Clinical and genetic aspects of Charcot-Marie-Tooth disease subtypes

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ABSTRACT

Charcot-Marie-Tooth disease (CMT) is one of the most common inherited neuropathies and is both genetically and clinically heterogeneous, with variable inheritance modes. With regard to clinical and genetic aspects, CMT is divided into several subtypes, including CMT1, CMT2, CMT3, CMT4, CMT5, CMT6, X-linked CMT, and intermediate CMT. Up to date, more than 90 causative genes for CMT have been identified. Furthermore, previous animal studies reported some molecules to have therapeutic effects on specific CMT subtypes, depending on the underlying genetic cause. Therefore, accurate genetic diagnosis is of crucial importance when performing customized therapy. Finally, recent investigations on induced pluripotent stem cells expanded the possibility of both patient-specific cell therapy and drug discovery. The current review focuses on the latest classification updates for accurate CMT diagnosis.

Keywords: Charcot-Marie-Tooth disease; Classification; Diagnosis; Genes; Mutation

INTRODUCTION

Charcot-Marie-Tooth disease (CMT) is the most common form of inherited peripheral neuropathy, with a prevalence of one in 2,500 people [1]. CMT patients usually present muscle atrophy, sensory loss, foot deformities, and areflexia [2,3]. However, CMT is a clinically and genetically heterogeneous disease, and some subtypes reveal unusual clinical features, including pyramidal features, vocal cord paralysis, hearing loss, or optic atrophy [4]. Furthermore, CMT is divided into three categories based on its pathology, namely demyelinating, axonal, and intermediate neuropathy [5,6]. Intermediate CMT neuropathy was reported to be characterized by both demyelination and axonal degeneration in peripheral nerve biopsies [7]. Demyelinating and axonal CMT neuropathy can be generally distinguished by assessing the median motor nerve conduction velocity (NCV), which is lower and higher than 38 m/sec, respectively [5,6]. Intermediate neuropathy usually ranges from 30 to 40 m/sec [7]. As more than 90 causative genes for CMT were found up to date, this disease is categorized into numerous subtypes [8-10]. In this review, the latest updates on the CMT subtypes and their clinical and genetic aspects were described, including Charcot-Marie-Tooth disease type 1 (CMT1), type 2 (CMT2), type 3 (CMT3), type 4 (CMT4), type 5 (CMT5), type 6 (CMT6), X-linked CMT (CMTX), and intermediate CMT.
CLASSIFICATION OF CHARCOT-MARIE-TOOTH DISEASE

Charcot-Marie-Tooth disease type 1
CMT1 is a group of autosomal dominant demyelinating peripheral neuropathies characterized by distal weakness and atrophy, sensory loss, foot deformities, and slow NCV. The peripheral myelin protein 22 (PMP22), myelin protein zero (MPZ), early growth response 2 (EGR2), lipopolysaccharide-induced tumor necrosis factor (TNF)-alpha factor (LITAF), and neurofilament light (NEFL) are known as causative genes (Table 1). The age of onset of CMT1 greatly varies, ranging from infancy to the fourth or subsequent decades of life. Although patients usually have their first symptoms between their first and the second decade of life, the several other clinical manifestations may appear later. Furthermore, its clinical severity is also variable, fluctuating between an extremely mild form of the disease, which remains unrecognized, to a considerably serious form, which is associated with weakness and disability. Affected individuals typically

Table 1. Mutations of the demyelinating Charcot-Marie-Tooth neuropathy subtypes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Gene</th>
<th>Locus</th>
<th>Heredity</th>
<th>Protein</th>
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<td>AD</td>
<td>Lipopolysaccharide-induced tumor necrosis factor-alpha factor</td>
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<td>EGR2/Krox20</td>
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<td>AD</td>
<td>Early growth response 2</td>
</tr>
<tr>
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<td>Neurofilament light polypeptide</td>
</tr>
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<td>AR</td>
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<td>FYVE, RhoGEF, and PH domain-containing protein 4</td>
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<td>SURF1</td>
<td>9q34.2</td>
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AD, autosomal dominant; AR, autosomal recessive; EGR, early growth response.
develop distal weakness, symmetric atrophy of muscles (mainly peroneal), and reduced-to-absent tendon reflexes. Additionally, sensory deficits of position, vibration, and pain/temperature commonly occur in patients’ feet and, at a later stage, hands. Finally, pes cavus with hammer toes is frequently present since childhood, and variable scoliosis may develop during adolescence.

**CMT1A**

CMT1A is caused by a duplication of the *PMP22* gene, which encodes the *PMP22*, or a mutation in such a gene. The inheritance is autosomal dominant [11,12]. PMP22, a 22 KDa protein, constitutes 2% to 5% of the peripheral nervous system (PNS) myelin being initially produced by Schwann cells and it is expressed in the compact portion of all the PNS myelinated fibers. The CMT1A caused by the duplication of the 17p11.2 site with the *PMP22* is the most common form of CMT and accounts for 60% to 70% of the demyelinating CMT patients (approximately 50% of all CMT cases). CMT1A usually occurs before the age of 20. It usually begins in patients’ feet and legs, and upper limb involvement also follows at a later stage. CMT1A is characterized by a slow progression, insidious onset, variable severity, and genetic heterogeneity. Allelic disorders with overlapping phenotype include the Dejerine-Sottas syndrome (DSS), hereditary neuropathy with liability to pressure palsies (HNPPs), and CMT with deafness. The main symptoms comprise muscle weakness, muscle atrophy, walking difficulties, and foot drop in distal limbs. Furthermore, muscle cramps, distal sensory impairment, hyporeflexia, and areflexia may also appear. Pes cavus, hammer toes, foot deformities, and claw hand deformities may be observed in the lower and upper extremities, respectively, kyphoscoliosis of the spine may also be seen. Moreover, the motor NCV is reduced in CMT1A and hypertrophic nerve changes may occur. Finally, while onion bulb formation and segmental demyelination/remyelination are detected via nerve biopsy, the number of myelinated fibers decreases and some patients experience myelin outfoldings.

**CMT1C**

CMT1C is caused by a heterozygous mutation in the *LITAF* gene (also referred to as SIMPLE) on chromosome 16p13 [15]. The inheritance is autosomal dominant. The *LITAF* gene was first identified as a regulator of the *TNFα* gene expression and its product is an early endosomal membrane protein enriched in peripheral nerves and Schwann cells. CMT1C develops mainly during childhood and is genetically heterogeneous. It is characterized by pes cavus, muscle weakness, and atrophy in distal limbs and by distal sensory impairment and hyporeflexia. Similarly to the other CMT1 subtypes, the motor NCV is also reduced in CMT1C and hypertrophic nerve changes are found. Finally, onion bulb formation and segmental demyelination/remyelination are observed through nerve biopsy.

**CMT1D**

This form of CMT1 is caused by a mutation in the *EGR2* gene [16-18]. The inheritance is autosomal dominant. Symptoms are present from an early age, specifically between the first and second decade of life, and usually begin in patients’ feet and legs, while upper extremities may be affected at later stages. CMT1D is also both clinically and genetically heterogeneous, and its phenotype overlaps, in part, with both congenital hypomyelinating neuropathy (CHN) and discrete subaortic stenosis. Distal limb muscle weakness, muscle atrophy, steppage gait, and foot drop are the main symptoms. The motor NCV is reduced.

**CMT1E**

Similarly to CMT1A, CMT1E is, at least in some instances, caused by a mutation in the *PMP22* gene [19]. The inheritance is au-
Other CMT1
CMT1F is caused by a mutation in the NEFL gene [20], which encodes a subunit of the type IV intermediate filament heteropolymers, a major component of the neuronal cytoskeleton. Although this CMT subtype is autosomal dominant in most cases, autosomal recessive inheritance was reported in two families. CMT1F onset occurs during either infancy or childhood, between 1 and 13 years of age, and usually begins from patients’ feet and legs, while upper limb involvement usually develops at a later stage. Furthermore, it presents varying severity and genetic heterogeneity. Among the main symptoms, delayed motor development, muscle weakness and muscle atrophy in distal limbs can be distinguished. Additionally, distal sensory impairment, hyporeflexia, areflexia, and pes cavus are also typically observed. Similarly to the previously mentioned subtypes, CMT1F is associated with a reduced motor NCV, segmental demyelination/remyelination, onion bulb formation, loss of myelinated fibers, irregular myelin folds, and clusters of axonal regeneration.

Charcot-Marie-Tooth disease type 2
Although CMT2 presents normal-to-slightly slower motor NCV, it was associated with a smaller activity potential and damages to the axons in neurolytic studies. Furthermore, CMT2 was reported to occur less frequently than CMT1 and to represent about one-third of the total CMT cases. However, this estimate may be undervalued considering that family history is not well understood and is classified as nonspecific axillary neuropathy. The age of onset greatly varies, even within families, ranging from childhood to older adulthood (> 60 years of age). Several genes associated with CMT2 were identified and studies were conducted to identify its mutation frequencies and specific clinical types (Table 2). Although deducing some CMT2 causative genes from the clinical features is possible, most CMT2 require the examination of a large number of genes. Mutations in the mitofusin 2 (MFN2) gene, which plays an important role in mitochondrial function, account for more than 33% of the CMT2 subtype [9].

