Hereditary motor neuropathies

Marina Frasquet[a,d] *and Teresa Sevilla*[b,c,d,e]

Purpose of review
Distal hereditary motor neuropathies (dHMN) are a clinically and genetically diverse group of disorders that are characterized by length-dependent axonal degeneration of lower motor neurons. In this review, we will provide an overview of dHMN, and we will correlate the distinct clinical subtypes with their causative genes, focusing on the most recent advances in the field.

Recent findings
Despite the massive use of new-generation sequencing (NGS) and the discovery of new genes, only a third of dHMN patients receive a molecular diagnosis. Thanks to international cooperation between researchers, new genes have been implicated in dHMN, such as *SORD* and *VWA1*. Mutations in *SORD* are the most frequent cause of autosomal recessive forms of dHMN. As a result of these findings, the potential benefits of some pharmacological compounds are being studied in cell and animal models, mainly targeting axonal transport and metabolic pathways.

Summary
Despite the wide use of NGS, the diagnosis of dHMN remains a challenge. The low prevalence of dHMN makes international cooperation necessary in order to discover new genes and causal mechanisms. Genetic diagnosis of patients and identification of new pathomechanism are essential for the development of therapeutical clinical trials.

Keywords
Charcot–Marie–Tooth disease, clinical trials, hereditary motor neuropathies, next-generation sequencing, prevalence

INTRODUCTION

Distal hereditary motor neuropathies (dHMN) are a clinically and genetically heterogeneous group of disorders characterized by slow and progressive degeneration of the distal lower motor neuron without significant sensory involvement. Nevertheless, many forms of dHMN have minor sensory abnormalities and mutations in the same gene and can be expressed as both dHMN and Charcot–Marie–Tooth 2 (CMT2) [1].

The classical dHMN phenotype consists of muscle weakness and atrophy beginning in distal lower limbs and presenting in either childhood or adulthood. There are also atypical forms, some dHMN present with predominantly upper limb onset and weakness, whereas others can associate different features like vocal cord and/or diaphragmatic palsy [1]. In addition, there is a clinical overlap between dHMN and other degenerative diseases, such as spinal muscular atrophy (SMA), amyotrophic lateral sclerosis (ALS), hereditary spastic paraplegia (HSP) and myopathies.

The prevalence of dHMN is not exactly known. Recently, the minimum prevalence of dHMN in the North of England and Eastern Spain has been estimated at 2.14 and 2.3 per 100 000 population, respectively [2,3▪]. The rate of diagnosis in a recent series is around 30–40%, and the majority of patients with a confirmed genetic diagnosis carry a mutation in *BICD2, GARS1, HSPB1* and *SORD* genes in several geographically diverse populations (Table 1) [2,3▪–5▪,6]. The high percentage of genetically undiagnosed cases may be a result of undiscovered causative genes, cases without a true genetic cause, or currently difficult to detect and/or

[a]Department of Neurology, Hospital Universitari Doctor Peset, [b]Neuromuscular Diseases Unit, Department of Neurology, Hospital Universitari i Politècnic La Fe, [c]Neuromuscular and Ataxias Research Group, Instituto de Investigación Sanitaria La Fe, [d]Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER) Spain and [e]Universitat de València, Valencia, Spain

Correspondence to Teresa Sevilla, Neuromuscular Diseases Unit, Neurology Department, Hospital Universitari i Politècnic La Fe, Avenida Fernando Abril Martorell 106, 46026 Valencia, Spain.
Tel: +34 606208280; e-mail: sevilla_ter@gva.es

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KEY POINTS

- One of the challenges of dHMN is the existence of great genetic variability and that each gene is responsible for a small percentage of cases.
- The variable clinical course, and occasional associated neurologic features can complicate the phenotype and are useful for the clinical subclassification of dHMN.
- The most frequent causes of dHMN are mutations in heat shock proteins (*HSP*), *GARS1*, *BICD2*, and *SORD*.
- The underlying pathophysiology of dHMN overlaps considerably with other neuromuscular disorders, mainly myopathies and motor neuron diseases.
- Several compounds are under study in cellular and animal models, and axonal transport is an important therapeutic target.

interpret variations, such as deep intronic, regulatory or structural ones [7▪].

