

Review

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Genetic approaches and pathogenic pathways in the clinical management of Charcot-Marie-Tooth disease

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How to cite this article: Estévez-Arias B, Carrera-García L, Nascimento A, Cantarero L, Hoenicka J, Palau F. Genetic approaches and pathogenic pathways in the clinical management of Charcot-Marie-Tooth disease. *J Transl Genet Genom* 2022;6:333-52. <https://dx.doi.org/10.20517/jtgg.2022.04>

Received: 19 Jan 2022 **First Decision:** 24 Apr 2022 **Revised:** 18 May 2022 **Accepted:** 9 Jun 2022 **Published:** 1 Aug 2022

Academic Editors: Andrea L. Gropman, C. Alexander Valencia **Copy Editor:** Fangling Lan **Production Editor:** Fangling Lan

Abstract

Charcot-Marie-Tooth (CMT) disease is the most common inherited neuromuscular disorder, affecting at least 1 in 2500 individuals. CMT refers to a heterogeneous group of inherited neuropathies from both phenotypic and genetic points of view. Over the last decades, there have been important advances not only in the identification of causative genes but also in understanding the molecular basis for many forms of CMT. In fact, to date, around 100 genes have been related to CMT disease, thanks to next generation sequencing techniques, and they have been proven to affect either the myelin or axon of peripheral nerves. Moreover, its genetic diagnosis has remarkably improved, although there are still difficulties when it comes to treatment. In this review, we explore in depth the eight most prevalent genes associated with CMT: *GDAP1*, *GJB1*, *HINT1*, *MFN2*, *MPZ*, *PMP22*, *SH3TC2*, and *SORD*. We also address the disrupted cellular processes and pathophysiological mechanisms involved in the disease. A better understanding of the pathogenic mechanisms responsible for each type of CMT would be essential to identifying molecular targets and therapeutic strategies.



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Keywords: Charcot-Marie-Tooth disease, genetic diagnosis, genetic neuropathies, inherited peripheral neuropathies, pathogenic pathways

THE CLINICAL AND GENETIC FEATURES

Charcot-Marie-Tooth (CMT) disease was described and named in 1886 by Charcot, Marie, and Tooth^[1,2]. Originally described as peroneal muscular atrophy, CMT is a hereditary motor and sensory neuropathy (HMSN) that primarily affects either myelin or the axon of peripheral nerves^[3]. This review is focused on CMT as well as other related genetic neuropathies, which include distal hereditary motor neuropathies (dHMN) with minimal or absent sensory involvement, and hereditary sensory and autonomic neuropathies (HSN and HSAN), with significant sensory involvement.

CMT is the most common inherited disorder of the peripheral nervous system (PNS), with an estimated prevalence of 28-40 individuals per 100,000 inhabitants, with global distribution and no ethnic predisposition^[4-6]. Individuals with CMT show symmetric, slowly progressive in a length-dependent manner, distal neuropathy of the legs and arms. CMT disease usually begins in the first to third decade of life, causing slowly progressive distal muscle weakness and atrophy, weak ankle dorsiflexion, depressed tendon reflexes, and *pes cavus* deformity^[7-11]. Other symptoms are ataxia, pyramidal signs, and hypoacusia. More aggressive phenotypes, in which the symptoms appear within the first two years of life, are characterized by hypotonia, areflexia, and ataxia that represent greater disability in patients, and in some cases, limit the patient's autonomous ambulation and can lead to significant motor disability^[12].

CMT types and classification

There is a remarkable heterogeneity in the spectrum of CMT and related disorders. In the very first instance, heterogeneity can be observed in symptomatology and severity of the disease^[3,8]. Once the symptoms are detected, ancillary tests (electrophysiologic and neuropathologic studies) help clinicians to classify patients into those with demyelinating or axonal primary involvement and, in some cases, intermediate forms^[13]. Clinical or phenotypic heterogeneity is complemented with high genetic heterogeneity^[3,14]. Since the discovery of the 1.4 Mb duplication in chromosome 17p11.2^[15,16], the number of CMT-associated genes has been increasing, and today almost 100 genes causing CMT disease and other genetic neuropathies are now known. The identification of the responsible gene and its inheritance pattern also helps the clinical practice make a correct classification of patients^[7,17]. The observed inheritance patterns include autosomal dominant, autosomal recessive, and X-linked (partially dominant and recessive) forms. However, many patients present apparent sporadic diseases, attributable to *de novo* mutations^[18].

We can distinguish two CMT neuropathies according to the type of cells primarily affected and the nerve conduction velocities (NCVs): demyelinating CMT which affects the myelin-forming Schwann cells and with NCVs below 38 m/s, and axonal CMT which affects the axons of neurons and usually presents NCVs above 38 m/s^[13,19]. Intermediate forms with overlapping demyelinating and axonal features, especially within the same family, are defined by NCVs lying between 25 and 45 m/s^[3,4,7,13]. Taking together the conduction velocity parameters and the mode of inheritance, we can stratify CMT into five different categories: demyelinating plus autosomal dominant inheritance (CMT1); axonal plus autosomal dominant or recessive (CMT2); demyelinating plus autosomal recessive (CMT4); and X-linked (dominant or recessive) (CMTX). The term CMT3 has been reserved to designate Dejerine-Sottas syndrome or neuropathy, which is a specific category related to a congenital or infantile-onset and a severe (usually demyelinating) phenotype. Further subdivision of these CMT types is based mainly on causative genes and assigned loci.

The increasing knowledge of CMT genetics and pathophysiology has led to changes in the way the different types were classified initially. Some efforts have been made to simplify its nomenclature, reducing the risk of denomination errors^[20,21], since the discovery of newly associated genes susceptible to being the cause made the classification more and more difficult. Specifically, Mathis *et al.* in 2015, opened a way for a precise denomination including: (1) the inheritance pattern; (2) the pathophysiological phenotype (by using “de” or “ax” for demyelinating and axonal forms, respectively); and (3) giving more importance to the causal gene^[21]. Based on it, CMT1A 17p11.2 duplication would be AD-CMTde-*PMP22*dup or CMT4A would become AR-CMTde-*GDAP1*^[21]. This is an informative denomination that, in fact, is helpful and understandable for both patients and clinicians. These types of proposals are an example of all the efforts that the scientific community has made to manage such a heterogeneous group of diseases^[20]. In any case, in our ambit, we still maintain the traditional nomenclature that, moreover, can be found in clinical databases such as OMIM. This is the reason this denomination is used in this review.