CMT1F
CMT1F is caused by a mutation in the NEFL gene [20], which encodes a subunit of the type IV intermediate filament heteropolymers, a major component of the neuronal cytoskeleton. Although this CMT subtype is autosomal dominant in most cases, autosomal recessive inheritance was reported in two families. CMT1F onset occurs during either infancy or childhood, between 1 and 13 years of age, and usually begins from patients’ feet and legs, while upper limb involvement usually develops at a later stage. Furthermore, it presents varying severity and genetic heterogeneity. Among the main symptoms, delayed motor development, muscle weakness and muscle atrophy in distal limbs can be distinguished. Additionally, distal sensory impairment, hyporeflexia, areflexia, and pes cavus are also typically observed. Similarly to the previously mentioned subtypes, CMT1F is associated with a reduced motor NCV, segmental demyelination/remyelination, onion bulb formation, loss of myelinated fibers, irregular myelin folds, and clusters of axonal regeneration.

CMT2A
CMT2A1 is caused by a heterozygous mutation in the kinesin family member 1B (KIF1B) gene on chromosome 1p36 [22]. The inheritance is autosomal dominant. One family was found with such a mutation. Disease development can occur between childhood and 50 years of age. Symptoms begin from patients’ feet and legs, while they may be observed in the upper limbs at a later stage. CMT2A1 progresses slowly and is genetically heterogeneous. The main signs of such a disease include distal limb muscle weakness, muscle atrophy, steppage gait, and foot drop. Additionally, pes cavus, hammer toes, and foot deformities appear in patients’ lower limbs. Furthermore, distal sensory impairment, hyporeflexia, and areflexia also appear. Motor NCV is normal or mildly reduced. Finally, axonal atrophy and degeneration/regeneration are observed through nerve biopsy, while small onion bulb formation and a reduced number of myelinated fibers may be found.

CMT2A2A
CMT2A2A is caused by a heterozygous mutation in the MFN2 gene on chromosome 1p36.2 [23-25]. The inheritance is autosomal dominant. Specifically, both mitochondrial size and arrangement differ with cell type, physiologic condition, and pathological state. In fact, mitofusins, including the MFN2, mediate mitochondrial fusion and contribute to their dynamic balance. The onset of the disease greatly varies between childhood and the age of 50, with an earlier onset being associated with increased severity, usually beginning from patients’ feet and legs, and eventually progressing to the upper limbs. Therefore, CMT2A2A greatly varies in severity, with the identification of family with a fatal subacute encephalopathy. However, it was found to progress at a slow pace. Additionally, up to 25% of patients are either asymptomatic or mildly affected, suggesting incomplete penetrance. The main symptoms include distal limb muscle

Other CMT1
Recent studies reported a dominant inheritance of PMP2 mutations in demyelinating CMT patients [21]. PMP2 is a major protein of the nerve compact myelin. It belongs to the fatty acid-binding protein family and is likely involved in intracellular trafficking of lipids. Its clinical and electrophysiologic phenotype is similar to the CMT1A subtype.

Charcot-Marie-Tooth disease type 2
Although CMT2 presents normal-to-slightly slower motor NCV, it was associated with a smaller activity potential and damages to the axons in neurolytic studies. Furthermore, CMT2 was reported to occur less frequently than CMT1 and to represent about one-third of the total CMT cases. However, this estimate may be undervalued considering that family history is not well understood and is classified as nonspecific
Table 2. Mutations of the axonal Charcot-Marie-Tooth neuropathy subtypes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Gene</th>
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<th>Heredity</th>
<th>Protein</th>
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AD, autosomal dominant; AR, autosomal recessive; HMSN, hereditary motor and sensory neuropathy; PNHHH, peripheral neuropathy, myopathy, hoarseness and hearing loss.
weakness, muscle atrophy, steppage gait, foot drop, distal sensory impairment, loss of pain and temperature sensation, and less severe loss of vibration and position sensation. Additionally, while hyporeflexia and areflexia are common, pyramidal signs, increased muscle tone, extensor plantar responses or hyperreflexia are rarely observed. Other signs associated with CMT2A2A are pes cavus, hammer toes, and foot deformities. In contrast, cognitive declines and spasticity are rarely seen in the central nervous system (CNS), while pyramidal features, tremor, or fatal subacute encephalopathy were also reported. Moreover, pain, skeletal contractures and sclerosis may occur in patients with an early disease onset, whereas hearing loss and optic atrophy are less likely. Although CMT2A2A is typically correlated with either normal or mildly reduced motor NCV, an absence in such a velocity is seen in patients with an early disease onset. Finally, axonal atrophy, degeneration/regeneration, and mitochondrial abnormalities are observed through nerve biopsy, while both decreases in myelinated fibers and small onion bulb formation may be found.

**CMT2B**

CMT2B is caused by either a homozygous or a compound heterozygous mutation in the *MFN2* gene on chromosome 1p36.2. The inheritance is autosomal recessive [26]. Its onset is during the first years of life and it shows variable severity, although most patients become wheelchair-bound. Distal sensory impairment, hyporeflexia, pes cavus, walking difficulty, foot drop, and loss of ambulation are CMT2A2B typical features, although other symptoms may include distal muscle weakness and atrophy, and occasional proximal muscle weakness in both the upper and lower extremities. Frequent observations are delayed gross motor development in the CNS and scoliosis and kyphosis in the spine. Furthermore, hearing impairment may also occur in some patients. Additionally, ophthalmologic features comprise optic atrophy and pale optic discs, while some patients develop either visual impairment at a later age or respiratory insufficiency due to muscle weakness. Finally, sural nerve biopsy shows a loss of large myelinated fibers.

**CMT2B1**

CMT2B1 is caused by a homozygous mutation in the lamin A/C (*LMNA*) gene on chromosome 1q22 [28]. The inheritance is autosomal recessive. The *LMNA* gene encodes laminin and laminin C. Lamins are the structural protein components of the nuclear lamina, a protein network underlying the inner nuclear membrane that determines nuclear shape and size. Lamins constitute a class of intermediate filaments and three types, namely A, B, and C, were described in mammalian cells. CMT2B1 onset begins during the second decade of life, mainly in patients’ feet and legs, while their upper extremities may be affected at a later stage. This subtype is genetically heterogeneous and has a severe course. The main symptoms include muscle weakness and atrophy in distal limbs, proximal muscle involvement, steppage gait, foot drop, pes cavus, foot deformities, distal sensory impairment, hyporeflexia, and areflexia. Furthermore, kyphoscoliosis of the spine may be found. Finally, axonal atrophy and degeneration/regeneration are observed through nerve biopsy, while small onion bulbs and decreased number of myelinated fibers may be found.

**CMT2B2**

CMT2B2 is caused by a homozygous mutation in the mediator complex subunit 25 (*MED25*) gene [29], which encodes a protein belonging to the Mediator complex, an evolutionarily conserved multisubunit RNA polymerase II transcriptional...
regulator complex. The inheritance is autosomal recessive. Only one family with such a mutation was reported. CMT2B2 onset is between 28 and 42 years of age and it usually begins from patients’ feet and legs, while it may progress to their upper limbs at a later stage. The main symptoms include muscle weakness and atrophy in the distal limbs, distal sensory impairment, hyporeflexia, and areflexia. Finally, motor NCV is normal or mildly reduced.

**CMT2C**

CMT2C also known as hereditary motor and sensory neuropathy type IIC (HMSN2C) is caused by a heterozygous mutation in the transient receptor potential cation channel subfamily V member 4 (TRPV4) gene on chromosome 12q24 [30,31]. The inheritance is autosomal dominant. The TRPV4 cation channel mediates calcium influx in response to physical, chemical, and hormonal stimuli in ciliated epithelial cells. CMT2C onset age varies between birth and the age of 60, with an earlier disease onset being associated with increased severity. In some cases, worsening of hand weakness with cold can be seen. It overlaps clinically with distal hereditary motor neuropathy type VII (dHMN VII) and it shows incomplete penetrance. The main symptoms include muscle weakness and atrophy in both the upper and lower distal limbs, early wasting of hand muscles, and impaired manual dexterity, whereas proximal limb muscles are involved in severe cases. Additionally, other signs involve pes cavus, high-arched feet, impaired gait, frequent falls, distal sensory impairment, and hyporeflexia. Furthermore, distal muscle weakness and atrophy in the lower limbs, and proximal muscle weakness may be found in some patients. The motor NCV are normal or slightly decreased, while decreased amplitudes were identified. Finally, neurogenic and myopathic changes are observed through electromyography (EMG) and muscle biopsy in some patients.

**CMT2D**

This form of CMT2 is caused by a mutation in the glycyl-tRNA synthetase (GARS) gene [33], which encodes an enzyme that is responsible for charging tRNA molecules with glycine via an aminoacylation reaction. The inheritance is autosomal dominant. The mean age of onset is 18 years; however, this type presents a slow disease progression. Distal spinal muscular atrophy type 5A (dSMASA) is an allelic disorder with a similar phenotype [33], although CMT2D presents more severe distal sensory involvement. Although distal limbs muscle weakness and atrophy occur, this subtype is predominantly characterized by weakness and atrophy of the upper limbs, such as the thenar muscle and the first dorsal intersossei muscle. Other symptoms include pes cavus, hammer toes, cold-induced hand cramps, balance impairment, hyporeflexia, distal sensory impairment and scoliosis. Finally, a normal motor NCV range is observed.