Careful clinical assessment and electrophysiological studies are essential for the diagnosis of patients with dHMN. MRI is taking an increasingly prominent role in the diagnosis of inherited neuromuscular diseases. Recently, a pattern was proposed to be useful to differentiate myopathic from neurogenic conditions, and it involved small areas of muscle tissue with normal signal intensity being surrounded by areas with a similar intensity to subcutaneous fat. This apparent fat replacement within normal muscle, referred to as 'islands', represents a promising potential discriminatory marker [9▪].

In this review, we will focus on the clinical subtypes of dHMN and the genetic heterogeneity seen in each of these. In addition, we will review the genes believed to cause dHMN that have been identified in recent years.

CLASSIC DISTAL HEREDITARY MOTOR NEUROPATHIES

One of the most common causes of dHMN are dominant mutations in *HSPB1*, the prevalence of which vary between 5 and 10% in different series [3▪–5▪,6,10]. Recessive inheritance has been reported in few cases [11,12]. Patients carrying the same *HSPB1* mutation can be diagnosed with either dHMN or CMT2 [3▪]. In last years, some patients with distal muscle weakness and atrophy caused by mutations in *HSPB1* have been diagnosed with a mixed 'neuromyopathic' condition based on muscle biopsy findings that show combined features of both neurogenic and myopathic processes and vacuoles in muscle fibers. The HSPB1 protein is part of the 'small heat shock protein' (sHSP) family. sHSPs act as molecular chaperones by binding to

Table 1. Genetic diagnosis rate and most prevalent genes in different hereditary motor neuropathy series from the last 5 years

		[a]Dierick *et al.*, 2008 [8]	Bansagi *et al.*, 2017 [2]	Frasquet *et al.*, 2021 [3▪]	Liu *et al.*, 2020 [4▪]	Wu *et al.*, 2022 [5▪]
Index cases with genetic diagnosis		17/112 15.1%	26/73 35.6%	37/108 34.2%	24/70 34.3%	33/90 36.7%
Distribution of patients with confirmed genetic diagnosis (only most frequent genes in each series are shown, not all diagnosed patients).						
Gene	Inheritance	*N* (total number of patients)				
AARS1	AD		6			
BICD2	AD		5	13		2
BSCL2	AD	8			2	
DNAJB2	AR			11		
GARS1	AD		5	16	2	
HSPB1	AD	4		17	8	6
SETX	AD	2				
IGHMBP2	AR		4		3	
MME	AR					3
SORD[a]	AR			5		2
HSPB8	AD	3				
SYT2	AD		6			

Only confirmed causative mutations are included. AD, autosomal dominant; AR, autosomal recessive; IC, index cases.
[a]Seven genes were studied in this series (*HSPB1, HSPB8, BSCL2, GARS1, SETX, DCTN1* and *VAPB*).
[b]*SORD* has only been studied in Frasquet *et al.* and Liu *et al.* series.

damaged or misfolded proteins to facilitate their repair or removal, thus preventing these from forming aggregates [13]. Heterozygous mutations in other chaperones of the sHSP family, such as *HSPB8*, have also been described as a cause of dHMN and CMT2, but they are much less frequent than *HSPB1* mutations [13].

The *DNAJB2* or *HSJ1* gene encodes a co-chaperone of the 'heat shock protein' family. Recessive mutations in *DNAJB2* cause dHMN and CMT2 [14], and in some series this is a relative common cause of dHMN [3▪,5▪]. Initially, weakness and atrophy affect distal muscles of the lower limbs, but later weakness spreads to proximal muscles of lower limbs, upper limbs, and after several decades also to bulbar and facial muscles, causing a severe impairment. In addition, some patients may present with early-onset parkinsonism [15]. Recently, loss of DNAJB2 expression and phospho-alpha-synuclein deposits were found in the skin biopsy in a patient with neuropathy and parkinsonism with a homozygous *DNAJB2* null mutation [16▪].

The classical presentation can be found in relation with many other genes, an alphabetical review can be found in Table 2.