The molecular genetics of CMT began in 1991 with the discovery of the 1.4 Mb duplication in the short arm of chromosome 17, which contains the dose-sensitive peripheral myelin protein 22 (*PMP22*) gene, causing CMT1A and became the most common cause of genetic neuropathies^[15,22]. By 1992, point or indel mutations in *GJB1* (encoding connexin 32 [Cx32]), *PMP22*, and *MPZ* had also been discovered^[17,23]. Loci and genes for CMT and related peripheral neuropathies were initially identified using linkage studies, positional cloning, or candidate gene approaches^[22]. Since the publication of the first draft of the human genome in 2001, the development of high-throughput technologies, such as genome mapping, whole-exome sequencing, and whole-genome sequencing, have accelerated the gene and mutation discovery in CMT research^[14,23]. As the Human Genome Project reached completion, the identification of CMT genes increased markedly, so the number of genes associated with the disease has been increasing in the last years.

Currently, around 100 genes have been identified in Mendelian inheritance of genetic neuropathies. Although there are myriad gene associations and pathophysiologic mechanisms, it is clear that the mutations associated with the disease are closely related to the formation, compaction, and maintenance of myelin (*PMP22*, *P₀*, *Cx32*, *EGR2*, *NDGR1*, *PRX*, etc.), the neuronal soma, axon and cytoskeleton conservation (*NEFL*, *LMNA*, *MORC2*, etc.), the axonal transport (*RAB7*), and the mitochondrial dynamics (*MFN2*, *GDAP1*, *GARS*, *HSP22*, *HSP27*, etc.)^[3,7]. This means that, independently of the defect (metabolic, cytoplasmic, or structural) that primarily affects the myelin or axon, as well as the Schwann cell-axon structure, the axonal degenerative process is the final common pathway in neuropathies that primarily affect the largest and longest fibers^[24].

CMT genes and their corresponding proteins have been classified according to their localization in the neuron, and general information about their main biological function and proposed pathomechanisms is explained here. The well-established proteins and their proposed pathogenic mechanisms for the nerve (either in myelin or in the neuronal axon and soma) are summarized in [Supplementary Table 1](#). The code of the MIM genes (*) and their mode of inheritance are indicated together with the MIM phenotype (#) of the neuropathy caused by the pathogenic variants of the corresponding gene. Information is updated each year in the context of all neuromuscular disorders^[25].

Genetic diagnosis

Due to the high heterogeneity in terms of gene associations, the approach to the diagnosis of CMT and genetic neuropathies has evolved from a purely clinical approach in the past to a combined clinical/genetic approach. As happens in many other diseases, genetic testing can also be used on the patient and their family for predictive, antenatal, or preimplantation assessment.

Because CMT1A (*PMP22*) duplication represents 50% of CMT patients (around 70.7% of demyelinating CMT), the very first step is to analyze them by multiplex ligation-dependent probe amplification (MLPA). This is the current technique for genetic testing of the CMT1A duplication (and hereditary neuropathy with liability to pressure palsies or HNPP deletion) in postnatal and prenatal diagnosis. However, in the case of preimplantation genetic diagnosis (PGD), segregation analysis of CMT1A linked microsatellites is still a molecular technique for genetic testing. After that, if negative, different algorithms help to perform sequential testing of individual genes using Sanger sequencing^[26,27]. In this scenario, the most promising candidate gene is analyzed and, if negative, the next most likely candidate is tested. Several publications provide the scientific community with algorithms and pipelines designed to maximize efficiency when diagnosing CMT disease^[14,27].

Nevertheless, this is a very expensive and time-consuming workflow, especially in those cases where the causative gene is individually rare. With the evolution of next generation sequencing (NGS, or massive parallel sequencing) techniques, it is now possible to analyze all CMT genes by a selection of genes (panels), the exome (containing only the protein-coding sequences), or the genome, and this strategy has become the most cost-efficient approach^[14,28,29]. This means that, as technology has advanced and the cost has dropped, these approaches have replaced the traditional screening gene by gene. Therefore, NGS technologies have helped not only to identify genes in association with CMT but also to develop more efficient workflows to couple a clinical diagnosis with the genetic diagnosis.

However, some challenges remain to be solved and are responsible for deficits in the diagnostic rates. A critical issue in this two-step process (clinical exam and genetic testing) is the analysis and interpretation of genomic data generated by NGS^[29]. Depending on different criteria, geneticists have to evaluate the relationship between a variant and the described phenotype to identify causative variants. Sometimes, the chosen criteria allow them to find a variant that could be considered causative in achieving the etiological diagnosis. However, the same workflow may be inconclusive, generally because of the identification of variants of uncertain clinical significance or VUS [according to the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP)]^[30].

Treatment

Historically, inherited peripheral neuropathies have been challenging to treat. There is little specific therapy for these neuropathies other than genetic counseling as well as symptomatic treatment, physical therapy, and rehabilitation^[31,32]. This represents supportive treatment, limited to rehabilitative therapy and surgical treatment of skeletal deformities and/or abnormalities of soft tissues^[33]. There are no established disease-modifying therapies to date. In clinical practice, patients are often evaluated and managed by a multidisciplinary team that includes adult and pediatric neurologists, physiatrists, orthopedic surgeons, and physical and occupational therapists^[34].

On the one hand, these supportive treatments are usually based on rehabilitation to improve patient's posture and balance and shoe modifications, orthoses, or other assistive devices that have been shown to improve patient's walking economy^[35]. Although data are limited, there is evidence that mild to moderate exercise is effective and safe for CMT patients and that it could be interesting to consider it as a therapeutic intervention^[36]. Moreover, many different approaches have been used to treat skeletal deformities (especially of the feet) from a surgical point of view^[37].

On the other hand, different pharmacological therapies have been considered in the treatment of CMT patients. First, a symptomatic drug therapy approach can be selected: pain can be an emerging feature of

CMT (usually an osteo-arthropathic type of pain). This treatment includes physical therapy, as explained above, but also drugs (both for neuropathic and non-neuropathic pain)^[35,38,39]. Then, specific drug therapies have been considered in the CMT research, mostly those related to commonly found mutated genes^[40-43], and several experimental models have been useful to explore different approaches (Available from: <https://www.jax.org/search?q=Charcot%20Marie%20Tooth>).