**CMT2DD**

CMT2DD is caused by a heterozygous mutation in the ATPase Na+/K+ transporting subunit alpha 1 (ATP1A1) gene on chromosome 1p13 [34]. The inheritance is autosomal dominant. This gene encodes the alpha-1 isoform of the Na (+), K (+)-ATPase, an integral membrane protein responsible for establishing and maintaining the electrochemical gradients of Na and K ions across the plasma membrane. CMT2DD onset varies between late childhood to the fifties, although most patients develop this disease in their teens or twenties. Given that this subtype has a slow progression, most of the patients maintain their ambulatory function, while others may have a subclinical course with minimal neurological findings. The main symptoms include steppage gait, foot drop, pes cavus,
Charcot-Marie-Tooth disease subtypes

CMT2E
CMT2E is caused by a heterozygous mutation in the *NEFL* gene on chromosome 8p21 [35], which encodes a subunit of the type IV intermediate filament heteropolymers, a major component of the neuronal cytoskeleton [36]. The inheritance is autosomal dominant. CMT2E onset age varies between the first to the third decade of life, with symptoms usually beginning in patients’ feet and legs, eventually progressing to their upper limbs. Similarly, its severity is very diverse and some patients may be wheelchair-bound. The main symptoms include distal limb muscle weakness and atrophy, steppage gait, foot drop, areflexia, hyporeflexia, and distal sensory impairment. Additionally, pes cavus, hammer toes and foot deformities in the lower limbs, and joint contractures may occur. Furthermore, claw hand deformities may also be seen in severe cases. While some patients may present scoliosis, facial muscle weakness, ptosis, and high-arched palate, others may show delayed motor development and shoulder muscle weakness. Moreover, both axonopathy and fiber-type is identified through nerve biopsy as well as fiber size variation and hypotrophy of the small hand muscles. Similarly, internal nuclei, increased connective tissue, nemaline rods, group fiber atrophy, or angular fibers are commonly found. Finally, giant axons with accumulation of disorganized neurofilaments are observed, while the EMG is consistent with chronic neurogenic disorder.

CMT2F
CMT disease type 2F is caused by a mutation in the heat shock protein family B (small) member 1 (*Hspb1*) gene encoding heat-shock 27-kD protein 1 (HSPB1) [37]. The inheritance is autosomal dominant. Heat shock proteins (HSPs) belong to a larger group of polypeptides, the stress proteins, and are involved in a variety of responses to both environmental challenges and developmental transitions. Additionally, the synthesis of the small (27-kD) HSP was shown to be correlated with the acquisition of thermotolerance. CMT2F age of onset varies between 15 and 60 years and it usually begins in patients’ feet and legs, although this subtype has genetic heterogeneity. The main symptoms include muscle weakness and atrophy in the distal limbs, eventually progressing to the upper limbs at a later stage. Furthermore, steppage gait, foot drop, pes cavus, distal sensory impairment, hyporeflexia areflexia, fasciculations, and muscle cramps are common. Furthermore, claw hand deformities may appear in severe cases. Finally, chronic axonal neuropa thy is shown through sural nerve biopsy.

CMT2H
CMT2H maps to the same region that contains the ganglioside-induced differentiation-associated protein 1 (*GDAP1*) gene [38]. The inheritance is autosomal recessive. The first symptoms of this subtype appears in the first decade of life, which include muscle weakness and atrophy in distal limbs, foot drop, steppage gait, pes cavus, distal sensory impairment, absent ankle reflexes, pyramidal features, hyperreflex ia in the upper limbs and in knees, and both the brisk Hoffman and palmomental reflexes. CMT2H has a normal motor NCV range, while a loss of myelinated fibers is observed through nerve biopsy. Finally, myelin sheaths are thin and axonal regeneration is rare.

CMT2I
CMT2I is caused by a heterozygous mutation in the *MPZ* gene on chromosome 1q23 [39,40]. The inheritance is autosomal dominant. The first symptoms of this subtype usually begin in patients’ feet and legs between the age of 40 and 60, eventually extending to their upper extremities in a later stage, given its genetic heterogeneity. The main symptoms include muscle weakness and atrophy in the distal limbs, pes cavus, steppage gait, hyporeflexia, and areflexia, and distal sensory impairment. Finally, while normal or slightly reduced motor NCV (39 to 40 m/sec) are seen, axonal degeneration/regeneration and loss of myelinated fibers can be observed through nerve biopsy.

CMT2J
CMT2J with hearing loss and pupillary abnormalities is also referred to as CMT2J, which is caused by a heterozygous mutation in the *MPZ* gene on chromosome 1q23 [39-41]. The inheritance is autosomal dominant. Its onset is between the fourth and sixth decade of life, usually beginning in patients’ feet and legs and extending to their upper limb at a later stage. The main presenting features include sensorineural hearing loss, muscle weakness and atrophy in the distal limbs, pes cavus, foot drop, steppage gait, distal sensory impairment, hy-
poreflexia, and areflexia. Furthermore, sensorineural hearing loss, progressive deafness, and brainstem auditory evoked potentials (BAEPs) suggest peripheral lesion in patients' ears. In contrast, both slow pupillary reaction with slow light convergence reflex and absent pupillary reaction can be found in their eyes. Another common symptom is gastrointestinal dysphagia. Finally, while normal to mildly decreased motor NCV is observed, axonal degeneration/regeneration is observed through nerve biopsy and secondary demyelination is present at later stages of disease progression.

**CMT2K**

Autosomal recessive axonal CMT disease type 2K is caused by either a homozygous or a compound heterozygous mutation in the GDAP1 gene on chromosome 8q [42], which encodes an integral membrane protein of the outer mitochondrial membrane expressed in both the CNS and PNS, particularly in Schwann cells. Some patients with a milder phenotype were found to carry heterozygous mutations in the GDAP1 gene, which is consistent with the autosomal dominant inheritance nature of this subtype [43,44]. CMT2K onset age is three years old and begins in patients' feet and legs, followed by severe progression. In fact, upper limb involvement occurs in the first decade. However, given its genetic heterogeneity, patients with autosomal dominant inheritance and a single GDAP1 mutation have a less severe course with later onset. This subtype shares the same phenotype of the CMT4A allelic disorder. The main symptoms include muscle weakness and atrophy in the distal limbs, possible involvement of proximal muscles, areflexia, talipes equinovarus, claw hand deformities, kyphoscoliosis and distal sensory impairment. While CMT2K has a normal or slightly reduced motor NCV, a loss of myelinated fibers, axonal regeneration and pseudo-onion bulb formations are observed through nerve biopsy.

**CMT2L**

CMT2L is caused by a mutation in the heat shock protein family B (small) member 8 (HSPB8) gene [45]. The inheritance is autosomal dominant. Distal hereditary motor neuronopathy type 2A (dHMN2A) is an allelic disorder with an overlapping phenotype. Its onset usually begins in patients' feet and legs between the age of 15 and 33 years, although it presents genetic heterogeneity. The main symptoms include muscle weakness and atrophy in the distal limbs, and the involvement of the upper distal limb muscles. In contrast, its progression to proximal muscle rarely occurs. Additional signs associated with this subtype are pes cavus, hyporeflexia, areflexia scoliosis, and distal sensory impairment. While CMT2L has a normal motor NCV range, decreased or absent SNAPs are observed. Furthermore, the EMG shows denervation and fibrillation potentials, whereas axonal neuropathy, loss of large myelinated fibers, and thin myelinated axons were found through nerve biopsy.

**CMT2M**

CMT2M maps to chromosome 19p and is caused by a heterozygous mutation in the dynamin 2 (DNM2) gene [46]. The inheritance is autosomal dominant. DNM2 is a ubiquitously expressed large GTPase involved in both clathrin-dependent and -independent endocytosis and in intracellular membrane trafficking. This protein has a strong interaction with the actin and microtubule networks and may have a role in centrosome function. The first symptoms associated with CMT2M appear between the first and second decade of life, beginning in patients' feet and legs. Although CMT2M shares most of the features with intermediate CMTDIB, this type is purely axonal CMT. Its common features include weakness and atrophy of distal limb muscles, distal sensory impairment, hyporeflexia, and areflexia. Additionally, the motor NCV value is low-to-normal range. Finally, the loss of myelinated fibers, rare segmental demyelination/remyelination, onion bulb formation, and axonal degeneration can be observed through nerve biopsy.

**CMT2N**

This form of axonal CMT disease type 2 is caused by a heterozygous mutation in the alanyl-tRNA synthetase (AARS) gene on chromosome 16q21 [47], which encodes the amino acid synthetases, responsible for the initiation of the attachment of their respective amino acids to the corresponding tRNA. The inheritance is autosomal dominant. CMT2N onset varies between the age of 6 to 54 years, with fluctuating severities. The most frequent presenting symptoms are muscle weakness and atrophy in the distal limbs, which affects the lower limbs the most. Additional symptoms include walking difficulties, foot drop, hypo- or areflexia, distal sensory impairment, foot deformities, pes cavus, hammertoes, and ankle sprains. Finally, sensorineural deafness was also reported in one household.