DISTAL HEREDITARY MOTOR NEUROPATHIES WITH UPPER LIMB PREDOMINANCE

In a subset of patients with dHMN and/or motor CMT2, the first symptoms are atrophy and weakness of the intrinsic muscles of the hands, mainly affecting the thenar and first dorsal interosseus muscles, without involvement of lower limbs until later in the disease course. Motor and sensorimotor phenotypes vary among different families and among members of the same family [1].

Dominant *GARS1* mutations are distributed throughout the gene, and they have been found in various populations [2,3▪–4▪]. Moreover, de novo variants in *GARS1* have been associated with infantile-onset SMA (iSMA) similar to childhood SMA caused by mutations in SMN1 [17]. Recently, variants that alter the same amino-acid residue (p. Pro336His and p.Pro336Arg) were seen to lead to distinct neuropathic phenotypes, which range from iSMA to CMT2D [18].

The molecular mechanisms underlying the effects of *GARS1* mutations are not completely understood, and both loss-of-function [19] and gain-of-function effects have been proposed [20▪].

Heterozygous *REEP1* mutations are a cause of HSP [21]. A single splice-site alteration in *REEP*1 (c.304–2A>G) has been found in a family with dHMN without upper motor involvement. Symptom-onset was in the first two decades. In some patients, the neuropathy started in distal upper limbs and in others in distal lower limbs. [22]. A recessive *REEP1*mutation was also associated with congenital axonal neuropathy and respiratory distress, provoking a clinical phenotype similar to that of patients with type SMA with respiratory distress type 1 (SMARD1) [23]. Dominant mutations in *BSCL2* are associated with a variety of different neuromuscular disorders, including dHMN, Silver syndrome, CMT2 and HSP [1]. Two recurrent mutations, N88S and S90L have been described as a common cause of dHMN starting in intrinsic hand muscles and in some cases, in association with upper motor neuron involvement. Muscle MRI in patients carrying the N88S variant showed a pattern of fat replacement that mainly affected the muscles of the thenar eminence and the soleus and tibialis anterior. Moreover, the MRI score correlated with clinical severity, probably serving as a reliable outcome measure for future clinical trials [24▪].

SLC5A7 encodes a presynaptic choline transporter (CHT), a critical determinant of synaptic acetylcholine synthesis and release at the neuromuscular junction. Recessive mutations in *SLC5A7* cause congenital myasthenic syndrome disorders [25] whereas autosomal dominant mutations cause distal weakness with upper limb predominance and vocal cord paresis [26]. Noteworthy, neither fatigue was reported in cases with dHMN caused by monoallelic mutations in this gene, nor signs of neuropathy were detected in cases with myasthenic syndrome and recessive mutations.

SPINAL MUSCULAR ATROPHY LOWER EXTREMITY DOMINANT (SMALED)

BICD2 and DYNCH1H1 proteins are part of the dynein/dynactin retrograde transport complex in axons [27▪]. Dominant mutations in *DYNC1H1* and *BICD2* are a cause of congenital or early-onset lower limb weakness that follows a static or minimally progressive course. Muscle MRI shows a characteristic common pattern of muscle involvement with fat deposition in most thigh muscles sparing the adductors and semitendinous [27▪] and selective involvement of gluteus medius and minimus at the pelvic level [28].

DISTAL HEREDITARY MOTOR NEUROPATHIES AND VOCAL CORD PARESIS

Dynactin 1 (DCTN1) is implicated in axonal retrograde transport [29▪▪]. *DCTN1* mutations are a rare cause of HMN. In the first described family, the phenotype was characterized by bilateral vocal cord paralysis appearing in adulthood followed by facial,

hand and finally distal leg weakness [1]. No other families with vocal cord paresis and *DCTN1* mutations have been described.

Mutations in the *TRPV4* gene are associated with several disease phenotypes that includes a spectrum of hereditary neuropathies with either sensorimotor or exclusively motor involvement and that are frequently associated with vocal cord paresis, diaphragmatic weakness, scapular winging and distal congenital SMA. The phenotypic variability among and within families is substantial with age of onset ranging from congenital to asymptomatic carriers in the eighth decade [1].

MYOPATHY AND NEUROMUSCULAR JUNCTION

Biallelic mutations in *GNE* were found in a family that initially displayed classic symptoms of dHMN. Muscle biopsy showed both neurogenic and myopathic features with rimmed vacuoles in muscle fibers [30].