Some clinical trials with pharmacologic agents aimed at reducing PMP22 expression in CMT1A patients, such as ascorbic acid, which did not improve the patient condition^[44]. After preclinical assays in a CMT1A rat model, the progesterone receptor antagonist onapristone was discarded because it was not safe in humans^[45]. Recently, high-dose PXT3003 (baclofen/naltrexone/D-sorbitol) has demonstrated significant therapeutic effects in patients with CMT1A and has emerged as a promising treatment option^[46]. HDAC6 inhibitors have shown positive effects on axonal defects in mouse models of several forms of CMT^[47-49], opening a new window in the pharmacological treatment of CMT disease^[50,51]. Antioxidant therapy with either the veterinary antibiotic florfenicol or mitoQ has also shown effectiveness in a knockout model of *GDAP1*-related CMT when starting administration very early in mouse life, but not in older mice^[52]. Gene therapy research in animal models is becoming more relevant. AAV9-mediated Schwann cell-targeted gene therapy of *Gjb1*-null mouse improves motor performance and sciatic nerve conduction velocities along with improved myelination and inflammatory processes in peripheral nerve tissues^[53]. Therefore, much work remains to be done for the treatment of CMT. The discovery of cellular mechanisms underlying the disease pathophysiology opens new options for preclinical studies searching for new treatments that include drug repositioning^[52]. An in-depth overview of current research in the pharmacological and biological treatment of CMT neuropathies is beyond the scope of this review. The current status of therapeutic investigations and ongoing clinical trials in CMT disease and genetic neuropathies was recently reported by Pisciotto *et al.*^[50]. In [Table 1](#), we summarize the mechanisms of action and the type of therapies and compounds that may be useful or indicated in the future treatment of CMT disease. Most candidate therapies are based on an understanding of disease mechanisms and affected pathways in cellular pathophysiology. In the next section, we address the pathogenic mechanisms involved in the different types of CMT neuropathies.

PATHOGENIC MECHANISMS AND NERVE PATHOPHYSIOLOGY

CMT and related diseases constitute a very heterogeneous group of disorders. From clinical to genetic diagnosis, variability among patients is very high and pathogenic mechanisms involve Schwann cell and neuron/axon pathways. [Figure 1](#) and [Supplementary Table 1](#) provide information on CMT genes and illustrate the cellular and molecular mechanisms that compromise the nerve physiology, either in the myelin sheath or the neuron soma and axon.

The following sections explain, in more detail and alphabetical order, the pathogenic mechanisms related to the genes that most frequently constitute the genetic cause of CMT. Together with this detailed description, [Table 2](#) summarizes this information and correlates with [Figure 2](#), which illustrates in detail the subcellular localization of the proteins and the mechanisms and pathways affected by the pathogenic variants.

GDAP1

Among the most commonly involved genes in the pathogenesis of CMT, we can find *GDAP1*. This gene encodes ganglioside-induced differentiation-associated protein 1 (GDAP1), which is an atypical glutathione S-transferase (GST)^[54] with glutathione-conjugating and membrane-remodeling functions^[55]. This protein can be found in the outer mitochondrial membrane (OMM) and the mitochondria-associated membranes (MAMs), and it is mainly expressed in neurons^[56-58].

Table 1. CMT therapeutics: target cell processes and pathways and drug strategies

Cell process or mechanism of action	Compound/therapeutic strategy
Reduction of gene expression	Ascorbic acid
Reduction of protein synthesis	Progesterone antagonists and modulators
Inhibition of Schwann cells proliferation and reduction of protein synthesis (baclofen: GABA _B receptor modulator)	PXT3003 (baclofen, sorbitol, naltrexone)
Partial silencing of gene expression	Gene silencing
Gene insertion (AAV1-NT3)	Gene therapy
Gene substitution	
Regulation of myelin thickness	Neuregulin pathways
UPR inhibition	Curcumin, sephin-1
TRPA1 and TRPV1 channels activation	FLX-787
Prevention of axonal degeneration	SARM1 inhibitors
Reduction of microtubules acetylation (axonal transport)	HDAC6 inhibitors
Myostatin pathway	ACE-083
Reduction of abnormal calcium influx in Schwann cells	P2X7 receptor modulators
Correction of defective lipid biosynthesis	Dietary lipid supplementation
Nav 1.8 channel blocking	Sodium channel blockers
Decreased number/activity of macrophages in the nerve	CSF1R inhibitors
PIKfyve inhibition and decrease of PI3,5P2 levels	PIKfyve enzyme inhibitors
Reduction of neurotoxic deoxysphingolipids	L-Serine
Purine nucleotides supply	S-adenosylmethionine (SAM)
Inhibition of aldose reductase	Aldose reductase inhibitors

GABA_B: Gamma-aminobutyric acid B receptor; AAV1-NT3: adeno-associated virus-mediated neurotrophin-3; UPR: unfolded protein response; TRPA1: transient receptor potential cation channel, subfamily A, member 1; TRPV1: transient receptor potential cation channel subfamily V member; SARM1: sterile alpha and TIR motif-containing 1; HDAC6: histone deacetylase 6; CSF1R: colony-stimulating factor 1 receptor; PIKfyve: phosphatidylinositol 3-phosphate 5-kinase. Summarized information in this table was extracted from Pisciotta *et al.* (2021)^[50].

The scenario of *GDAP1* mutations is quite different from other CMT disease-causing genes due to its heterogeneity: mutations in this gene have been related to axonal forms (AR-CMT2K with vocal cord paresis (CMT2K), an intermediate form (CMTRIA), and a demyelinating (CMT4A) form of the disease. Both recessive and dominant modes of inheritance have been reported^[56]. To date, more than 100 mutations in *GDAP1* gene have been related to CMT phenotype^[59].

Clinically, CMT caused by mutations in this gene is characterized by severe distal motor and sensory neuropathy. Nevertheless, a diverse spectrum of phenotypes should be considered due to the variability in inheritance patterns^[56,60,61]. It has been proposed that, while autosomal recessive mutations are responsible for early-onset and severe neuropathies, dominant mutations cause a milder course of the disease^[62]. Regarding the histological abnormalities, the sural nerve biopsy of severe affected segregating the disease in an autosomal recessive manner shows a pronounced depletion of myelinated fibers, regenerative clusters and signs of axonal atrophy. Additionally, a small proportion of thin myelinated fibers and proliferation of Schwann cells forming onion bulb structures have also been found. The most relevant cytoplasmic feature would be the mitochondrial abnormalities^[63].