**CMT2O**

CMT2O is caused by a heterozygous mutation in the dynein cytoplasmic 1 heavy chain 1 (DYN1H1) gene on chromosome 14q32 [48]. The inheritance is autosomal dominant.
The DYNC1H1 gene encodes a large (>530 kD) crucial subunit of the cytoplasmic dynein complex. Dyneins are a group of microtubule-activated ATPases that support the conversion of chemical energy into mechanical energy. CMT2O onset is during childhood and has a slow progression. Only one family was reported to have such a mutation. Although multiple phenotypes exist, ambulation is usually maintained throughout adulthood. In contrast, the disease main symptoms include muscle weakness and atrophy in the distal limbs, involvement of the upper limbs, pes cavus, recurrent falls, neuropathic pain, hyporeflexia, running difficulty, and varying distal sensory impairment. Furthermore, delayed motor development is observed in the CNS, whereas learning difficulties are less frequent. Finally, while motor NCV is normal or mildly reduced, axonal degenerative processes are found through sural nerve biopsy.

CMT2P (autosomal dominant, autosomal recessive)
CMT2P is caused by either a homozygous or heterozygous mutation in the leucine-rich repeat and sterile alpha motif-containing 1 (LRSAM1) gene on chromosome 9q33 [49]. The LRSAM1 is a multifunctional RING finger protein that selectively regulates cell adhesion molecules, has ubiquitin ligase activity, and plays a role in receptor endocytosis and viral budding. Its onset varies between childhood and the age of 76, although the disease is usually developed during adulthood. The peak age of onset was reported to be in the second decade of life, when it begins in patients' feet and legs and eventually progresses to the upper limbs. Although this type has a slow progression, some patients become wheelchair-bound. Furthermore, incomplete penetrance may also be present. Patients with this type of CMT lose their ability to run given their lower limb weakness and have difficulty in heel-to-toe walking. The main symptoms associated with this disease include foot drop, steppage gait, fasciculations, hyporeflexia, and areflexia. Considering that CMT2P is a sensorimotor axonal neuropathy, distal sensory loss, distal limb muscle weakness and atrophy is observed, mainly affecting the lower limbs. Additionally, cramping and foot deformities occur, while some patients may develop pes cavus or hammertoes. Finally, the number of myelinated fibers may also decrease.

CMT2Q
CMT2Q is caused by a heterozygous loss-of-function (LOF) mutation in the dehydrogenase E1 and transketolase domain containing 1 (DHTKD1) gene on chromosome 10p14 [50], as reported in a 5-generation Chinese family. The inheritance is autosomal dominant. The DHTKD1 is predicted to be a thiamine diphosphate-dependent 2-oxoacid dehydrogenase responsible for the reduction of the protein-bound lipoyl group. The main symptoms include weakness of distal lower limbs, muscle atrophy in distal forearms and hands, decreased or absent deep tendon reflexes, mild-to-moderate deep sensory impairment and walking difficulty. Additionally, small, angulated muscle fibers, sarcomere disappearance, disorganized myofilaments, and mitochondrial vacuolization are seen through muscle biopsy. Finally, both symmetrical muscle wasting and atrophy were observed.

CMT2R
This form of the CMT disease is caused by either a homozygous or a compound heterozygous mutation in the tripartite motif containing 2 (TRIM2) gene on chromosome 4q [51]. The inheritance is autosomal recessive. The TRIM2 functions as an E3 ubiquitin ligase that directs the proteasome-mediated degradation of target proteins. Two unrelated patients with such a disease were reported, one with a more severe phenotype. CMT2R onset age is during early childhood and is characterized by muscle weakness and atrophy in both the upper and lower limbs. Furthermore, broad-based gait, delayed walking, inability to walk on heels, pes cavus, pes equinovarus, areflexia, hypotonia, and muscle mass are found, together with atrophy of the small hands and feet muscles. Specifically, one patient presented knee contractures, respiratory insufficiency, tracheomalacia, and vocal cord paralysis. Moreover, this disease is associated with slow motor NCV (<30 m/sec), and decreased sensory and motor nerve amplitudes. Finally, nonspecific axonal degeneration was found through sural nerve biopsy, as well as the loss of myelinated fibers, accumulation of neurofilaments within axons, and swollen myelinated fibers.

CMT2S
CMT2S is caused by either a homozygous or a compound heterozygous mutation in the immunoglobulin mu DNA binding protein 2 (IGHMBP2) gene on chromosome 11q13 [52]. The inheritance is autosomal recessive. Its age of onset is the first decade and, although its slow progression, most patients become wheelchair-bound. This type of axonal sensorimotor neuropathy affects both the upper and lower limbs. The main features of this disease are distal sensory and motor impairment, foot drop, impaired gait, steppage gait, areflexia, and hyporeflexia. Furthermore, a reduction in large myelinated fibers is seen through sural nerve biopsy. Addi-
Present at onset, decreased sensory and motor nerve amplitude, axonal degeneration, distal muscle weakness and atrophy, and mild proximal muscle weakness may occur in some patients. Finally, symptoms such as pes equinovarus, scoliosis, and abnormal tongue shape may also be characteristic of some patients.

**CMT2T**
CMT2T is caused by either a homozygous or a compound heterozygous mutation in the membrane metalloendopeptidase (**MME**) gene on chromosome 3q25 [53]. However, some patients may carry heterozygous mutations as well. The **MME** gene encodes a widely expressed MME that degrades several substrates, with its active site facing the extracellular space. This type first develops at a late age (between 36 and 56 years) and shows a slow progression. Furthermore, those patients having heterozygous mutations may present a slightly later onset. The main symptoms associated with this subtype include distal sensory impairment, foot drop, gait instability, hyporeflexia, and areflexia. Additionally, distal muscle weakness and atrophy are observed, whereas the loss of large myelinated fibers is seen through sural nerve biopsy.

**CMT2U**
CMT2U is caused by a heterozygous mutation in the methionyl-tRNA synthetase (**MARS**) gene on chromosome 12q13 [54]. The inheritance is autosomal dominant. This type is characterized by late-adult onset (age of 50 or later) and shows a slow progression, as reported in two unrelated families. The main features of this subtype comprise foot drop, steppage gait, areflexia, and distal sensory impairment. Moreover, distal muscle weakness and atrophy of both the upper and lower limbs are observed.

**CMT2V**
CMT2V is caused by a heterozygous mutation in the N-acetyl-alpha-glucosaminidase (**NAGLU**) gene on chromosome 17q21 [55]. The inheritance is autosomal dominant. The mean age at onset is 41 years (ranging from 18 to 61 years), as indicated by one family of French-Canadian origin. This subtype is characterized by a pain feeling in the lower extremities and following paresthesia in the upper extremities. Furthermore, distal sensory impairment and hyporeflexia are additional common symptoms. Moreover, patients show difficulty in tandem gait with disease progression. Additionally, sleep disturbances are found in some patients given the presence of sensory ataxia. Although normal motor NCV are present at onset, decreased sensory and motor nerve amplitudes are detected at a later disease stage.

**CMT2W**
This type of CMT disease is caused by a heterozygous mutation in the histidyl-tRNA synthetase (**HARS**) gene on chromosome 5q31 [56]. The inheritance is autosomal dominant. HARS catalyzes the covalent ligation of histidine to its cognate tRNA, representing an early step of protein biosynthesis. Its age of onset greatly varies, ranging from childhood to late adulthood; similarly, its severity also highly fluctuates. The main symptoms include pes cavus, hammertoes, impaired gait, steppage gait, distal sensory impairment, brisk patellar reflexes, and absent ankle reflexes. Additionally, distal muscle weakness and atrophy of the lower limbs are observed, whereas distal muscle weakness and atrophy of the upper limb occur only in some patients. Finally, electrophysiological studies suggest normal or mildly decreased motor NCV.

**CMT2X**
CMT2X is caused by either a homozygous or a compound heterozygous mutation in the spatacacin vesicle trafficking associated (**SPG11**) gene on chromosome 15q21 [57]. The inheritance is autosomal recessive. The **SPG11** gene encodes the protein spatacin, which has a role in axonal growth, function, and intracellular cargo trafficking. The mean age at onset is 11.4 ± 5.9 years (ranging from 4 to 35 years). CMT2X has a slow progression and shows variable phenotypes. The most common symptoms include gait impairment, foot drop, hypo- or dysflexia, and distal sensory impairment. Additionally, it is characterized by ankle contractures, foot deformities, pes cavus, hand deformities, kyphoscoliosis, urinary dysfunction, mild cognitive impairment, or thin corpus callosum. Furthermore, distal muscle weakness and atrophy also occur, specifically affecting lower limbs the most. Finally, chronic denervation/reinnervation is seen on EMG, whereas the loss of large caliber myelinated fibers is observed through sural nerve biopsy.

**CMT2Y**
CMT2Y is caused by a heterozygous mutation in the valosin-containing protein (**VCP**) gene on chromosome 9p13 [58], which encodes a ubiquitously expressed multifunctional protein, member of the AAA+ (ATPase associated with various activities) protein family. The inheritance is autosomal dominant. Only one family and one unrelated patient were reported to present such a mutation. The age at onset ranges from early childhood to older adulthood (>50 years of age) and the disease is characterized by a highly varying severity.

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Commonly, CMT2Y patients show walking, running and balance difficulties, distal sensory impairment, hypo- or areflexia, and distal muscle weakness and atrophy in both the lower and upper limbs. Finally, neurogenic atrophy was identified in one patient through muscle biopsy.

