

Early onset hereditary neuropathies: an update on non-5q motor neuron diseases

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Hereditary motor neuropathies (HMN) were first defined as a group of neuromuscular disorders characterized by lower motor neuron dysfunction, slowly progressive length-dependent distal muscle weakness and atrophy, without sensory involvement. Their cumulative estimated prevalence is 2.14/100 000 and, to date, around 30 causative genes have been identified with autosomal dominant, recessive, and X-linked inheritance. Despite the advances of next generation sequencing, more than 60% of patients with HMN remain genetically uncharacterized. Of note, we are increasingly aware of the broad range of phenotypes caused by pathogenic variants in the same gene and of the considerable clinical and genetic overlap between HMN and other conditions, such as Charcot-Marie-Tooth type 2 (axonal), spinal muscular atrophy with lower extremities predominance, neurogenic arthrogryposis multiplex congenita and juvenile amyotrophic lateral sclerosis. Considering that most HMN present during childhood, in this review we primarily aim to summarize key clinical features of paediatric forms, including recent data on novel phenotypes, to help guide differential diagnosis and genetic testing. Second, we describe newly identified causative genes and molecular mechanisms, and discuss how the discovery of these is changing the paradigm through which we approach this group of conditions.

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Keywords: dHMN; HMN; paediatric neuropathies; distal SMA; SMA-LED

Introduction

Hereditary motor neuropathies (HMN) are a heterogeneous group of disorders that were first defined by the following characteristics: (i) slowly progressive, length-dependent distal muscle weakness and atrophy; (ii) signs of chronic denervation on needle EMG in presence of normal/slightly reduced motor nerve conduction velocity (NCV) and normal/reduced compound motor action potential (CMAP); and (iii) absence of clinical and/or electrophysiological

sensory involvement, which should mark the difference with Charcot-Marie-Tooth (CMT) type 2.^{1,2}

The estimated pooled prevalence of HMNs is 2.14/100 000 and, to date, around 30 causative genes have been identified, including forms inherited in an autosomal dominant (AD), recessive (AR), and X-linked pattern (Table 1).³ Despite the great advances achieved through next-generation sequencing (NGS), the diagnostic yield in patients with a pure HMN phenotype is still ~32.5%, at latest estimate.^{3–5}

Received July 08, 2022. Revised October 21, 2022. Accepted November 12, 2022. Advance access publication November 29, 2022

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Table 1 Summary of main early-onset motor neuronopathies

Gene symbol	OMIM ref	Inheritance	Protein/Function	Associated conditions
Conditions with predominant distal involvement				
HSPB1	608634	AD/AR	UPR; stabilization of microtubules?	HMN2B, CMT2F
HSPB8	158590	AD	UPR	HMN2A, CMT2L
HSPB3	613376	AD	-	HMN2C, CMT2
ATP7A	300489	X-linked	Copper transport	X-linked HMN (SMA3)
WARS	617721	AD	Tryptophanyl-tRNA synthetase	HMN9
FBXO38	615575	AD	Transcriptional activator	HMN2D
DNAJB2	614881	AR	Co-chaperone	DSMA5
HINT1	137200	AR	Purine phosphoramidase	HMN with neuromyotonia
IGHMBP2	604320	AR	Helicase	HMN6/SMARD, CMT2S
GARS	600794	AD	Aminoacyl-tRNA synthetases. Disruption of the VEGF/Nrp1 signalling pathway?	CMT2D, HMN5A, SMARD like phenotype
REEP1	614751	AD	ER-mitochondrial interactions	HMN5B, HSP31
BSCL2	619112	AD	UPR	HMN5C, Silver syndrome
TRPV4	600175, 181405	AD	Ion channel—possible disruption of mitochondrial axonal trafficking	HMN7, CMT2C, SPSMA, AMC, skeletal dysplasia
SLC5A7	158580	AD	Presynaptic choline transporter	HMN7A, CMS 20
DCTN1	607641	AD	Axonal transport along the microtubules	HMN7B, juvenile ALS, Perry syndrome
SIGMAR1	605726	AR	ER chaperone	DSMA2, Juvenile ALS
SETX	606002, 602433	AR, AD	RNA and DNA helicase	HMN + pyramidal
AAAS	231550	AR	Nuclear protein import	Triple A syndrome
SORD	618912	AR	Oxidation of sorbitol to fructose	N/A
COQ7	*601683	AR	Coenzyme Q10 biosynthesis	N/A
MFN2	n/a	AD	Mitochondrial fusion	CMT2A
SMA-LED or neuronopathies with early proximal weakness				
DYNC1H1	58600	AD	Axonal retrograde transport + other housekeeping functions	SMALED 1, HMN1, AMC, ID + MCD
BICD2	615290, 618291	AD	Cargo adaptor protein, interact with dynein/kinesin complex. Localize Rab6 to Golgi	SMALED2A, SMALED2B, AMC
SYT2	616040	AD	Ca ²⁺ sensors for vesicular trafficking and exocytosis	Presynaptic CMS (AR)
PLEKHG5	611067	AR	Nuclear factor kappa-B activator	CMT-RIC
VWA1	619216	AR	ECM component	N/A