A complex phenotype of peripheral neuropathy, myopathy, hoarseness and hearing loss has been described in relation with autosomal dominant variants on *MYH14*. Histopathologic and electrophysiological studies revealed both chronic neuropathic and myopathic features in the affected patients [31].

Mutations in *SYT2* cause an autosomal dominant form of presynaptic neuromuscular junction (NMJ) dysfunction with motor neuropathy in most cases indistinguishable from a 'classic dHMN'. Electrophysiological studies are key for the diagnosis as they demonstrate NMJ dysfunction [32].

SPINAL MUSCULAR ATROPHY WITH RESPIRATORY DISTRESS

SMA with respiratory distress type 1 (SMARD1), is caused by biallelic mutations in the *IGHMBP2* gene [1]. Recessive mutations in the *IGHMBP2* gene have also been described as causing childhood-onset CMT2 and 'typical' dHMN with no respiratory involvement [2]. A similar clinical picture, coined SMARD2, has been described in a patient carrying a de-novo c.1430G.A (p.S477N) mutation in the *LAS1L* gene [33].

UPPER MOTOR NEURON

Recessive mutations in *VRK1* and *SIGMAR1* can cause a broad spectrum of phenotypes, the most frequent one is dHMN combined with upper motor neuron signs, which can range from brisk reflexes to frank spasticity or mimic ALS or Silver syndrome [29▪▪,34,35]. Upper motor neuron signs are frequently found in other genes responsible for dHMN (Table 2).

NOVEL GENES

Biallelic mutations in *SORD* were identified as a cause of dHMN and CMT2, with an estimated frequency in undiagnosed dHMN and CMT2 cases of up to 10% [40▪▪]. Subsequently, several studies have confirmed that biallelic *SORD* mutations are a frequent cause of dHMN in different populations [3▪,41▪,42]. Almost all described patients carry the c.757delG (p.Ala253GlnfsTer27) variant in homozygosity or in a compound heterozygous state with a second likely pathogenic variant [40▪▪,41▪,42]. Only one patient who is compound heterozygous for c.404A>G and c.908+1G>C without the c.757del variant has been described [43]. Patients present a pure motor (dHMN) or sensory-motor (CMT2) neuropathy with motor symptoms more evident than sensory involvement [40▪▪]. In addition to the classical presentation, some patients show a nonlength-dependent neuropathy with prominent upper limb involvement and motor conduction slowing and block in electrophysiological studies [44].

Mendoza-Ferreira *et al.* [45▪] identified pathogenic variants in *GBF1* in four unrelated families with individuals affected by sporadic or dominant HMN/CMT2. GBF1 is mainly involved in maintenance and function of the Golgi apparatus and mitochondria migration and positioning.

Mutations in the *VWA1* (Von Willebrand factor A domain containing 1) gene have recently been identified as a cause of recessive dHMN [46▪▪,47▪▪]. Specifically, Pagnamenta *et al.* identified 17 patients belonging to 15 different families with biallelic mutations in *VWA1*. All families but one shared a common mutation, p.(G25Rfs*74), a 10-bp repeat expansion in exon 1 [46▪▪]. In a simultaneous work by Deschauer *et al.* [47▪▪], six different truncating variants in *VWA1* were identified in 15 affected individuals from 6 families of different ethnic origins. In both cases, the clinical profile described was very similar. Symptom onset occurs usually in childhood, and there is a nonlength-dependent weakness in lower limbs. Many patients associate foot deformities, and the presence of joint contractures and lumbar hyperlordosis is also frequent. The course is very slowly progressive. In the study by Pagnamenta *et al.*, patients were diagnosed with motor neuropathy, whereas in the Deschauer *et al.* study, patients were diagnosed with a mixed 'neuromyopathic' entity based on mixed electrophysiological and muscle biopsy results. WARP (von Willebrand factor A-domain-related protein) is an extracellular matrix protein expressed in the peripheral nervous

Table 2. List of distal hereditary motor neuropathies-associated genes with corresponding phenotypes, genotypes and presumed pathological mechanism