**CMT2Z**

CMT2Z is caused by a heterozygous mutation in the MORC family CW-type zinc finger 2 (MORC2) gene on chromosome 22q12 [59,60]. The inheritance is autosomal dominant. The MORC2 is a DNA-dependent ATPase that relaxes chromatin to ensure the repair of DNA double-strand break. Furthermore, cytosolic MORC2 appears to be involved in lipid metabolism and homeostasis. The age at onset of this disease is between the first and the second decade of life (ranging from infancy to early adulthood). Although CMT2Z is characterized by a slow progression, various phenotypes exist and some patients become wheelchair-bound. Asymmetric muscle involvement is one of the main symptoms of this subtype. Additionally, decreased motor and sensory action potential amplitudes, distal sensory impairment, hypo- or isflexia, and pes cavus are frequently seen in patients. Similarly, delayed development, learning disabilities, pyramidal signs, and extensors can occur in this subtype. Distal and proximal (at a later disease stage) muscle weakness and atrophy occur in both the upper and lower limbs. Other features associated with such a condition are muscle cramps, foot drop, walking difficulties, hypotonia, spontaneous muscle activity, fasciculations, and myokymia. Increased muscle tone was observed in some patients. Moreover, claw hands, scoliosis, or urinary incontinence are often reported in some patients. Hearing loss was found in two members of a family, whereas high-pitched voice was described in another family. Neck flexion weakness appears with disease progression. Finally, while the motor NCVs are normal or near-to-normal, the loss of large myelinated fibers is identified through sural nerve biopsy. In contrast, both onion bulbs and regenerative fibers are observed rarely, whereas thinly myelinated axons and fibrosis are common.

**Other CMT2**

Recently, mutations in the TRK-fused gene (TFG) in HMSN-P patients with proximal muscle weakness were reported in both the Korean and Japanese populations [61-63]. Although CMT is generally characterized by weakened distal muscle strength, HMSN-P is associated with decreased proximal muscle weakness, late age of onset and rapid progression after onset. Peripheral neuropathy, myopathy, hoarseness and hearing loss (PNMHH) is caused by mutations of the myosin heavy chain 14 (MYH14) [64], and is characterized by peripheral neuropathy, muscular dysfunction and hearing loss. This gene mutation occurs at a young age, showing the initial symptoms of hearing impairment and muscle weakness. In addition, the mutation of the histidine triad nucleotide-binding protein 1 (HINT1) was confirmed to be the cause of autosomal recessive axonal neuropathy, which is mainly involved in neuroblastomas [65]. Lastly, the diacylglycerol O-acyltransferase 2 (DGAT2), which catalyzes the final step of the triglyceride biosynthesis, was found in a Korean family with a CMT2 early onset dominance, showing sensory ataxia and low triglyceride levels [66].

**Charcot-Marie-Tooth disease type 3 (CMT3, DSS)**

DSS is caused by mutations in the following genes; the MPZ, PMP22, periaxin (PRX), and EGR2 genes [67-71]. Furthermore, evidence of the contribution of mutations in the gap junction protein beta 1 (GJB1) gene to this phenotype exists (Table 1). Its onset occurs between infancy and early childhood, with the emergence of symptoms in patients’ feet and legs, which eventually extend to the upper limbs with disease progression. This type is clinically and genetically heterogeneous. With regards to its clinical aspect, although it overlaps with demyelinating CMT type 1, it presents more severe phenotypes. Similarly, its clinical phenotypes also overlap with CHN. The main symptoms of this disease include distal sensory impairment, sensory ataxia, hyporeflexia, and areflexia during muscle development, as well as muscle atrophy and weakness of the distal limbs. Moreover, cerebrospinal fluid (CSF) protein levels are increased. Additional features are pes cavus, hammer toes, and foot deformities in the lower extremities, together with claw hand deformities in the upper extremities. Kyphoscoliosis of the spine and nystagmus may be observed in some patients. While the motor NCV is severely reduced, hypertrophic nerve changes may occur. Onion bulb formation and segmental demyelination/remyelination are observed through nerve biopsy. Furthermore, the number of myelinated fibers was found to decrease. In contrast, CMT3A (DSS-A) is usually caused by a point mutation on chromosome 17q11.2-12, given the dominant inheritance of chromosomal dominance [67]. Patients with such a disease exhibit clinical symptoms similar to those of CMT1A with gene duplication, even though they occasionally develop early neuropathy during their neonatal period and present severe clinical symptoms. Moreover, CMT3B (DSS-B) is
caused by the MPZ gene mutation of the dominant or recessive chromosome 1q22 [68,69]. Genetic damage resulting in CMT3C (DSS-C) was suggested to be associated with chromosome 8q23-q24 in a family of dominant inheritance patterns in Iowa, USA [70]. Finally, the PRX gene mutation located on chromosome 19q13.1-13.2 induces a recessive inheritance pattern of CMT3D [71].

Charcot-Marie-Tooth disease type 4

CMT4 belongs to the genetically heterogeneous group of CMT peripheral sensorimotor polyneuropathies (Table 1). These autosomal recessive forms are usually associated with very severe progression, onset at early infancy, delayed motor milestones, and complex phenotypic manifestations.

CMT4A

Autosomal recessive demyelinating CMT disease type 4A is caused by a mutation in the gene encoding GDAP1 on chromosome 19q13.1-13.2 induces a recessive inheritance pattern of CMT3D [71].

CMT4B

CMT4B1 is caused by a mutation in the myotubularin-related protein-2 (MTMR2) gene [75,76], which encodes a protein belonging to the myotubularin family, that is characterized by the presence of a phosphatase domain. The inheritance is autosomal recessive. The mean age of disease onset is 34 months, beginning in patients’ feet and legs, progressing through a severe clinical course, and leading to their death between 40 and 50 years of age. Although CMT4B1 presents genetic heterogeneity, its common features are muscle weakness and atrophy in the distal limbs, muscle weakness in the proximal limbs, and facial weakness. Additional symptoms include delayed motor development, abnormal auditory evoked potentials, talipes equinovarus, foot deformities, distal sensory impairment, and scoliosis. While the motor NCV is severely reduced (15 m/sec), irregular loops and focal folding of the myelin sheaths are observed.

CMT4B2

This form of CMT disease is caused by a mutation in the SET binding factor 2 (SBF2) gene [77], which encodes a catalytically inactive pseudolipid phosphatase that functions as a scaffold for the myotubularin-related protein lipid phosphatase MTM1. The inheritance is autosomal recessive. SET binding factor 1 (SBF1) is another pseudophosphatase, which contain inactivating substitutions at the catalytic cysteine. CMT4B2 onset is between the first and second decade of life (ranging from 4 to 13 years), beginning in patients’ feet and legs and involving the upper limbs with disease progression. Although CMT4B2 has genetic heterogeneity, its common features are muscle weakness and atrophy in the distal limbs, walking difficulties, steppage gait, foot drop, severe distal sensory impairment, hyporeflexia, and areflexia. Furthermore, CSF protein contents were identified to be increased or at the upper limit of their normal concentration. Additional signs associated with CMT4B2 are pes cavus, talipes equinovarus, hammer toes, and foot deformities in the lower extremities, and claw hand deformities in the upper extremities in severe cases. Furthermore, kyphoscoliosis may be present, while sensorineural hearing loss was described in one family. Moreover, glaucomas can occur in the early stages of patients with either nonsense or truncating mutations in the SBF2 gene and may precede the development of neuropathy. While the motor NCV is reduced (15 to 30 m/sec), onion bulb formation and segmental demyelination/remyelination are observed through nerve biopsy. Finally, a decreased number of large and small myelinated fibers, thin myelin sheaths, and abnormal myelin folding of globular masses of irregular myelin thickening are also characteristic.

CMT4B3

CMT4B3 is caused by either a homozygous or a compound
heterozygous mutation in the SBF1 gene on chromosome 22q, as reported in two families [78,79]. The inheritance is autosomal recessive. Its age of onset is between 5 and 20 years and, given the progressive nature of this type, patients may become wheelchair-bound in adulthood. One consanguineous Saudi family had the additional features of microcephaly, brain atrophy, mental retardation, ophthalmoplegia, and syndactyly. This peripheral neuropathy causes distal leg weakness, gait abnormalities, distal sensory impairment, scoliosis, and areflexia. Furthermore, a family presented pes planus, syndactyly, microcephaly, strabismus, ophthalmoplegia, and urinary incontinence. The position and vibratory senses are increasingly impaired compared to the pain and temperature senses. While distal limb muscle atrophy and weakness mainly affect the lower limbs, proximal muscles may be mildly involved. The NCVs are found to be decreased, whereas the loss of large myelinated fibers is observed through sural nerve biopsy. Focally folded myelin, onion bulb formation, and regenerating clusters of axons are also observed in one family. Finally, muscle biopsy identified neurogenic angulated fibers and fiber-type grouping.