AMC = arthrogryposis multiplex congenita; CMT = Charcot Marie Tooth; CMS = congenital myasthenic syndrome; HSP = hereditary spastic paraplegia; ID = intellectual disability; LL = lower limbs; MCD = malformation of cortical development; UL = upper limbs; UPR = unfolded protein response.

A more comprehensive table describing salient clinical features and age of onset is provided in the [Supplementary material](#).

The first classification made by Harding and colleagues in 1993 was based on the mode of inheritance, clinical findings, and the age at symptoms onset. This resulted in the definition of seven subtypes (HMN 1–7).⁶ However, the advent of NGS has progressively revealed the complexity underlying this group of disorders, which cannot be exhaustively captured by the original phenotypical classification.⁷

There is indeed a considerable clinical and genetic overlap with conditions ranging from axonal CMT (CMT2) to spinal muscular atrophy with lower extremities predominance (SMA-LED), neurogenic arthrogryposis multiplex congenita (AMC), juvenile amyotrophic lateral sclerosis (ALS), hereditary spastic paraplegias (HSP), and even distal myopathies.^{3,8,9} Moreover, pathogenic variants in the same gene can cause heterogeneous and variable phenotypes.^{9–13}

Most HMNs present during childhood or even at birth. In this review we primarily aim to give a detailed characterization of paediatric HMN, highlighting the clues that may help direct genetic testing (Fig. 1). Second, we aim to report on novel phenotypes and genes, and how the discovery of these is expanding the paradigm through which we approach this group of conditions.

Importantly, we acknowledge that the terminology commonly used (e.g. HMN, dHMN, distal SMA) may oversimplify pathophysiology as it does not necessarily reflect a biological substrate or clinical

phenotype.^{14,15} Hence, we would rather use the general term ‘motor neuronopathies’, which we have subdivided in the following grouping:

- (i) HMN: this group reflects the original classification by Harding et al.,⁶ in which the key finding is a length-dependent (i.e. distal > proximal) pattern of weakness and atrophy in the absence of sensory involvement. For a matter of clarity, we listed every gene presenting with these features according to its predominant phenotype [e.g. predominant distal lower/upper limb (LL/UL) involvement, presence of significant respiratory involvement, vocal cord paresis, pyramidal signs].
- (ii) CMT2 overlap: this group includes conditions with a very similar phenotype to HMN, but in which sensory abnormalities are usually found.
- (iii) SMA-LED: this group was first defined by the congenital or infantile onset of non-length dependent lower limb predominant weakness.¹⁶ While the evident discrepancy between UL and LL involvement is suggestive for the diagnosis, exceptions exist. We included in this section those conditions in which distal and proximal weakness can be equally observed, i.e. those in which length dependent weakness is not found.
- (iv) Neurogenic AMC.
- (v) Juvenile ALS: this group of progressive disorders is the differential diagnosis of HMN, mainly defined by the coexistence of lower and upper motor neuron signs and early bulbar involvement.
- (vi) Motor neuronopathies associated with brain involvement: conditions sometimes termed SMA-plus (e.g. SMA plus pontocerebellar hypoplasia, seizures, severe bulbar involvement), and riboflavin transporter deficiency associated