Although the explicit molecular mechanism underlying the *GDAP1* function remains unclear, several studies have explored its role in mitochondria physiology: morphology, function, and dynamics^[59]. Firstly, the consequence of *GDAP1* mutations can impair these mitochondrial functions through mitochondrial membrane potential reduction, ATP production changes, or a disbalance of their dynamics^[57,64,65]. Second, *GDAP1* may also interact with transport proteins involved in mitochondrial transport and movement.

Table 2. Most common CMT genes: inheritance, phenotype, and cell pathophysiology

Gene	OMIM (*)	Mol	Phenotype neuropathy type			OMIM (#)	Localization		Protein function/pathway	Disrupted process
			A	D	I		Schwann cell	Soma/axon		
Most commonly involved genes										
GDAP1	606598	AR AD	√	√	√	AR-CMT2K CMT2K CMT4A	607706 607831 214400	√	Mitochondria fission	Mitochondria
GJB1	304040	XL	√	√	√	CMTX	302800	√	Cx32: gap junction formation + myelin assembly and transport	Channel
HINT1	601314	AR	√			Neuromyotonia Axonal neuropathy	137200	√	Modulation of transcriptional activity	Nuclear envelope, mRNA processing
MFN2	608507	AR AD	√			CMT2A2A CMT2A2B CMT6A	609260 617087 601152	√	Mitochondrial fusion	Mitochondria
MPZ	159440	AD	√	√	√	CMT1B DI-CMTD CMT2I CMT2J	118200 607791 607677 607736	√	Myelin assembly	Myelin assembly
PMP22	601097	AD	√			CMT1A CMT1E	118220 118300	√	Myelin assembly	Myelin assembly
SH3TC2	608206	AR	√			CMT4C	601596	√	Targets to intracellular endosome recycling	Endosomal sorting and cell signaling
SORD	182500	AR	√	√		Peripheral neuropathy	618912	√	Polyol pathway	Polyol pathway (cytosolic)

Mol: Mode of inheritance; A: axonal; D: demyelinating; I: intermediate; AR: autosomal recessive; AD: autosomal dominant; XL: X-linked; CMT: Charcot-Marie-Tooth; DI: dominant intermediate. Information about genes and protein functions was extracted from databases such as OMIM (Available from: <https://www.omim.org/>), GeneCards (Available from: <https://www.genecards.org/>), Reactome (Available from: <https://reactome.org/>), and UniProt (Available from: <https://www.uniprot.org/>). *indicates the OMIM number entry associated to the gene; # indicates the OMIM number entry associated to the disorder.

Therefore, the alteration of this process could be an explanation for the axonal loss that can be seen in CMT patients carrying *GDAP1* mutations^[56]. Finally, the recently established relationship between *GDAP1* and mitochondrial-associated membranes (MAMs) would support the idea that *GDAP1* mutations could affect the formation and functioning of the ER-mitochondria contacts^[66]. This would explain the alteration of store-operated Ca²⁺ entry (SOCE) and calcium homeostasis, together with mitochondrial dynamics and transport, too. On the other hand, recent studies have shown that *GDAP1* participates in membrane contact sites (MCSs) between the mitochondria and the lysosome, supporting the idea that *GDAP1* enables the proper function of mitochondrial MCSs^[62,67]. Finally, it has been reported that it also influences the structure and probably the function of the Golgi apparatus^[59]. In addition, functional studies have characterized the phenotype derived from *GDAP1* mutations. As expected, these include the disruption of mitochondrial fission-fusion events, changes in mitochondrial distribution, impairment of the mitochondrial membrane potential, increases in the concentration of reactive oxygen species, reductions in glutathione content, and alteration in the bioenergetics of mitochondria^[57,64,65,68-71].

GJB1

The X-linked form of Charcot-Marie-Tooth disease (CMT1X) is the second most common form of HMSN^[13,72,73] and accounts for 90% of all CMTX cases^[74]. This form of the disease is caused by mutations in *GJB1* gene, which encodes the gap junction protein connexin32 (Cx32). *GJB1* disorders are typically characterized by peripheral motor and sensory neuropathy with or without fixed central nervous system abnormalities and/or acute, self-limited episodes of transient neurologic dysfunction^[75]. Peripheral neuropathy typically manifests in affected males between ages 5 and 25 years. Although both men and

