age of onset of the disease is in the first or second decade of life and the MNCVs[72].

CMT2G maps to chromosome 12q12-q13.3 but associated gene mutations are still unknown[73,74]. The age of onset varies from the first to the eighth decade, although most patients developed symptoms in the second decade. Clinical symptoms include foot deformity and difficulty in walking, with very slow progression and absent ankle reflexes[73]. MNCVs are normal or mildly decreased.

CMT2H and CMT2K are caused by mutations in the ganglioside induced differentiation associated protein 1 (*GDAP1*) gene on chromosome 8q21.11[75,76]. *GDAP1* mutations also cause axonal recessive CMT (CMT4C4) or demyelinating recessive CMT (CMT4A)[76-78]. The clinical symptoms in CMT2H/K appear in the second decade with a mild to moderate and slowly progressive phenotype with vocal cord paralysis and occasionally with optic nerve atrophy and normal or slightly reduced MNCVs[79].

CMT2I and CMT2J are caused by mutations in the *MPZ* gene[80,81]. The first symptoms appear very late (between 45 and 60) with a typical CMT2 phenotype, although there are some patients with pupillary abnormalities, deafness and sensory disturbances[16,81]. MNCVs are normal or slightly reduced (> 38 m/s), but during the progress of the disease they are decreased (< 38 m/s)[3].

CMT2L is caused by mutations in the heat shock 22 kDa protein 8 (*HSPB8*) gene, also known as heat shock protein 22 (HSP22) on chromosome 12q24[82,83]. HSPB8 is highly expressed in the spinal cord and in the motor and sensory neurons and is mainly localized to the plasma membrane. Also it possesses chaperone-like activity and inhibits protein aggregation and degrades misfolded proteins[57]. Clinical symptoms start between 15-35 years old and include distal muscle weakness and atrophy, mild sensory loss and scoliosis present in some patients. MNCVs are normal or near-normal.

CMT2M is caused by mutations in the dynamin 2 (*DNM2*) gene located on chromosome 19p13[84,85]. DNM2 is a large GTPase protein involved in membrane trafficking and endocytosis[86]. CMT2M is characterized by distal muscle weakness and atrophy of the lower extremities, mild weakness of upper extremities and foot deformities, including pes cavus and toe clawing[87,88]. The symptoms appear between the age of 20-55 years and the MNCVs are normal to slightly reduced.

CMT2N is caused by mutations in alanyl-tRNA synthetase (*AARS*) gene on chromosome 16q22.1[89]. AARS protein is an aminoacyl-tRNA synthetase (ARS). ARSs are ubiquitously expressed, essential enzymes that ligate amino acids to produce tRNAs needed for global protein synthesis[90]. Clinical features include mild to moderate weakness of lower limbs and milder or absent weakness of the upper limbs. Some patients had foot drop, pes cavus, hammer toes, absent ankle reflexes and hyporeflexia[89,91,92]. The age of onset is varying (6-54 years old) and MNCVs are normal.

CMT2O is caused by mutations in the dynein cytoplasmic 1 heavy chain 1 (*DYNC1H1*) gene on chromosome 14q32.31[93]. Dyneins are a group of ATPases that help to convert chemical into mechanical energy. Cytoplasmic dynein is a large motor protein complex that is involved in intracellular functions, including reversing axonal transport in neurons[93,94]. Clinical features include progressive distal lower limb weakness, pes cavus, variable sensory loss and in some patients proximal weakness and waddling gait[93]. The first symptoms occur in childhood and the MNCVs are normal.

CMT2P is caused by mutations in the leucine rich repeat and sterile alpha motif containing 1 (*LRSAM1*) gene on chromosome 9q33.3. The inheritance can be autosomal recessive (AR-CMT2)[95] or autosomal dominant (CMT2P)[96,97]. LRSAM1 is a multifunctional RING finger E3 ubiquitin ligase that plays an important role in endocytosis and in neuronal cells adhesion[98,99]. The first symptoms for CMT2P appear between the second and fifth decade of life and include distal weakness in the lower limbs and in some patients also present in the upper limbs. Other features have been reported in some patients including episodic cramps, bilateral pes cavus, foot drop, absent tendon reflexes, severe loss of sensation in feet and legs and mild loss of sensation on fingertips, sensory and motor dysfunction[95-97]. MNCVs are normal to slightly reduced.