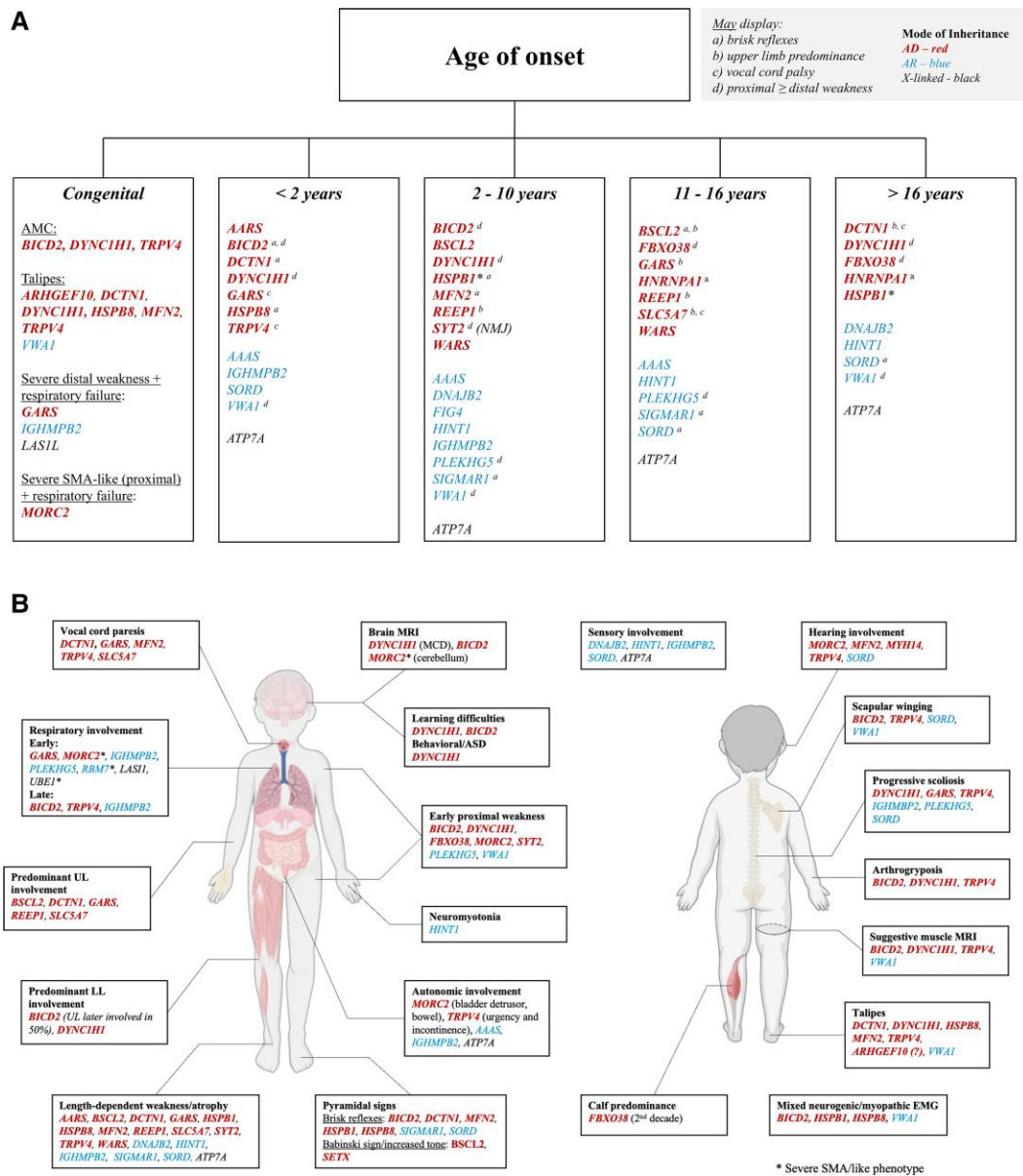


Figure 1 Diagnostic clues based on age of onset (A) and relevant clinical features (B). Relevant clinical features (B) may or may not be present due to disease spectrum or stage at assessment. Genes are listed in alphabetical order and according to mode of inheritance: autosomal dominant (AD) pattern, bold font and red; autosomal recessive (AR), regular font and blue; X-linked in black (*LAS1L* and *ATP7A*). Asterisk indicates when more than one mode of inheritance has been associated with the same gene. EMG = electromyography; MCD = malformation of cortical development.

disease,¹⁷ will not be covered in this article. A summary is provided in [Supplementary Table 1](#) and detailed review is provided by Teoh et al.¹⁸ and Farrar et al.¹⁹

To conduct the present review, we searched in PubMed for the following keywords: ‘HMN’, ‘dHMN’, ‘Distal SMA’, ‘SMA-LED’, ‘neuronopathies’ and ‘CMT2’.

Additionally, we searched for genes listed in papers or book chapters that have been previously associated with motor neuronopathies, in order to retrieve detailed information regarding the spectrum of phenotypes associated with each condition.