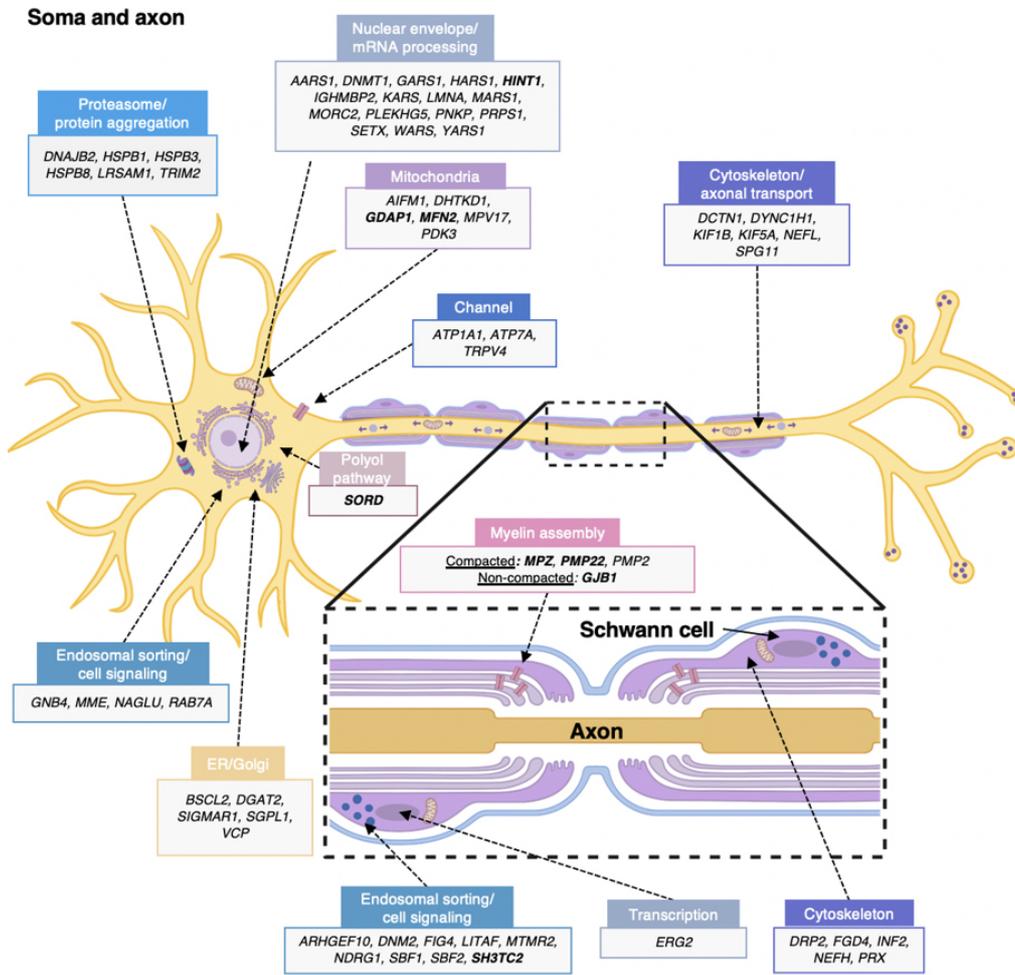


Figure 1. Schematic summary of genes causing CMT hereditary neuropathy. Gene products are assigned either to the neuron body and axon or to the myelinating Schwann cell (cross-sectional view in box). Proteins are classified according to their main functions or pathways and their proposed pathomechanisms in CMT. The most commonly involved genes are indicated in bold. More information about each gene and/or protein is available in [Table 2](#) and Supplementary Table 1. ER: Endoplasmic reticulum. Illustration created with BioRender (Available from: <https://biorender.com/>).

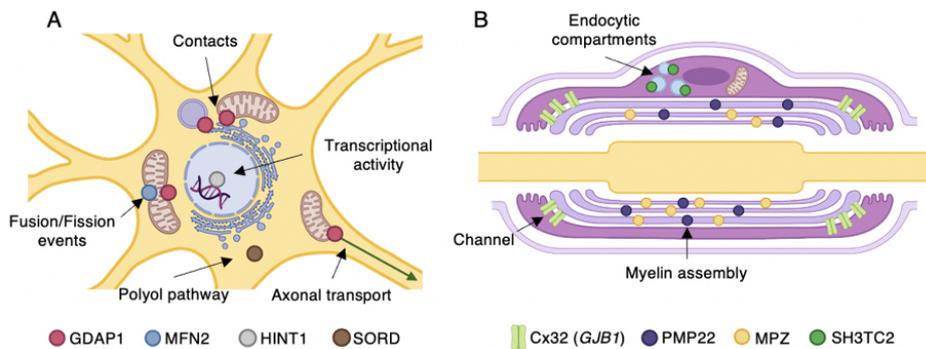


Figure 2. Most common CMT-associated genes and their proposed pathomechanisms. Subcellular localization and the main functions of gene products are indicated. (A) Diagram showing a neuron soma. (B) A myelinating Schwann cell. Illustration created with BioRender (Available from: <https://biorender.com/>).

women are affected, males have moderate to severe symptoms, while heterozygous females may remain asymptomatic or may have mild CMTX1, being the skewed X-inactivation the likely explanation for the reduced severity. It should be noted that in those cases where women are severely affected, the most promising explanation is the non-random X-inactivation in each myelinating cell^[76].

It should be noted that the nerve conduction velocities in patients with CMT-*GJB1* are in the intermediate range: faster than in patients with the demyelinating forms (CMT1) and slower than axonal/neuronal forms (CMT2); however, in female cases, NCVs are often preserved. Moreover, median nerve conduction appears to be generally more severely affected than those of the ulnar nerve^[77,78]. Finally, in nerve biopsies, the most prominent finding is the increasing number of regenerated axon clusters, together with an age-related loss of myelinated fibers^[79].

The *GJB1* gene encodes a member of a large family of connexins. Specifically, *GJB1* encodes connexin 32, a protein that is remarkably present in Schwann cells and oligodendrocytes, which are the myelinating glia of the peripheral and central nervous systems, respectively^[74]. This explains why patients with CMT1X can have both central and PNS manifestations.

Six connexins molecules form a hemichannel, arranged around a central pore. Two of these hemichannels form a gap junction channel, allowing the formation of a link between two cells. Tens to thousands of these connexin channels are localized along the cell membrane, creating what is known as gap junction plaques^[72]. Thanks to these channels, ions, signaling molecules, and/or small metabolites can diffuse between cells, helping them to couple in electrical and chemical ways, between other functions^[74]. In Schwann cells, Cx32 is localized to the non-compact myelin of the paranodes and Schmidt-Lantermann incisures, where it forms gap junctions between adjacent loops of non-compact myelin, predicted to provide a radial diffusion pathway^[80-85]. This means that, in Schwann cells, Cx32 forms a reflexive pathway between the abaxonally located nucleus of the Schwann cells and the adaxonal region^[80].

Since the first report that mutations in *GJB1* cause CMT1X, more than 400 mutations were predicted to impact protein function. Many of them could be predicted to cause loss-of-function effect, although the mechanisms could differ: nonsense or frameshift mutations that affect the N-terminal part, mutations that affect the promoter region^[86,87], or large deletions involving the entire coding region of the gene would not be expected to produce functional channels^[88].

The biological mechanisms by which the different mutations can lead to this total or partial loss of function are diverse: reduction of the minimal luminal dimension (that would affect the diffusion of specific small molecules)^[89], increasing sensitivity to acidification-induced closure, or stabilization of the closed state of the channel^[90] are some examples of the biophysical alterations that have been explored. Moreover, it has been analyzed how the junctional coupling can be affected by mutations in this gene, due to reduced steady-state levels of the protein^[90].