Gene	Inheritance	Phenotype	Presumed mechanism
AARS1	AD	Classic dHMN/CMT2	tRNA aminoacylation activity [29▪▪]
AIFM1	X-linked, recessive	Early onset dHMN * Cowchock syndrome, mitochondrial encephalomyopathy, hearing loss.	Misassembling OXPHOS complexes [29▪▪]
ATP7A	X-linked, dominant	Classic HMN. Some patients have dysautonomic features. *Menkes disease. *Occipital horn syndrome.	Ion homeostasis/Copper transport [29▪▪]
ATXN2	AD	dHMN + cerebellar involvement *SCA2	RNA metabolism and DNA integrity [29▪▪]
BICD2	AD	SMALED2 Athrogryposis/classic dHMN	Axonal transport [29▪▪]
BSCL2	AD	dHMN upper limb predominant (dHMN–V) Classic dHMN *Silver syndrome: upper limb predominance+ spasticity *Berardinelli–Seip congenital lipodystrophy (AR)	Endoplasmic reticulum stress [29▪▪]
CHCHD10	AD	Lower motor neuron syndrome with late-adult onset (LOSMoN) Spinal muscular atrophy Jokela type (SMAJ)	Mitochondrial function [36,37]
DCTN1	AD	dHMN-VIIB (dHMN, upper limb predominant with vocal cord palsy) *Perry syndrome (AD). 'ALS susceptibility'	Axonal transport [29▪▪]
DHTKD1	AD	dHMN *CMT2	Mitochondrial function [2]
DNAJB2	AR	dHMN with progressive course ('ALS mimic' in late stages of the disease). Sensory involvement appears as the disease progresses. In some patients, parkinsonism and pyramidal signs are present	Axonal transport/molecular chaperone [29▪▪]
DYNC1H1	AD	SMALED1 Arthrogryposis. SNC can be affected	Axonal transport [27▪]
FBXO38	AD	dHMN with calf predominance	Abnormal signal transduction [29▪▪]
	AR	Congenital dHMN with classic pattern associated with hearing loss and organic malformations	
GARS1	AD	dHMN upper limb predominant (dHMN-V) CMT2D SMAi	tRNA aminoacylation activity [29▪▪]
GBF1	AD	Classic dHMN/late-onset motor CMT2	Golgi fragmentation [45▪]
GNE	AR	dHMN/myopathy	Surface modification [38▪]
HARS1	AD	dHMN CMT2, motor CMT2, demyelinating or intermediate CMT (AD) Others: ataxia, multisystem (AR)	tRNA aminoacylation activity [29▪▪]
HINT1	AR	dHMN/motor CMT2 with neuromyotonia	tRNA aminoacylation activity [29▪▪]
HSPB1	AD (rarely AR)	dHMN and motor CMT2 'Neuromyopathy' with high CKs levels (>1000 U/l) and vacuoles in muscle biopsy	Axonal transport/molecular chaperone [29▪▪]

Table 2 (*Continued*)