Early onset neuronopathies

Hereditary motor neuropathies

HMN usually beginning in the lower limbs

HSPB1 (AD/AR), HSPB8 (AD) and HSPB3 (AD)

The HSPB genes encode for small heat-shock proteins characterized by the highly conserved alpha-crystallin domain, whose complex biological function ranges from cellular housekeeping to unfolded protein response and regulation of microtubule stability. A detailed discussion regarding the molecular function of heat-shock protein 27-kD (HSPB1²⁰), heat-shock protein 22-kD (HSPB8²¹) and heat-shock

protein B3 (HSPB3²²) is provided by Rossor *et al.*⁹ HSPB1 and HSPB8 related phenotypes are considered similar, but variants in HSPB1 are far more common, accounting for up to 10% of all HMN cases (when considering adult-onset forms).^{5,23,24} The mode of inheritance is usually autosomal dominant, but recessive cases have been reported as well.²³ Interestingly, HSPB1 mutants have also been associated with adult-onset motor neuropathy and distal vacuolar myopathy.²⁵

HSPB1-related disease usually manifests in the fourth decade of life (median 30 years, but up to the seventh decade) with muscle weakness and atrophy in the distal lower limb muscles, and diminished deep tendon reflexes (DTR). Upper limbs involvement occurs many years later. Few cases presenting within the first decade of life and with brisk rather than diminished reflexes have been reported.^{23,24} While to our best knowledge no HSPB1 patient presented with congenital onset, HSPB8-related HMN may manifest at birth with talipes and congenital hip dysplasia. Delayed acquisition of walking is followed by a mild disease course despite the presence of distal atrophy. DTR can be brisk.

Variants in HSPB3 have been exclusively identified in adult-onset HMN.

ATP7A (X-linked)

The ATP7A gene encodes a transmembrane copper-transporting P-type ATPase with numerous functions within the cells.²⁶ Its deficiency has been primarily associated with Menkes disease and occipital Horn syndrome (OHS).²⁷ Missense variants causing aminoacidic substitutions within or near the C-term transmembrane segments of the protein have however been described in ATP7A-related distal motor neuropathy, also named X-linked distal spinal muscular atrophy (SMAX3). Preclinical studies on SMAX3-causing variants suggest that mutant ATP7A might be mislocalized within the axon, possibly due to its impaired binding to adaptor proteins 1 and 2 (AP1 and 2). However, the reason why such changes cause axonal damage remains elusive.²⁸

ATP7A-related HMN usually begins with distal muscle weakness and atrophy of the lower extremities, feet deformities (i.e. pes cavus, hammer toes, curled fingers), later followed by involvement of the upper limbs. DTR are usually reduced or absent. A clinical (e.g. reduction in tactile and vibratory sensation) and neurophysiological mild sensory involvement has been documented in some cases. Disease onset is highly variable even within the same family and may occur as early as 1 year of age, but more commonly in the second and third decade.²⁹ Nerve conduction studies show normal conduction velocities and a diffuse reduction of CMAPs.

Of note, while once considered separate clinical entities with different clinical and biochemical profiles (in SMAX3 serum copper and ceruloplasmin levels are expected to be normal), recent reports suggested that OHS and SMAX3 might represent a continuum³⁰: some SMAX3 patients indeed present with features typical of OHS, such as skin abnormalities and dysautonomia.³¹

WARS (AD)

Autosomal dominant pathogenic variants in the WARS gene, encoding for cytoplasmic tryptophanyl-tRNA synthetase (TrpRS), have been recently found to be the cause of HMN9 and mostly but not exclusively reported in patients of Asian origin.³² The disease is characterized by slowly progressive weakness and atrophy of the feet, legs and subsequently of the hands.^{33,34} The onset usually occurs at the beginning of the second decade (juvenile onset) and close to all reported patients were able to walk independently in

adulthood. Electrophysiological studies demonstrate pure axonal motor neuropathy without sensory involvement.

FBXO38 (AD)

FBXO38 is a known coactivator of the transcription factor Krüppel-like factor 7 (KLF7), which regulates several genes required for axonal outgrowth and repair. A dominant variant leading to the disruption of this transcriptional activity was found in individuals presenting during early adulthood (range 13 to 48 years; more commonly between the second and third decade) with weakness beginning in the calves and subsequently progressing to both distal and proximal leg and arm muscles. Particularly, the triceps and intrinsic hand muscles (i.e. abductor pollicis brevis and first dorsal interosseus) were the most affected muscles in the hands. DTR were absent. Clinical severity ranges from mild weakness in the eighth decade, to inability to walk independently in adulthood. EMG reveals chronic neurogenic changes and active denervation, and nerve conduction studies show reduced cMAP and normal sensory responses. Cognition and bulbar function are normal.³⁵

DNAJB2 (AR)

DNAJB2, also known as HSJ1a (heat-shock protein J1a), encodes a molecular co-chaperone belonging to the HSP40/DNAJ co-chaperone family. Co-chaperones participate in the chaperone systems, which are in turn tightly connected to the protein turnover pathways, the ubiquitin–proteasome system, and the autophagy–lysosome system, thus playing a crucial role in preventing protein aggregation.³⁶