Although the most common pathogenic mechanism of *GJB1* mutations is this loss-of-function, some studies have reported gain-of-function mechanisms of some Cx32 mutants^[91]. Overall, clinical studies suggest that the peripheral manifestations of CMT1X are likely to be due to loss-of-function, while in the central nervous system gain-of-function may contribute^[80].

HINT1

In 2012, the histidine triad nucleotide-binding protein 1 gene (*HINT1*) was identified in recessive forms of axonal CMT (accounting for 10% of recessive CMT patients). At that time, it was reported that around 80% of patients carrying *HINT1*-causative variants showed neuromyotonia^[92]. This phenotypic sign guided the clinical diagnosis of these cases, and it was considered that *HINT1*-associated peripheral neuropathy represented a distinct clinical and genetic entity that needed to be differentiated from other CMT types^[93] described as axonal, motor-greater-than-sensory polyneuropathy with a childhood-onset, combined with neuromyotonia^[92,94-96]. However, the identification of more patients and/or causative mutations extended the clinical spectrum. From the histological point of view, sural nerve biopsies of some reported cases showed axonal neuropathy, even in the absence of clinical sensory abnormalities.

Interestingly, *HINT1* has a non-random geographic distribution of patients. The majority of causative mutations are found in Central and Eastern European individuals^[97], and this has been attributed to three different founder mutations, p.Arg37Pro, p.Cys84Arg, and p.His112Asn.

HINT1 encodes a member of the histidine triad (HIT) protein family. Specifically, it is a globular protein that acts as a homodimer and binds purine nucleosides and nucleotides. Both its HIT motif and C-terminal loop are essential to establishing nucleotide contacts and maintaining substrate specificity^[98], respectively. Furthermore, dimerization is required to maintain catalytic activity^[98]. Several studies have reported that *HINT1* mutations cause a loss-of-function effect through several mechanisms. For instance, they can affect critical residues for catalytic activity, they can be related to nonsense mediated decay of mRNA, or they can cause protein instability and, consequently, proteasome-mediated degradation^[92].

MFN2

CMT type 2A is the most common axonal form of CMT and is caused almost exclusively by mutations in the *MFN2* gene^[99]. This type of CMT is characterized by peripheral neuropathy that can also involve the central nervous system^[100]. Mutations in *MFN2* usually have an autosomal dominant pattern of inheritance, but, occasionally, *MFN2* mutations can be recessive or even semidominant.

About 100 mutations in *MFN2* related to CMT2A2 have been described^[101], but the exact relationship between the genotype and the phenotype of *MFN2* patients remains to be clarified. Interestingly, a childhood onset of autosomal dominant CMT2A2 is the most predictive marker of significant disease severity^[102]. In general, in comparison to demyelinating CMT1A, axonal CMT2A2 is more severe and shows a motor-predominant phenotype that usually carries a greater burden of disability^[103,104]. *MFN2* neuropathy can also be associated with sensorineural hearing loss, optic atrophy, and, in some cases, cerebellar atrophy, spastic paraparesis, and cognitive deficits.

Mitofusin-2 and -1 are homologous proteins, members of a mitochondrial transmembrane GTPase family. They show ubiquitous expression in eukaryotic cells, where they play a role in the dynamic mitochondrial remodeling process^[102]. Both of them are known to play a critical role in the mitigation of mitochondrial stress, helping to maintain mitochondrial “quality control” and facilitate apoptosis if necessary (under severe cellular stress)^[105].

Mitofusin-2 has two main functions: the promotion of mitochondrial fusion and the mediation of endoplasmic reticulum (ER)-mitochondrial tethering at mitochondria-associated ER membranes (MAMs)^[106-108]. MAMs are essential to regulate key cellular functions regarding lipid and calcium homeostasis^[106,109-111], as well as mitochondria dynamics and bioenergetics. In addition, it has been shown

that MFN2, similar to GDAP1, is a tethering protein between mitochondria and lysosomes^[67]. Studies to shed light on the pathophysiology of *MFN2* mutations have been performed in nervous tissues and fibroblasts from patients, as well as in mice and motor neurons derived from induced pluripotent cells (iPSCs) obtained from fibroblasts. However, the results are quite controversial since some of the changes can only be observed in some studies but do not extend to all of them: for instance, there is still little agreement regarding whether there are alterations in *MFN2* protein levels, in the respiratory chain capacity and oxidative phosphorylation, in mitochondrial membrane potential, or mtDNA content^[101,112-114].

Most missense variants reside within MFN2 dynamin-GTPase domain^[115,116], and there is recent evidence that a dominant-negative or gain-of-function effect may be responsible for the pathogenicity. Other evidence shows that some variants are responsible for mitochondrial hypofusion, while others can cause mitochondrial hyperfusion^[117]. Moreover, as explained above, autosomal recessive and semidominant forms of CMT2A2 have been reported. This further illustrates the allelic heterogeneity of this condition^[118].

Even with differences between studies, it is clear that there are mitochondrial abnormalities in *MFN2* patients. Mitofusin-2 represents a key player in several mitochondrial activities: fusion, trafficking, turnover, and contacts with other organelles and the consequences of mutations in the *MFN2* gene disbalance the appropriate mitochondrial shape, function, and distribution within the cell^[119]. Alterations in mitochondrial transport and distribution likely cause a bioenergetics impairment, especially in highly metabolic cells, which is the case for neurons. These disrupted and affected processes lead to a loss of myelinated fibers and mitochondrial abnormalities, visible in nerve biopsies.

MPZ

Mutations in *MPZ* commonly result in autosomal dominant neuropathy and are estimated to account for 5% of cases of CMT^[26]. In this gene, the phenotypical heterogeneity that can be found is remarkable, in regards to both the severity of the symptoms and the neurophysiological parameters.

Myelin protein zero (P₀), which is part of the immunoglobulin gene superfamily, is a major peripheral protein that acts as a homophilic adhesion molecule and is crucial for compact myelin formation and maintenance in the PNS^[120]. It is the most abundant myelin protein produced in myelinating Schwann cells. It has been related to CMT and can cause the three different types of the disease: demyelinating, axonal, and intermediate forms. Consequently, individuals carrying *MPZ* mutations have a variety of clinical phenotypes, from severe disease with early onset of weakness and sensory loss in the neonatal period associated with very low NCVs (Dejerine-Sottas syndrome) to a much milder disease with onset of symptoms in the fourth decade of life with minimal slowed NCVs (CMT2). However, variability also exists, since late-onset patients can be quite severe, too (even confined to a wheelchair), and onset can last until the eighth decade of life. In nerves, signs of demyelination/remyelination with myelin outfoldings and onion bulb formations are the most characteristics features.