Gene	Inheritance	Phenotype	Presumed mechanism
HSPB3	AD	Classic dHMN, onset: third or fourth decade	Axonal transport/molecular chaperone [29▪▪]
		CMT2. Myopathy.	
HSPB8	AD	Classic dHMN. Early adulthood-onset. CMT2, myofibrillar myopathy	Axonal transport/molecular chaperone [29▪▪]
IGHMBP2	AR	Spinal muscular atrophy with respiratory distress type 1 – SMARD1 dHMN and CMT2. Childhood onset with or without respiratory involvement	RNA metabolism and DNA integrity [29▪▪]
KBTBD13	AR	Classic dHMN *Nemaline myopathy type 6 (AD)	Cytoskeletal stability [38▪]
LAS1L	X-linked	Spinal muscular atrophy and respiratory distress type 2 (SMARD2)	Ribosomal biogenesis and translation [33]
MYH14	AD	Classic dHMN (+/- distal myopathy), hoarseness, and hearing loss.	Dysfunction of mitochondria [31]
		*Neurosensorial hearing loss Myopathy	
NOTCH2NLC	AD	dHMN and vacuolar myopathy, some patients present tremor and cerebellar involvement	Chaperone activity? [49▪]
PLEKHG5 (PNPK)	AR	dHMN Spinal muscular atrophy (SMA) most patients CMTi	Axonal transport [29▪▪]
REEP1	AD	dHMN upper limb predominant (dHMN-V) Classic dHMN *Congenital axonal neuropathy with arthrogryposis and respiratory distress (AR)	Endoplasmic reticulum stress [29▪▪]
SCO2	AR	Early onset dHMN. Some patients have white matter alterations *CMT2 early onset	Mitochondrial respiratory chain [38▪]
SETX	AD	dHMN with upper motor neuron signs/juvenile ALS (ALS 4) *Ataxia and oculomotor apraxia type 2 (AR)	RNA metabolism and DNA integrity [29▪▪]
SIGMAR1	AR	dHMN with pyramidal signs dHMN Jerash *ALS-frontotemporal dementia (AR)	Endoplasmic reticulum stress [29▪▪]
SLC25A21	AR	dHMN starting in childhood with severe progression. Brisk reflexes, mitochondrial features in muscle biopsy (variant K232R) *Synpolydactyly (AD)	Ion channels transporters [29▪▪]
SLC5A7	AD	dHMN with upper limb predominance and vocal cord paresis (dHMN-VII) Some patients have brisk reflexes * Congenital myasthenic syndrome (AR).	Ion channels and transporters [29▪▪]
SLC12A6	AD	Early-onset dHMN, rapidly spread to proximal muscles (variant T991A). *Agenesis of corpus callosum and CMT (AR)	Ion channels and transporters [29▪▪]
SOD1	AD	Classic dHMN (p.E22G variant)	Protein folding [3▪]
SORD	AR	Classic dHMN. CMT2 and intermediate CMT, conduction blocks may be present in electrophysiological studies	Sorbitol metabolism [40▪▪]
SPTAN1	AD	Classic dHMN phenotype. *Epileptic encephalopathy. *Hereditary spastic paraplegia (AR).	Axonal transport [29▪▪]
SYT2	AD	Classic dHMN with presynaptic NMJ dysfunction in electrophysiological studies	Axonal transport [29▪▪]

Table 2 (*Continued*)

Gene	Inheritance	Phenotype	Presumed mechanism
TDRKH	AD	Classic dHMN phenotype with facial and neck flexor muscle impairment	Related with survival of motor neuron [39]
TRPV4	AD	dHMN and vocal cord palsy Others: CMT2, scapuloperoneal muscular atrophy, congenital muscular spinal atrophy with arthrogryposis	Ion channels and transporters [29▪▪]
VRK1	AR	Classic dHMN. dHMN and pyramidal features	Nuclear envelope [34]
VWA1	AR	HMN with nonlength-dependent pattern	Axonal development and synapse formation [46▪▪,47▪▪]
WARS	AD	Classic dHMN	tRNA aminoacylation activity [29▪▪]

The associated phenotypes are annotated as follows: (*), other phenotypes; AD, autosomal dominant; ALS, amyotrophic lateral sclerosis; AR, autosomal recessive; CMT, Charcot–Marie–Tooth; dHMN, distal hereditary motor neuropathy; SCA, spinal cerebellar atrophy; SMAi, infantile spinal muscular atrophy. Motor CMT2 refers to CMT2 with predominantly motor involvement.

system that interacts with collagen VI and perlecan [46▪▪,48▪▪].

A GGC repeat expansion in the 5′-untranslated region (5′-UTR) of the *NOTCH2NLC* gene has been associated with distal motor neuropathy and rimmed vacuolar myopathy with autosomal dominant inheritance [49▪]. Clinical onset occurs in early adulthood with progressive distal lower limb weakness. In some cases, weakness is severe and spreads to proximal muscles, causing severe disability. Some patients also present with tremor. Nerve conduction studies in these patients have been interpreted as compatible with a demyelinating motor neuropathy, although motor conduction velocities were in axonal range in nerves with preserved compound muscle action potential (CMAP) amplitudes. EMG showed neurogenic changes and myotonic discharges in some cases. Muscle biopsies showed mixed myopathic and neuropathic changes as well as rimmed vacuoles. Pathological studies also revealed the presence of p62-positive intranuclear inclusions in the Schwann cells and muscle cells as well as in the rimmed vacuoles. Recently, another family with six affected individuals and lower motor neuron syndrome was associated to GGC repeat expansion in *NOTCH2NLC*, which validates this gene as a cause of HMN [50▪].