CMT2Q is caused by mutations in the dehydrogenase E1 and transketolase domain-containing 1 (*DHTKD1*) gene on chromosome 10p14[100]. This gene encodes a mitochondrial 2-oxoglutarate-dehydrogenase-complex-like protein that is involved in the degradation of several amino acids pathways[100,101]. The age of onset is in the first and second decade and the phenotype is typical CMT2, including distal muscle weakness of the lower limbs, decreased or absent tendon reflexes, and mild to moderate sensory loss[100]. MNCVs are normal (> 40 m/s).

Late onset CMT2 is caused by mutations in the methionyl-tRNA synthetase (*MARS*) gene[102]. This type has recently been identified in one CMT2 family. Clinically it is characterized by late onset (> 50 years old) and a mild CMT2 phenotype[102]. MNCVs studies confirmed an axonal neuropathy.

DI-CMT: Autosomal dominant intermediate CMT

Dominant intermediate CMT types (DI-CMT) are characterized by intermediate MNCVs (25-45 m/s) and the

clinical symptoms are moderate to severe. Electrophysiological and pathological features include both axonal and demyelinating types.

DI-CMTA has been mapped to chromosome 10q24.1-q25.1, but the responsible gene is unknown[103,104]. The phenotype is typical CMT and the MNCVs are moderately reduced[103].

DI-CMTB is caused by mutations in the *DNM2* gene that also cause axonal dominant CMT (CMT2M). Patients present with a classic CMT phenotype at the age of 2-50 years old. MNCVs are ranging from 26 to 54 m/s.

DI-CMTC is caused by mutations in the tyrosyl-tRNA synthetase (*YARS*) gene located on chromosome 1p35.1[105,106]. YARS plays an important role in protein synthesis and in signal transmission from nerves to muscles[106]. The age of onset is between the first and sixth decades with a classic CMT phenotype and numbness in some patients[106]. MNCVs are from 30-40 m/s.

DI-CMTD is caused by mutations in the *MPZ* gene[10]. MPZ mutations are also associated with CMT1B and CMT2I/2J. DI-CMTD is characterized by a variable severity, distal muscle atrophy, weakness, and sensory loss in the lower and upper limbs. MNCVs are 30-40 m/s.

DI-CMTE is caused by mutations in the inverted formin-2 (*IFN2*) gene on chromosome 14q32.33[107]. The encoded protein may function in polymerization and depolymerization of actin filaments. INF2 mutations disrupt actin dynamics in peripheral Schwann cells, leading to disturbed myelin formation and maintenance resulting in CMT[107]. The clinical phenotype is typical CMT, including distal muscle weakness and atrophy and distal sensory loss, with focal segmental glomerulonephritis (FSGS) including proteinuria that progresses to renal disease. The first symptoms appear between the first to third decade and MNCVs are normal to moderately reduced (23-45 m/s).

DI-CMTF is caused by mutations in the guanine nucleotide binding protein, beta polypeptide 4 (*GNB4*) gene[108]. GNB4 protein may play a role in peripheral nerve regeneration. DI-CMTF is characterized by slowly progressive distal muscle atrophy and weakness, and atrophy of the upper and lower limbs, steppage gait and distal sensory loss with decreased reflexes with onset around adolescence. MNCVs are between 16 to 45 m/s.

CMT4: Autosomal recessive demyelinating CMT

CMT4 is a demyelinating type of hereditary polyneuropathy with autosomal recessive inheritance[109].

CMT4A is caused by mutations in the *GDAP1* gene. Clinically severe motor disturbances and progressive scoliosis are observed[110]. CMT4A is characterized by an early age of onset and reduced MNCVs (25-35 m/s).

CMT4B1 is caused by mutations in the myotubularin-related protein 2 (*MTMR2*) gene on chromosome 11q22[111,112]. MTMR2 protein has phosphatase activity and influences transcription and cell proliferation[112]. The phenotype of the disease is severe CMT1 and diaphragmatic and facial weakness may occur, as may scoliosis in adult patients[113-115]. Onset is usually in childhood and MNCVs are severely reduced (10-25 m/s).

CMT4B2 is caused by mutations in the set binding factor 2 (*SBF2*) or myotubularin related protein 13 (*MTMR13*) gene located on chromosome 11p15[116,117]. The encoded protein is a pseudophosphatase that is involved in membrane trafficking[118]. The clinical phenotype, age of onset and MNCVs are similar to CMT4B1[116,119].