The structure of P₀ is divided into three different domains: extracellular, transmembrane, and cytoplasmic domains. Interestingly, most of the described mutations can be found in the extracellular part, which is essential for establishing interactions. P₀ forms homotetramers within the cell membrane: each homotetramer interacts *in trans* with a similar homotetramer on the opposing membrane surface. Furthermore, P₀ tethers appose lipid bilayers together through its extracellular immunoglobulin-like domain^[121]. This is the reason it was proposed as having a key role in myelination, as P₀ holds together adjacent wraps of myelin membrane through these homotypic interactions. Not only the extracellular part is essential to establish these interactions, but also the cytoplasmic domain, as has been shown in different

studies^[122]. P₀ participates in an adhesion-mediated signal transduction cascade, which even further supports its essential role in myelination.

As mentioned above, from the clinical point of view, *MPZ* mutations have been linked to both infantile and late onset of the disease, and some reports have proposed that early-onset neuropathy is related to mutations that disrupt the tertiary structure of P₀ and, thus, interfere with P₀-mediated adhesion and myelin compaction, while late-onset neuropathy is caused by those that more subtly alter myelin structure, probably disrupting Schwann cell-axonal interactions^[122]. This suggests that *MPZ* mutations that predominantly affect myelination during development cause early-onset disease, while those that affect axons cause late-onset disease.

Although the exact mechanism by which mutations in *MPZ* can lead to CMT disease is unknown, mutated P₀ has been linked to the unfolded protein response (UPR), which would cause defects in translation rate, folding, and/or membrane insertion. Furthermore, misfolded protein toxicity or reduced amounts of P₀ could be the etiology behind the phenotypic manifestations in patients carrying *MPZ* mutations^[121]. Given that P₀ is known to interact with lipid membrane surfaces^[123,124], mutations within P₀ could also have direct effects on the formation of mature compact myelin at a molecular level^[125].

Although a complete genotype/phenotype relationship has not been established, it is clear that two groups of disease expressions can be delineated to classify the more than 200 different disease-causing mutations that have been reported in *MPZ* until today.

PMP22

The *PMP22* gene has been linked to CMT since the beginning of the genetic findings in this disease, and to different phenotypic neuropathies since three mechanisms can lead to different disorders: (i) *PMP22* overdose within CMT1A duplication causes the most common cause of the disease; (ii) point mutations of *PMP22* may be the underlying cause of more severe and early-onset forms, CMT types 1A or 1E; and (iii) the monoallelic lack of *PMP22* at 17p11.2 as a consequence of the 1.4 Mb deletion in the CMT1A locus^[126] or point pathogenic variants^[127] can lead to hereditary neuropathy with liability to pressure palsies (HNPP). As explained above, the overall prevalence of CMT is 1:2500, where 1:3800-12,500 corresponds to CMT1A^[128-130].

The consequence of the 1.4 Mb CMT1A duplication or HNPP deletion is the expression of three copies or one copy, respectively, of dose-sensitive *PMP22*. Thus, gene dosage has been the proposed pathological mechanism, supported by the finding of increased protein and mRNA levels in CMT1A sural nerve biopsies. Since *PMP22* gene is under tight regulation, small changes can be expected to cause defects in myelination and motor and sensory functions^[131]. Furthermore, regulation of *PMP22* expression also occurs during protein synthesis and translocation. From a histological point of view, *PMP22* mutations are characterized by onion bulb formations (CMT1A duplication) or tomaculae (HNPP deletion). A reduction of myelinated fibers with signs of demyelination can be observed as a consequence of the functional impact on *PMP22* protein.

PMP22 encodes a 22 kDa glycoprotein produced primarily in Schwann cells and comprises 5% of proteins of the PNS myelin^[131]. It is expressed in the compact portion of essentially all myelinated fibers in peripheral nerves. It has been proposed as a key role player during Schwann cell growth and differentiation^[130]. Nevertheless, the exact biological function is not clear yet. Proper folding and regulation of *PMP22* are essential for myelinating Schwann cells. Additionally, *PMP22* promotes the organization of membrane

structure in compact myelin, plays a role in the maintenance of cholesterol homeostasis in Schwann cells, and is involved in adhesion and cell proliferation^[131]. Finally, *PMP22* point mutations are known to disrupt *PMP22* plasma membrane trafficking, resulting in misfolded proteins that are targeted by the ER, associated with degradation for clearance. As this process is not 100% efficient, there is an accumulation of the misfolded protein, which produces cellular stress^[131].

It is important to remark that, apart from *MPZ* mutations, *PMP22* mutations can be the cause of Dejerine-Sottas syndrome, which occurs in the first two years of life^[132].

Since this gene has been studied from the very beginning of genetic analysis in CMT, the knowledge around it has been sufficient to design several drugs and/or therapeutic approaches, with the objective of regulating its expression levels.

SH3TC2

SH3TC2 is associated with autosomal recessive demyelinating CMT type 4C (CMT4C)^[133]. This type of CMT shows an early onset, characterized by unsteadiness, distal weakness, occasional cranial nerve involvement (hearing loss, pupillary abnormalities, and/or tongue atrophy), and foot and spinal deformities^[134,135]. Traditionally, these features have been explained by the important sensory loss inherent to this type of CMT. However, the important vestibular impairment that was confirmed in previous depth characterizations of CMT4C patients should also be mentioned^[134]. *SH3TC2*-related CMT cases are not distributed randomly, and several studies have shown substantial differences between countries^[132,133,136]. Specifically, *SH3TC2*-causative variants have been proven to have a high prevalence in Spanish Gypsy cohorts of patients^[137].