In a cohort of 343 patients with axonal CMT without genetic diagnosis. Bis-Brewer *et al.,* [7▪] performed an exome-wide rare variant burden analysis and identified *EXOC4* as a candidate CMT gene. EXOC4 is abundantly expressed at the *Drosophila* neuromuscular junction and required for in-vivo regulation of synaptic microtubule formation. Although EXOC4 has biological plausibility, the authors advise to be extremely cautious about overstating any potential involvement of EXOC4 in disease pathogenesis.

TREATMENT

There is currently no effective treatment for dHMN, although several compounds are under investigation [51▪]. One of the difficulties in this area is the great genetic diversity and different pathomechanisms involved in dHMN. In some cases, finding a specific targeted therapy seems feasible, as in the case of inherited neuropathies caused by *SORD* mutations, in which aldolase reductase inhibitors have shown to normalize intracellular sorbitol levels in patient fibroblasts and improve the motor phenotype of a *Drosophila* model of the disease [40▪▪]. The alternative is finding therapies that have an effect on common pathomechanisms involved in different types of dHMN, such as axonal transport. Acetylation of α-tubulin facilitates axonal transport [52]. Histone deacetylase 6 (HDAC6) is the major deacetylating enzyme of α-tubulin. Treatment with HDAC6 inhibitors improved α-tubulin acetylation and ameliorated motor performance as well as electrophysiological parameters in HSPB1 mice [52]. HDAC6 inhibition was recently found to improve the functional phenotypes observed in *GARS1* mutant neurons [53▪]. SIRT2 belongs to class III histone deacetylases (HDACs) and controls the acetylation status of several proteins, including α-tubulin. Zhao *et al.* showed that genetic knockdown of SIRT2 rescues *GARS*-induced axonal neuropathy and prolongs lifespan in a *Drosophila* model ($GARS^{G526R}$) of the disease. This study demonstrates the pathogenic role of SIRT2-dependent α-tubulin deacetylation in mutant GARS-induced neuropathies and

provides new insights to target SIRT2 as a potential therapy in hereditary axonopathies [54▪▪].

Neurotrophin 3 (NT-3) is an autocrine factor involved in Schwann cell survival, maintenance of the NMJ, and radial growth of muscle fibers. Ozes *et al.* tested the efficacy of *NT-3* gene transfer therapy via intramuscular injection of adeno-associated virus setoype-1 in *GARS1*-CMT mice models. The study showed that *NT-3* gene transfer therapy produced significant functional and electrophysiological improvement in mice. It also increased both myelin thickness and muscle fiber size and improved the denervated state of NMJ. On the basis of the multiple effects of this molecule, a potential benefit could be predicted in patients with mutations in *GARS1* and other aminoacyl tRNA synthetases [55▪▪]. Zuko *et al.* found that mutant glycyl-tRNA synthetases cause an impairment in mRNA translation elongation and that transgenic $tRNA_{Gly}$ overexpression rescues protein synthesis and peripheral neuropathy in mice and fly models of GARS1-CMT/CMT2D. These data suggest that increasing $tRNA_{Gly}$ may constitute a therapeutic approach for CMT2D [56▪].

CONCLUSION

HMN are a group of diseases that affect lower motor neurons. Although there are characteristic phenotypic profiles, they do not always correspond to a single genetic cause and frequently overlap with other neuromuscular diseases. To optimize the genotype–phenotype correlation in clinical practice and in research studies, we have attempted to combine phenotypic profiling with the most frequent causal genes. However, as more causal variants have been described, there are practically no genes that correspond to a unique 'pure' phenotype. Here we have reviewed the new genes that have been discovered in recent years and the genetic diagnosis rate of several clinical series. In the future, important efforts and collaborative networks will be needed in order to discover new genes or causal mechanisms related to dHMN.

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Conflicts of interest

There are no conflicts of interest.

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