CMT4C is caused by mutations in the SH3 domain and tetratricopeptide repeat domain 2 (*SH3TC2*) gene that is located on chromosome 5q32[119,120]. SH3TC2 protein is expressed in Schwann cells of the peripheral nerves and localizes to the membrane with a possible function in myelination and in regions of axoglial interactions[121]. CMT4C is characterized by early-onset, distal weakness, foot deformities, walking difficulty, scoliosis and occasionally facial and bulbar weakness, sensorineural deafness and respiratory insufficiency[119,122-124]. MNCVs are reduced (10-35 m/s).

CMT4D (HMSN-L) is caused by mutations in the N-myc downstream-regulated gene 1 (*NDRG1*) on chromosome 8q24.3[125]. NDRG1 protein appears to play a role in growth arrest and cell differentiation[126]. CMT4C is characterized by distal muscle wasting and atrophy, foot and hand deformities, absent tendon reflexes, and sensory loss. The age of onset is between the first and second decade. Deafness is an invariant feature of the phenotype and usually develops in the third decade.

CMT4E (Congenital Hypomyelinating Neuropathy-CHN) is caused by mutations in the *EGR2* gene[37]. EGR2 mutations are also associated with CMT1D. CMT4E is characterized clinically by an early age of onset, hypotonia, absent of reflexes, distal muscle weakness, and extremely reduced MNCVs (< 10 m/s).

CMT4F is caused by mutations in the periaxin (*PRX*) gene located on chromosome 9q13.2[127-129]. PRX is a Schwann cell protein that plays an important role in axon-glial interactions and is needed for the maintenance of peripheral nerve myelin and regenerating axons[130,131]. CMT4F is characterized, by distal muscle weakness and atrophy, affecting the lower more than the upper limbs, by distal sensory loss and occasionally sensory ataxia. The age at onset is variable, from first to fifth decade and the MNCVs are severely reduced (< 15 m/s)[128,132]. *PRX* mutations also cause DSS (CMT3D)[128].

CMT4G or CMT-Russe (HSMNR) is caused by mutations in the Hexokinase 1 (*HK1*) gene that is located on chromosome 10q23.2[133,134]. HK1 protein is involved in the controlled production of ATP and in the regulation of cell survival. Also HK1 is highly expressed in the nervous system and it is involved in NGF-mediated neurite outgrowth[57,134]. Clinically it is characterized by an early age of onset (5-16 years old), distal muscle weakness progressing to severe on lower limbs, prominent sensory loss, hand and foot deformities[133,135]. MNCVs are mildly reduced (30-35 m/s).

CMT4H is caused by mutations in the FYVE, RhoGEF and PH domain containing 4 (*FGD4*) gene, on chromosome 12p11.21[136,137]. FGD4 (or Frabin) protein

is involved in the myelination process, although the molecular mechanisms by which *FGD4* mutations cause CMT4H are completely unknown[57,137,138]. CMT4H is characterized by distal muscle weakness and atrophy, areflexia, sensory loss, foot abnormalities and occasionally scoliosis, hypotrophy of thenar and hypothenar muscles[136,139,140].

CMT4J is caused by mutations in the FIG4 homolog, SAC1 lipid phosphatase domain containing (*FIG4*) gene, located on chromosome 6q21[141]. FIG4 protein has been shown to possess phosphoinositide phosphatase activity and plays a key role in intracellular transport vesicles[141,142]. The clinical phenotype is severe CMT1 with early onset (childhood but sometimes adult onset) and severely reduced MNCVs (< 10 m/s)[3].

AR-CMT2: Autosomal recessive axonal CMT

AR-CMT2 also called CMT4C is a recessive axonal hereditary neuropathy that is very rare.

AR-CMT2A or CMT2B1 or CMT4C1 is caused by mutations in the lamin A/C (*LMNA*) gene on chromosome 1q22. Lamin A/C is an intermediate filament protein that forms the nuclear lamina[57]. Lamin proteins are involved in nuclear stability, chromatin structure and gene expression, and also the A-type lamins are important in the protection of the cell from mechanical damage[29,143]. Clinical symptoms usually appear in the second decade (onset between 5-25 years old) with a severe CMT phenotype including proximal muscle involvement although some have a milder phenotype. *LMNA* mutations have also been associated with other phenotypes including Emery-Dreifuss muscular dystrophy, cardiomyopathy and Dunnigan-type familial partial lipodystrophy[144,145]. MNCV are normal or just slightly reduced.