SH3TC2 encodes an effector molecule of Rab11, which is found in myelinating Schwann cells and expressed late during myelination, thus is essential in the maintenance of the structural integrity of peripheral nerve myelin sheaths^[133]. To date, more than 70 mutations in this gene have been reported (dispersed throughout the protein) and proven to influence the peripheral nerve pathophysiology. Specifically, *SH3TC2* participates in the endocytic pathway of cell traffic, and, therefore, it can be found in clathrin-coated vesicles (including the trans-Golgi-network, early and late endosomes, and specific domains of the plasma membrane). This localization is dependent on protein myristoylation and interactions, for which both its SH3 and TRP domains are essential^[138]. Furthermore, evidence has been presented on its role in the Nrg1/ErbB signaling pathway during early postnatal development of the PNS, suggesting that CMT4C patient's hypomyelination may be explained, at least in part, as a consequence of the dysregulation of this signaling pathway^[139]. As a consequence of these molecular abnormalities, in biopsies of *SH3TC2*-patients, concentric Schwann cell proliferation with multiple small onion bulbs can be observed, with the involvement of unmyelinated fibers.

SORD

Sorbitol dehydrogenase gene (*SORD*) has recently been identified as a causative gene of recessive forms of hereditary neuropathy, both CMT type 2 and distal hereditary motor neuropathy (dHMN)^[140]. This gene encodes a protein that acts as a key enzyme in the polyol pathway, which is an alternate route for sugar metabolism^[141]. *SORD* catalyzes the interconversion between glucose and fructose via sorbitol, together with aldose reductase. Due to that, this protein is believed to be involved in the development of diabetic neuropathy^[141].

The historical deficit in the diagnostic rate of *SORD* cases is a consequence of *SORD2P*, a *SORD* pseudogene. The homology between them is quite high, with an identity of 2295 out of 2320 bases, with three gaps. Pseudogenes are usually not actively transcribed or translated, and they can be recognized by the presence of nonsense mutations or a frameshift that interrupts the open reading frame^[142].

Biallelic mutations in *SORD* gene were initially described in May 2020 and, until now, 14 mutations have been identified^[141]. Among them, the most prevalent mutation is c.757delG, which is common to all the reported patients (either in homozygous or heterozygous states, except for one patient with dHMN). Among these 14 variants, most are frameshift or splicing mutations causing a loss of function of sorbitol dehydrogenase.

Some studies have found a complete loss of *SORD* protein and increased intracellular sorbitol levels in fibroblasts derived from patients. Some inhibitors of aldose reductase led to the rescue in *Drosophila* of synaptic degeneration and motor deficiency caused by *SORD* orthologs deletion^[141]. However, the exact mechanism that produces the axonal damage that can be seen in *SORD* cases has not been elucidated yet. Mechanisms such as the increase of sorbitol levels, cellular osmolarity, oxidative stress, and the decrease of NADPH levels have been proposed as responsible for the phenotype^[141]. Few data on nerve pathology are available. Recently, Chen *et al.* (2022) described the neuropathology in the sural nerve of a 25-year-old woman with dHMN phenotype, which confirmed slight changes, including thin myelin sheath fibers and separation from the myelin sheath in very few fibers^[143]. These authors identified microvascular basement membrane thickening, something that has also related to diabetic neuropathy.

In a clinical setting, some efforts should be made to reanalyze those undiagnosed patients suffering from hereditary axonal neuropathies since it has been proven that *SORD* might play an important causative role. The recognition of the biallelic variants in this gene would help to increase the diagnostic rates of autosomal recessive and axonal types of neuropathies^[144].

To check *SORD*-related CMT cases, it is important to consider three different aspects: (1) the clinical homogeneity of cases with an onset in the second or third life decade and axonal neuropathy with distal muscle weakness and atrophies; (2) the c.757del variant, which is common and facilitates genetic screening; and (3) if direct analysis of this gene is selected, the primers should be designed with special attention to discriminate *SORD* and *SORD2P*. Furthermore, in the case of NGS techniques, an optimization of the analysis pipeline should be considered, selecting proper parameters, especially regarding alignment settings^[144].

Although we are far from understanding the exact mechanism of pathogenesis of *SORD* variants, there is no doubt that this gene is a key role player in axonal neuropathies. The analysis of its sequence should help to reduce the diagnostic deficit in cohorts of neuropathic patients.

CONCLUSION

Over the last decades, there have been significant advances in deciphering the genetic causes of CMT disease. The number of genes associated with this peripheral neuropathy increased markedly, and improvements have been made in the genetic diagnosis. To manage such a heterogeneous group of disorders, it is essential to make a correct classification of its different types and elucidate which is the particular mechanism that underlies the pathological effect of the variants in the associated genes. Thanks to the efforts made to characterize them, it is clear that CMT-associated genes are closely related to the formation, compaction, and maintenance of myelin, the neuronal soma, axon and cytoskeleton

conservation, the axonal transport, and the mitochondrial dynamics. As a consequence, a degenerative axonal process can be expected as the final common pathway in genetic neuropathies, regardless of the metabolic/cytoplasmic/structural defect underlying the affection of either the myelin, the axon, or the Schwann cell-axon structure. In the case of the most commonly involved genes, such as *GDAP1*, *GJB1*, *HINT1*, *MFN2*, *MPZ*, *PMP22*, *SH3TC2*, and *SORD*, a more in-depth analysis is carried out in this review to shed light on the pathophysiological mechanisms. This has proven to be useful in pinpointing molecular targets, thereby helping to identify and design therapeutical approaches. In conclusion, although nowadays we lack disease-modifying treatments, increasing knowledge on the molecular basis of CMT will help to reach them, which poses a promising future.

DECLARATIONS

Authors' contributions

Made substantial contributions to concept, design and writing of the review: Estévez-Arias B, Carrera-García L, Nascimento A, Cantarero L, Hoenicka J, Palau F

Performed critical revision of the manuscript for important intellectual content and approved the final version: Estévez-Arias B, Carrera-García L, Nascimento A, Cantarero L, Hoenicka J, Palau F

Availability of data and materials

Not applicable.

Financial support and sponsorship

This work was supported by the Agencia Estatal de Investigación (Spanish Ministry of Science and Innovation) grant PID2020-114655RB-I00; the CIBERER-ACCI 2019-16; the Generalitat de Catalunya and European Regional Development Fund grants 2015 FEDER/S21, and 2017/SGR1308; the Fundación Isabel Gemio and the Torró Solidari-RAC1 i Torróns Vicens. The Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER) is an initiative of the Instituto de Salud Carlos III, and the Department of Genetic Medicine of Sant Joan de Déu Children's Hospital is part of the Centre Daniel Bravo de Diagnòstic i Recerca de Malalties Minoritàries.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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