**CMT4C**

CMT disease type 4C is caused by either a homozygous or a compound heterozygous mutation in the SH3 domain and tetratricopeptide repeats 2 (SH3TC2) gene [80]. Similarly, mild mononeuropathy of the median nerve (MNMN) is a less severe allelic disorder caused by a heterozygous mutation in such a gene. The SH3TC2 gene encodes a protein expressed in Schwann cells of peripheral nerves, which is localized to the plasma membrane and to the perinuclear endocytic recycling compartment, suggesting a possible function in myelination and/or regions of axoglial interactions. Although its onset age is usually between the first and the second decade of life, later onsets were also reported (i.e., between the third and fourth decades). This CMT subtype is prevalent among Europeans, especially in the Spanish and Romani population. Considering the genetic heterogeneity of the disease, its phenotypes are highly variable, even within families. Usually, symptoms begin in patients' feet and legs eventually leading to disability in patients, who may become wheelchair-bound. Furthermore, abnormalities in the pupillary light reflexes, nystagmus, tongue fasciculations, facial weakness, cranial nerve involvement, deafness, prolonged BAEPs, tongue weakness and atrophy, delayed motor development, and cranial nerve involvement are also common. Additionally, while distal lower limb muscle weakness and atrophy often occur, distal upper limb involve-ment is more frequent in later stages. Specifically, the distal sensory impairment of touch, vibration, and proprioception is found. Similarly, the disease may affect proximal lower limbs. Finally, while the motor NCV is reduced, segmental demyelination, secondary axonal degeneration and regeneration, basal lamina onion bulb formation, large cytoplasmic Schwann cell extensions around axons, and loss of large myelinated fibers are also characteristic.

**CMT4D**

CMT disease type 4D, also referred to as the Lom type of the hereditary motor and sensory neuropathy, is caused by a homozygous mutation in the N-myc downstream regulated 1 (NDRG1) gene on chromosome 8q24 [81]. The inheritance is autosomal recessive. Its onset age is in the first decade of life, usually affecting patients' feet and legs, to then extend to the upper limbs with disease progression. This subtype was first described in the Romani group from Bulgaria. The main symptoms associated with CMT4D include muscle weakness and atrophy in the distal limbs, gait disorder, foot deformities, talipes cavus equinovarus, hand deformities, deafness (often in the third decade of life), hyporeflexia and areflexia, and distal sensory loss. Furthermore, while NCV are severely reduced (may become unattainable), onion bulb formation and segmental demyelination/remyelination are observed through nerve biopsy. Finally, axonal loss and intra-axial accumulation of curvilinear profiles are observed, whereas abnormal BAEPs are detected, suggesting demyelination.

**CMT4E**

CMT4E is a CHN with early-onset slow NCVs and a Déjérine-Sottas syndrome-like presentation, which is caused by either homozygous and heterozygous mutations in the EGR2 gene on chromosome 10q21 or by a heterozygous mutation in the chromosome 1q23 [16]. Disease onset is at birth, with symptoms usually beginning in patients' feet and legs, and extending to the upper extremities with disease progression. Allelic disorders with clinical overlap include the DSS and CMT1B. The main features of this subtype are neonatal hypotonia, delayed motor development, areflexia, cranial nerve involvement, and respiratory failure. Additionally, arthrogryposis multiplex congenita may also occur as well as muscle weakness and atrophy in the distal limbs. Finally, while the motor NCV is severely decreased (as low as 3 m/sec), rare onion bulb formation and severe hypomyelination are observed through nerve biopsy.
CMT4F
CMT4F is caused by either a homozygous or a compound heterogeneous mutation in the PRX gene on chromosome 19q13 [82]. The inheritance is autosomal recessive. The PRX gene encodes two isoforms, namely the L- and S-periaxin, which are structural proteins mainly expressed by myelinating Schwann cells in the PNS. The PRX interacts with the dystroglycan complex via the dystrophin related protein 2 (DRP2), linking the basal lamina to the Schwann cell cytoskeleton [83]. CMT4F age of onset varies between early childhood and mid-adulthood, presenting a slow progression. The main symptoms include distal lower limb muscle weakness and atrophy, and possibly proximal lower limb involvement. In contrast, it may affect distal upper limbs in a later stage of the disease. Additional signs associated with this subtype are walking difficulties, pes cavus, scoliosis, distal sensory impairment, areflexia, and delayed motor development. Moreover, vocal cord paresis was reported in one patient, whereas sensory ataxia occurs less frequently. While the motor NCV is reduced, demyelination and basal lamina onion bulb formation were described through sural nerve biopsy. Finally, focal myelin thickening, focally folded myelin, and loss of large myelinated fibers are also characteristic of CMT4F.

CMT4G
CMT4G, also known as, the HMSN Russe is caused by a homozygous mutation in the hexokinase 1 (HK1) gene on chromosome 10q22 [84]. The inheritance is autosomal recessive. CMT4G patients present distal limb weakness and paralysis, hyporeflexia, and deformities of the feet and hands. Scoliosis may also occur in some patients. The age of distal lower limb weakness onset is between 8 and 16 years, while the upper limb involvement occurs between 10 and 43 years. While distal muscle weakness commonly occurs, proximal lower limb muscle weakness is frequent in later stages of the disease in some patients. Finally, while the NCVs are reduced (demyelinating range), the loss of larger myelinated nerve fibers, thin myelin sheaths, regenerative activity and hypomyelination are observed through nerve biopsy.

CMT4H
CMT4H is caused by mutations in the FYVE, RhoGEF and PH domain containing 4 (FGD4) gene encoding frabin (FGD4), which is a guanine nucleotide exchange factor (GEF) for the Rho GTPase cell division cycle-42 (CDC42) [85]. The inheritance is autosomal recessive. Specifically, FGD4 shows actin filament (F-actin)-binding activity. Its onset occurs before the age of 2 years. Although its genetic heterogeneity, this subtype is severe and usually begins in patients’ feet and legs. Furthermore, while distal lower limb muscle weakness and atrophy are frequently found, upper limb involvement may only be described with disease progression. The main symptoms associated with CMT4H include ‘Waddling’ gait, distal sensory impairment, hyporeflexia, areflexia, pes cavus, pes equinovarus, delayed motor development, and scoliosis. Finally, while the motor NCV is reduced, nerve biopsy shows demyelination/remyelination, onion bulb formation, and loss of myelinated fibers.

CMT4J
CMT4J is caused by compound heterozygous mutations in the FIG4 phosphoinositide 5-phosphatase (FIG4) gene on chromosome 6q21 [86]. The inheritance is autosomal recessive. Although its onset usually occurs during early childhood, adult onset is also possible. In this subtype, motor impairment is more significant than sensory impairment. Furthermore, CMT4J is progressive and traumas may accelerate its symptoms, also leading to disability in some patients, who become wheelchair-bound. Both proximal and distal asymmetric muscle weakness is found in the upper and lower limbs. The main symptoms are gait difficulties, frequent falls, areflexia, muscle amyotrophy, ankle contractures, distal sensory impairment, and delayed motor development in the CNS. Finally, while the motor NCVs and nerve amplitudes are decreased, sural nerve biopsy shows axonal loss, thinly myelinated nerve fibers, onion bulb formation, demyelination, and remyelination.

CMT4K
CMT4K is caused by either a homozygous or a compound heterogeneous mutation in the cytochrome c oxidase assembly factor (SURF1) gene on chromosome 9q34 [87]. The inheritance is autosomal recessive. Specifically, the SURF1 gene encodes an assembly factor of the mitochondrial complex IV (COX), the terminal component of the mitochondrial respiratory chain. Disease onset occurs in the first decade of life and has a slow progression. Three patients from two unrelated families were found to report such a mutation and presented differing severities. Typical symptoms include walking difficulties, hypo- or areflexia, kyphoscoliosis, mild hearing loss, and nystagmus. Furthermore, while late-onset cerebellar ataxia was observed in some patients, hyperintense lesions in the putamina and peri-aqueductal white mat-
Charcot-Marie-Tooth disease type 5 (CMT5, HMSN5)
CMT5, also referred to as HMSN5 is sometimes defined as peroneal muscular atrophy with pyramidal features. CMT5 was originally described in patients with peroneal muscular atrophy and hereditary spastic paraparesis [88]. However, this type is pathologically heterogeneous and is not limited to one definite genetic cause. It was suggested a mutation (H165D) in the MFN2 gene, some mutations in KIF5A gene or chromosome 4q34.3-q35.2 as the genetic causes of this type (Table 2). The disease age of onset varies between 4 and 47 years. It usually begins in patients’ feet and legs, and shows a slow progression. Slow paraparetic gait, mild pyramidal signs, brisk tendon reflexes, increased muscle tone, extensor plantar responses, spasticity, spastic dysphonia, and leg cramps and pain can occur in this subtype. Distal limb muscle weakness and atrophy, walking difficulty, foot drop, frequent falls, and distal sensory impairment are also observed. Motor NCV and sensory nerve activity potential are decreased. Nerve biopsy often shows the axonal neuropathic phenotypes.

Charcot-Marie-Tooth disease type 6 (CMT6, HMSN6)
CMT6, also known as HMSN6, is caused by a heterozygous mutation in the MFN2 gene on chromosome 1p36 (Table 2) [89]. The inheritance is autosomal dominant. This type of CMT sees an early onset (mean age, 2.1 years; ranging from 1 to 10 years), whereas optic atrophy develops at a later stage during disease progression (mean age, 19 years; ranging from 5 to 50 years). However, optic atrophy is characterized by incomplete penetrance. CMT6 shares the phenotype with the CMT2A2 allelic disorder. Furthermore, autosomal recessive inheritance was also identified. Most patients become wheelchair-bound, given the muscle weakness and atrophy present in their distal limbs. Common symptoms include steppage gait, pes cavus, lumbar hyperlordosis, positive Romberg sign, proximal muscle weakness, distal sensory impairment of all modalities, hyporeflexia, and areflexia. While mild hearing loss, tinnitus, or anosmia may occur in rare cases, scoliosis or vocal cord paresis are characteristic of severe cases of this subtype. Additionally, optic atrophy, pale optic disks, subacute deterioration of visual acuity, color vision defects, central scotoma, abnormal visual-evoked potentials, cogwheel ocular pursuit, and dysmetric saccades appear in the eyes. However, recovery of the visual acuity occurs in 60% of patients. Finally, axonal degeneration/regeneration were identified through nerve biopsy.