AR-CMT2B or CMT2B2 or CMT4C3 is caused by mutations in the mediator complex subunit 25 (*MED25*) gene, also known as *ACID1*, that is located on chromosome 19q13.33[146-148]. The encoded protein is a component of the Mediator complex that plays a role in gene transcription and also is important in myelination[146,149]. Clinical phenotype is typical CMT2 with late onset, in the third to fifth decade of life, and normal or mildly decreased MNCVs[147,148].

AR-CMT2C or CMT4C2 is caused by mutations in the *NEFL* gene. The clinical phenotype is severe CMT2 with early onset (< 2 years old) and severely reduced MNCVs (10-25 m/s)[150].

AR-CMT2D or CMT4C4 is caused by mutations in the *GDAP1* gene. The clinical phenotype is more severe than CMT2H/K, with early onset and normal MNCVs[76,151,152].

AR-CMT2E is caused by mutations in the *LRSAM1* gene with a more severe clinical phenotype than CMT2P and earlier age of onset (first and second decade)[95-97].

CMTX: X-linked CMT

CMTX is an X-linked CMT with dominant or recessive inheritance. Clinically heterozygous females are more mildly affected (or asymptomatic) than hemizygous males[153].

CMTX1 is the second commonest form of demyelinating CMT with a frequency of 12% among all CMT patients[16,20]. CMTX1 has both demyelinating and axonal features and is caused by mutations in the gap junction binding 1 (*GJB1*) gene that is located on chromosome Xq13.1[154]. The encoded protein CX32 (connexin 32) is a transmembrane protein that forms gap junction channels that allow the transfer of small molecules between cells[153]. Clinically males have more severe symptoms, than females. Symptoms in males appear in childhood and later in females[35,155]. MNCVs are slightly reduced, between 30-40 m/s in affected males and 30-50 m/s in affected females[156]

CMTX2 has been mapped to chromosome Xp22.2 and the associated gene mutations are still unknown[157,158]. CMTX2 also has both demyelinating and axonal features and the clinical phenotype is characterized by onset in infancy, weakness and atrophy of the lower limbs, absent reflexes and pes cavus in males. MNCVs are normal to slightly reduced.

CMTX3 has been mapped to chromosome Xq26 and the associated gene mutations are also still unknown[159]. The disease onset is in first and second decade are patients and clinically characterized by progressive weakness of lower limbs and decreased tendon reflexes[157,158]. Electrophysiological findings are compatible with both axonal and demyelination features with MNCVs in the range of 25-57 m/s.

CMTX4 (Cowchock syndrome) is caused by mutations in the apoptosis-inducing factor, mitochondrion-associate 1 (*AIFM1*) gene on chromosome Xq26.1[160,161]. CMTX4 is characterized by an early childhood onset, distal muscle weakness and atrophy, sensory loss, areflexia and in some patients (approximately 60%) deafness and mental retardation[160]. Heterozygous females are asymptomatic[162]. MNCVs are normal to slightly reduced (33-56 m/s) with decreased sensory conduction velocities.

CMTX5 is caused by mutations in the phosphoribosylpyrophosphate synthetase 1 (*PRPS1*) gene located in chromosome Xq22.3[163-165]. PRS1 protein is an enzyme critical for nucleotide biosynthesis[57]. Symptoms appear in the first decade of life and the phenotype is characterized by severe peripheral neuropathy with sensorineural deafness, and optic atrophy[165]. MNCVs are normal (43-51 m/s). Heterozygous females are asymptomatic.

CMTX6 is caused by mutations in the pyruvate dehydrogenase kinase isoenzyme 3 (*PDK3*) gene on chromosome Xp22.11[166]. PDK3 is involved in the regulation of the pyruvate dehydrogenase complex (PDC). PDC catalyzes the oxidation of pyruvate to acetyl-CoA that is a key enzyme involved in the Krebs cycle and lipogenic pathways[166,167]. Disease onset is in the second decade and includes progressive moderate-to-severe wasting below the knees, minimal weakness of the hand muscles, foot deformity, steppage gait, absent ankle reflexes distal lower limb weakness and sensory abnormalities[166]. MNCVs are normal (> 38 m/s).