X-linked Charcot-Marie-Tooth disease
Several loci and genes are considered responsible for the following CMTX subtypes: Xq13 (GJB1; CMTX1), Xq26 (apoptosis-inducing factor mitochondria-associated 1 [AIFM1]; CMTX4), Xq22 (phosphoribosyl pyrophosphate synthetase 1 [PRPS1]; CMTX5), and Xp22 (pyruvate dehydrogenase kinase 3 [PDK3]; CMTX6) (Table 3).

CMTX1
X-linked dominant CMT disease type 1 (CMTX1) is caused by either hemizygous or heterozygous mutations in the GJB1 gene on chromosome Xq13. Connexins are membrane-spanning proteins that assemble to form gap junction channels, which allow the transfer of ions and small molecules between cells. Mutations in GJB1 that cause CMTX1 represent about 10% to 20% of CMT cases. Its onset occurs during childhood, usually starting from patients’ feet and legs, eventually extending to the upper limbs with disease progression. CMTX1 has both demyelinating and axonal features, showing variable phenotypes, slow progression, and incomplete penetrance. For example, heterozygous females are more mildly affected than hemizygous males [90,91]. The main features of this subtype include muscle weakness and atrophy in the distal limbs, pes cavus, Achilles tendon contractures, gait disturbance, toe-walking, difficulties in walking on heels, hyperreflexia, and distal sensory impairment. Furthermore, hearing loss rarely occurs, while nystagmus and the CNS involvement may be found in some patients. CMTX1 is generally characterized by symptoms such as delayed motor development, transient and reversible neurologic deficits, paraparesis, monoparesis, numbness, motor aphasia, dysarthria, dysphagia, and tremor; whereas spinocerebellar ataxia, pyramidal signs, hyperreflexia in the lower limbs, extensor plantar responses, and cerebellar atrophy are identified in some patients only. Moreover, white matter abnormalities are seen on magnetic resonance imaging over time. While the motor NCV is reduced or in the normal range (< 38 m/sec to normal) [92-94], a loss of myelinated fibers is described through nerve biopsy. Finally, axonal degeneration, regenerative nerve sprouting, thin myelin sheaths, and onion bulb
formations can also be identified, whereas muscle biopsy suggests neurogenic changes, fiber size variation, type 1 fiber predominance, and distal muscle atrophy.

**CMTX2**
The causative gene of CMTX2 is yet to be defined. Its onset occurs during infancy, with the symptoms usually beginning on patients’ feet and legs, eventually extending to the upper extremities with disease progression. Although CMTX2 has both demyelinating and axonal features, common features can be described, including distal muscle weakness and atrophy, pes cavus, steppage gait, foot drop, areflexia, and mild-to-moderate distal sensory impairment. Furthermore, decreased NCVs are observed, indicating demyelination, while EMG findings suggest axonal involvement. Finally, mental retardation was reported as well [95,96].

**CMTX3**
Similar to CMTX2, the causative gene of CMTX3 is yet to be found. Its onset age varies between the age of 10 to 14 years, with the symptoms usually beginning on patients’ feet and legs, eventually extending to the upper extremities with disease progression. In concordance, CMTX2 has both demyelinating and axonal features. However, distal limb muscle weakness, muscle atrophy, steppage gait, and foot drop are commonly found, whereas areflexia, mild-to-moderate distal sensory impairment, and spastic paraparesis were reported in some cases. This CMT subtype presents decreased NCV, indicative of demyelination, while EMG findings suggest axonal involvement [95,96].

**CMTX4**
X-linked recessive CMT disease type 4 (CMTX4), also referred
to as Cowchock syndrome (COWCK), is caused by a mutation in the AIFM1 gene on chromosome Xq26 [97]. Specifically, the AIFM1 gene encodes a mitochondrial flavin adenine dinucleotide (FAD)-dependent oxidoreductase that plays a role in oxidative phosphorylation (OxPhos) and redox control in healthy cells. While CMTX4 onset occurs between infancy and early childhood, it is characterized by various features which mostly affect the lower limbs, such as axonal motor neuropathy, axonal sensory neuropathy, and distal sensory impairment. Additionally, hearing loss and cognitive impairment were described in some patients. Moreover, T2-weighted hyperintensities were found in the supratentorial white matter, while the occurrence of distal muscle wasting and weakness was reported. Finally, neurogenic atrophy is seen through muscle biopsy, whereas the number of abnormally-shaped mitochondria in the subsarcolemmal areas is increased.

**CMTX5**

X-linked recessive Charcot-Marie-Tooth disease-5 (CMTX5) is caused by a LOF mutation in the PRPS1 gene on chromosome Xq22 [98]. However, LOF PRPS1 mutations, which result in reduced enzyme activity, can also cause Arts syndrome (ARTS) and X-linked deafness-1 (DFNX1). Therefore, both a considerable phenotypic overlap between CMTX5, Arts syndrome and DFNX1, and an intrafamilial variability depending on gender, X-inactivation ratio, residual enzyme activity and additional factors are found. For example, males tend to be more severely affected than females in all three disorders, although a limited number of females also shows severe features. These disorders are considered a phenotypic spectrum. While the motor disturbances onset is during childhood, disease severity is variable. Female carriers may report hearing loss and/or subclinical peripheral neuropathy. Furthermore, both autosomal dominant and recessive forms exist. The common features associated with CMTX5 include muscle weakness and atrophy in the distal limbs, delayed motor development, pes cavus, impaired gait, areflexia of the lower limbs, distal sensory impairment, and hearing loss. Additionally, progressive vision impairment, optic nerve, and retinitis pigmentosa may occur in some patients. While NCVs are normal or mildly decreased, a loss of both large and small myelinated fibers is seen through sural nerve biopsy. Finally, increased endoneurial collagen, segmental demyelination/remyelination, and onion bulb formation are also characteristic of this CMT subtype.

**CMTX6**

X-linked dominant CMT disease-6 (CMTX6) is caused by a mutation in the PDK3 gene on chromosome Xp22 [99], as reported in one family. Specifically, PDK3 belongs to the family of pyruvate dehydrogenase (PDH) kinases, which reversibly inactivate the mitochondrial PDH complex through the ATP-dependent serine phosphorylation of the alpha subunit of the complex E1 component. Disease onset is in the first decades of life in males. The symptoms associated with CMTX6 include pes cavus, steppage gait, distal muscle weakness and atrophy, distal sensory impairment, ankle hyporeflexia, hand muscle weakness, hand tremor, and auditory brainstem responses. Furthermore, hearing loss is identified in some patients.

**Intermediate Charcot-Marie-Tooth disease (CMTDII or CRTXI)**

Several loci and genes are considered responsible for both the following autosomal dominant intermediate CMT (CMTDII) subtypes: 10q24.1-q25.1 (CMTDIA), 19p12-13.2 (DNM2; CMTDIB), 1p34-p35 (tyrosyl-tRNA synthetase [YARS]; CMTDIC), 1q22 (MPZ; CMTDID), 14q32.33 (inverted formin-2 [INF2]; CMTDIE), 3q26.33 (G protein subunit beta 4 [GNB4]; CMTDIF), 8p21 (NEFL; CMTDIG); and the following autosomal recessive intermediate CMT (CRTXI) subtypes: 8q21 (GDAP1; CMTRIA), 16q23 (lysyl-tRNA synthetase [KARS]; CMTRIB), 1p36 (pleckstrin homology and RhoGEF domain containing G5 [PLEKHG5]; CMTRIC), 12q24 (cytochrome c oxidase subunit 6A1 [COX6A1]; CMTRID) (Table 3). The dominant genetic intermediate CMT type exhibits the electrophysiological and pathological characteristics of both the CMT1 and CMT2 subtypes. Finally, the motor NCV of the median nerve is usually between 25 and 45 m/sec.

**CMTDIA**

In concordance with other CMT subtypes, the causative gene of CMTDIA is yet to be identified. Its onset is in the second decade of life, with the symptoms beginning in patients’ feet and legs. This type presents a rapid disease progression, which occurs between the age of 40 and 50 years. Features intermediate between demyelinating and axonal CMT are reported. Although its genetic heterogeneity, the appearance of muscle weakness and atrophy in the distal limbs is observed, and the following symptoms are commonly found: pes cavus, muscles cramps, steppage gait, foot drop, hyporeflexia, areflexia, and distal sensory impairment. Furthermore, while motor NCV is low-to-normal (ranging between 25 and 45 m/sec), axonal degeneration/regeneration are observed through
CMTDIB

Like CMT2M, CMTDIB is caused by a mutation in the DNM2 gene on chromosome 19p13, encoding DNM2 [101]. Its onset age is between the first and the second decade of life, with the symptoms starting in patients’ feet and legs. Features intermediate between demyelinating and axonal CMT. Although it presents genetic heterogeneity, the appearance of muscle weakness and atrophy in the distal limbs is characteristic, while pes cavus, hyporeflexia and areflexia, and distal sensory impairment are commonly observed symptoms. Moreover, the motor NCV is low-to-normal (ranging between 25 and 54 m/sec). Finally, a loss of myelinated fibers is observed through nerve biopsy, whereas rare segmental demyelination/remyelination, onion bulb formation, and axonal degeneration are also present.