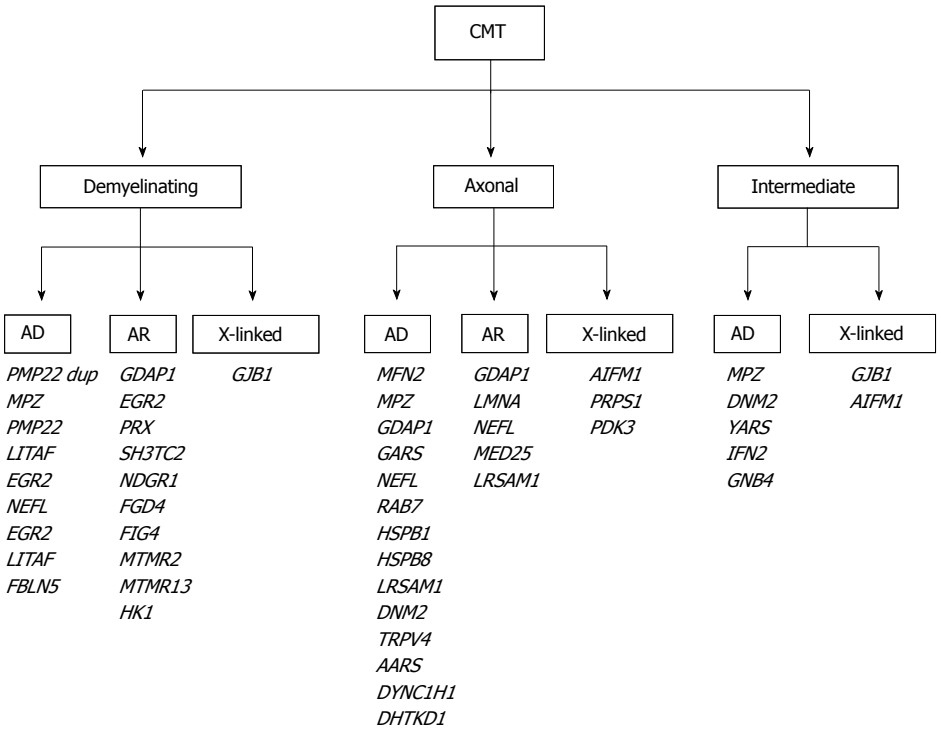

Figure 1 Molecular genetic analysis algorithm for Charcot-Marie-Tooth diagnostics. CMT: Charcot-Marie-Tooth; AD: Autosomal dominant; AR: Autosomal recessive.

MOLECULAR GENETIC TESTING

As outlined above the CMT group of disorders is characterized by a high variability in the clinical phenotype, and great differences exist in the age of the onset, disease progression and severity. There are many types of CMT and a large number of causative genes. As a result of this complexity and the considerable cost of molecular studies, it is useful to establish an algorithm for targeted molecular analysis. Several studies have been published that suggest particular methodologies for performing genetic analysis based on clinical and electrophysiological findings, age of onset of symptoms, family history and relative frequencies of gene mutations[19,20,34,35,145,168,169]. However, some laboratories are currently switching to new screening methods, such as the next generation sequencing (NGS) technology for whole exome and whole genome analysis, slowly replacing the more traditional Sanger sequencing based screening methods. The established flowchart is based on the different CMT types that are determined following the clinical and electrophysiological evaluation of the patient and the existing frequency of causative mutations (Figure 1). PMP22 duplication is the most frequent genetic abnormality and accounts for about 40% of CMT patients, GJB1 for 15%, MFN2 for 10%, MPZ for 5%, PMP22 point mutation for 2.5%; mutations in each of the other CMT genes account for less than 1%[16,19,35,170].

FUTURE STRATEGIES

Traditional Sanger sequencing based screening methods are important tools in genetic research. However, the NGS technology already used as a diagnostic tool in some centers will provide new potential capabilities in molecular diagnostic services. NGS is a high throughput technique with low cost and enables sequencing of multiple known and unknown genes in a single run. Additionally, NGS, in combination with other new technologies, such as proteomics and cellular reprogramming may play an important role in the effort to elucidate the pathogenic mechanisms of the disease and lead to the discovery of new therapeutic approaches in CMT and other diseases.

CONCLUSION

Despite the progress in molecular genetics and the development of new techniques, molecular diagnosis of patients with CMT is still challenging. New genes causing CMT continue to be identified and there exist many more that need to be identified. Increased understanding of the biological processes involved in CMT will enable better understanding of the CMT neuropathy pathogenetic mechanisms and contribute further towards the goal of inventing more effective therapeutic strategies.

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