CMTDIC

CMTDIC is caused by a heterozygous mutation in the YARS gene on chromosome 1p35 [102,103]. The age of onset is variable, specifically between the age of 7 and 59 years, starting in patients’ feet and legs. Features intermediate between demyelinating and axonal CMT are observed. Although its genetic heterogeneity, the appearance of muscle weakness and atrophy in the distal limbs and the following involvement of upper limbs with disease progression are characteristic. Additionally, distal sensory impairment was identified. Foot deformities may occur as well. The NCV in this subtype is low-to-normal (ranging between 30 and 40 m/sec). Finally, while axonal regeneration is found through nerve biopsy, nerve fiber density, and thickness are decreased whereas onion bulb formation is not found.

CMTDID

CMTDID is caused by a heterozygous mutation in the MPZ gene on chromosome 1q23 [104]. It begins in patients’ feet and legs, while upper limb involvement may occur at later stages of the disease. Features intermediate between demyelinating and axonal CMT are observed. The main features associated with this subtype include muscle weakness and atrophy in the distal limbs, hyporeflexia, areflexia, and distal sensory impairment. While the NCV is low-to-normal (ranging between 24 and 41 m/sec), axonal degeneration/regeneration are found through nerve biopsy. Additionally, segmental demyelination/remyelination are also characteristic of the CMTDID subtype.

CMTDIE

CMTDIE with focal segmental glomerulonephritis (FSGS) is caused by a heterozygous mutation in the inverted formin, FH2 and WH2 domain containing (INF2) gene on chromosome 14q32 [105]. While the median onset of proteinuria is 18 years of age (ranging from 10 to 21 years), the median onset of the neurological symptoms is 13 years of age (ranging from 5 to 28 years). This type of progressive disorder is associated with both neurological and renal symptoms, distal limb muscle weakness and atrophy. The main symptoms include steppage gait, foot drop, pes cavus, hammertoes, claw hands, hyporeflexia, areflexia, and distal sensory impairment. Furthermore, while distal amyotrophy occurs in both the upper and lower limbs, deafness may be found in some patients. While focal segmental glomerulosclerosis and proteinuria can be described in patients’ kidneys, end-stage renal disease may also define some cases. Finally, the motor NCVs are low-to-normal (ranging from 23 to 45 m/sec), whereas axonal loss and onion bulb formation were identified through sural nerve biopsy.

CMTDIF

CMTDIF is caused by a heterozygous mutation in the GNB4 gene on chromosome 3q26 [106], as reported by one Chinese family and an unrelated patient. Heterotrimeric G proteins, comprised of an alpha, a beta (e.g., GNB4), and a gamma subunit, relay signals from cell surface receptors to internal effectors. Specifically, the alpha subunit is a GTPase that interacts with GDP-bound beta-gamma dimers. Considering that disease onset occurs during adolescence in males and later in females, males are severely affected. This CMT subtype is characterized by distal muscle weakness and atrophy of the upper and lower limbs, while its main symptoms include steppage gait, pes cavus, hammertoes, hyporeflexia, and distal sensory impairment. While variable NCVs (ranging from 16.5 to 45.7 m/sec) can be detected in CMTDIF, the loss of myelinated fibers, onion bulb formation, and axonal regeneration can be identified through sural nerve biopsy.

CMTDIG

CMTDIG is caused by a heterozygous mutation in the NEFL gene on chromosome 8p21 [107]. This CMT subtype presents highly variable phenotypes and a slow progression. Although its onset age is usually between the first and the second decade of life, later onset was also reported. CMTDIG shows mixed axonal and demyelinating features. However, some common symptoms include pes cavus, pes calcaneovalgus,
claw hand deformity, distal sensory impairment, hyporeflexia, and areflexia. Moreover, while distal amyotrophy and muscle weakness occur in both the upper and lower limbs, both proximal muscle weakness and the Gower sign may be found in some patients. Furthermore, impaired blink response is reported in some patients whereas nystagmus and abnormal saccades are more frequent. Additional signs associated with this subtype are delayed motor development, impaired gait, waddling gait, steppage gait, extensor planter responses, spasticity and loss of ambulation. In addition, cerebellar ataxia was identified in one patient. CMTDig is characterized by intermediate NCVs (ranging from 30 to 45 m/sec) and by preserved CMAPs. In contrast, a loss of large myelinated fibers is seen through sural nerve biopsy.

**CMTRIA**

CMTRIA is caused by a homozygous mutation in the *GDAP1* gene on chromosome 8q21 [108]. Mutations in the same gene result in several forms of autosomal recessive CMT disease. CMTRIA onset is in early childhood, specifically between the age of 2 and 4 years, and it is characterized by a severe course. The main symptoms associated with this subtype are lower and upper limb muscle weakness and atrophy, clumsy gait, steppage gait, foot drop, pes cavus, talipes equinovarus, claw hand deformity, scoliosis, hyporeflexia, areflexia, and distal sensory impairment. Furthermore, neuropathic changes are seen on EMG. While the NCVs are normal-to-decreased, a loss of large myelinated fibers is seen through nerve biopsy. Finally, regenerating axons, demyelination, thin myelination, and occasional early onion bulb formation can be observed.

**CMTRIB**

CMTRIB is caused by a compound heterozygous mutation in the *KARS* gene on chromosome 16q23 [109], as reported in one patient. Specifically, such a synthetase catalyzes the aminoacylation of tRNA-lys in both the cytoplasm and mitochondria. This CMT subtype is characterized by lower limb muscle weakness and atrophy, pes cavus, clumsy gait, steppage gait, foot drop, hyporeflexia, areflexia, and distal sensory impairment. Additionally, delayed development, self-abusive behavior, dysmorphic features, and vestibular Schwannoma are frequently found. Finally, EMG findings show neuropathic changes, whereas the NCVs vary from normal to decreased in this subtype.

**CMTRIC**

CMTRIC is caused by either a homozygous or a compound heterozygous mutation in the *PLEKHGS* gene on chromosome 1p36 [110]. Its onset age varies between childhood and adulthood. CMTRIC is characterized by muscle weakness and atrophy in the distal limbs, which mainly affect the lower limbs more. Additional features associated with this CMT subtype include pes cavus, hammertoes, foot deformities, distal sensory impairment, and areflexia. While the motor NCVs are decreased, thin myelination and loss of large myelinated fibers were identified through sural nerve biopsy. In contrast, neurogenic atrophy was seen through muscle biopsy.

**CMTRID**

CMTRID is caused by a homozygous mutation in the *COX6A1* gene on chromosome 12q24 [111]. Specifically, COX is the terminal enzyme of the respiratory chain and the expression of the mRNAs encoding all the subunits varies throughout development. Its onset is in early childhood, precisely between the age of 4 and 5 years. This type presents a mixed axonal and demyelinating neuropathy and shows a slow progression. The main features associated with this CMT subtype include distal muscle weakness and atrophy of both the upper and lower limbs, whereas the main symptoms are foot drop, steppage gait, pes cavus, clawed toes, finger contractures, hyporeflexia, areflexia, and distal sensory impairment. However, hearing loss was found in one adult-onset patient. While NCVs are either decreased or normal, a loss of myelinated fibers is seen through sural nerve biopsy. Finally, decreased myelinated axon caliber and onion bulb formation are characteristic of CMTRID.

**Other CMT-related neuropathies**

Both HNPP and giant axonal neuropathy (GAN) are the most common disorders associated with genetic neuropathy (Table 3). Specifically, when the chromosomal 17p11.2-p12 region is deleted, HNPP, an asymmetric demyelinating neuropathy characterized by temporary weakness and loss of sensation, is induced [112,113]. In fact, HNPP is known to occur due to decreased mRNA expression resulting from the deletion of the *PMP22* gene and it is rarely caused by a frame shift mutation of the *PMP22* gene. Pathological findings in HNPP patients suggest the presence of the tomacula (i.e., an inexperienced herbaceous area) and a decreased structural integrity of the herpes simplex, which result in a structure which can be easily damaged by physical traumas.

In contrast, GAN is an autosomal recessive genetic disorder
caused by a mutation of the gigaxonin, a new cytoskeletal protein expressed in neurons [114]. The formation of nerve microfibrillation around the Ranvier nodule is mainly a result of the swelling of the axon, which causes in turn a remarkable increase in its diameter and an abnormal shape. Interestingly, neurofibrillary tangles are also found in the brain of such patients, suggesting a correlation with the mental retardation reported in this disease.

CONCLUSION

In the present review article, an accurate description of the latest clinical and genetic features related to CMT disease was attempted, aiming at improved diagnoses. In fact, given that CMT is a rare disease with different phenotypes depending on their causative mutations, understanding the genetic mutations behind CMT and their etiology is essential for both an appropriate diagnosis and future therapeutic approaches. Furthermore, as the approach to treatment becomes possible, the diagnosis of the causative genes assumes a crucial role and the recognition of the genotype-phenotype correlation is required. Finally, this review article summarizes the necessary items needed for the patient-specific diagnosis of the CMT subtypes, which will be helpful to clinicians and CMT researchers.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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