Biallelic pathogenic variants in DNAJB2 are a relatively common cause of HMN, particularly in young adults (onset between 16–23 years).⁵ The disease usually manifests at the end of the second decade with gait abnormalities (e.g. foot drop, stumbling). Distal weakness and absent reflexes are noted first, then a progression towards severe distal paresis and proximal weakness leading to wheelchair dependency in the 4–5th decade of life is common, but not invariable. Upper limbs are usually spared or only mildly affected.³⁷ Sensory involvement (i.e. a predominant CMT2 phenotype) has been reported in few cases.³⁸ Interestingly, few families also showed early-onset parkinsonism with neuropathy and pyramidal signs.^{5,39}

HINT1 (AR)

Loss-of-function, biallelic variants in HINT1 (histidine triad nucleotide-binding protein 1) cause axonal neuropathy with neuromyotonia.⁴⁰ HINT1 primarily hydrolyses nucleoside 5'-phosphoramidates (preferentially purines) with a monophosphate group and acyl-AMP, although additional roles include modulation of transcriptional activation, p53/TP53-mediated apoptosis and proteasomal degradation of target proteins.

Disease onset is typically in the first decade, with severe distal weakness and atrophy of both lower and upper limbs. Most of the reported patients maintained the ability to walk without support in their thirties. Notably, some patients may present with muscle stiffness, myotonia (50%) or cramps in the hands and legs. Patients presenting later in life, with asymmetric weakness and without myotonia, have been reported as well.

Neurophysiological studies show an axonal neuropathy, which can be pure motor or mixed sensorimotor (CMT2 phenotype) in around a half of patients. Needle EMG findings are typical, with high-frequency motor unit action potentials consistent with neuromyotonic or myokymic discharges. Of note, about 20–30% of patients carrying HINT1 mutations lack clinical or

electrophysiological signs of neuromyotonia.^{41,42} CK can be elevated, and skeletal muscle biopsies may reveal signs of chronic denervation. Aspects of axonal damage on sural nerve biopsies even in the absence of clinical sensory abnormalities have been reported.

HMN usually beginning in the upper limbs (HMN5)

GARS (AD)

The GARS gene encodes for a glycyl-tRNA synthetase (GlyRS), an enzyme that covalently attaches glycine to its cognate transfer RNA (tRNA), a necessary step in protein translation. GARS is not only part of the cytosolic translational apparatus but is also involved in the translation of mitochondrial DNA. Dominantly inherited variants have been associated with both CMT2D (onset in the second decade) and with HMN with upper limbs predominance (HMN5).⁴³ Recessive variants have been reported in a mitochondrial disorder with cardiac involvement and in a child with a complex multi-system neurological disease with severe mental retardation and brain structural abnormalities, in both cases without neuropathy.^{44,45}

Based on the evidence that dominant variants in five distinct tRNA synthetases caused axonal and intermediate forms of CMTs (i.e. GARS, YARS, AARS, HARS, MARS), it was first hypothesized that disease causing mechanism could be linked to a common function of these enzymes, for instance aminoacylation. However, the evidence that disease-causing mutations did not affect such activity, together with subsequent studies on *Drosophila* mutants, disputed such theory.⁴⁶ A recent report showed that dominant variants in the gene cause neomorphic binding of GlyRS that directly antagonizes an essential signalling pathway for motor neuron survival. In fact, GlyRS mutants bind to the neuropilin 1 (NRP1) receptor, thus competing and interfering with the binding of the cognate ligand vascular endothelial growth factor (VEGF)⁴⁷ (Fig. 2B).

The prototypical phenotype of GARS-associated neuronopathy is characterized by distal muscle weakness and atrophy predominantly affecting upper limbs (Fig. 3E) with onset in the first decades of life (usually starting after 10 years of age). The disorder is slowly progressive, but most patients eventually develop lower limb weakness and foot deformities (pes cavus).⁴⁸

However, more recent finding suggests that forms with earlier onset may also occur. These are characterized by the involvement of both lower and upper limbs and a congenital presentation. Patients can display signs of severe distal weakness as early as 6 months. Although motor milestones up to independent walking may be attained, the disease seems progressive.⁴⁹ The occurrence of distal muscle wasting, scoliosis, pes planus, vocal cord palsy and even respiratory distress requiring ventilatory support have been variably described.^{50,51}

The most severe end of the spectrum resembles SMA with diaphragmatic involvement (SMARD).⁵² Remarkably, such severe and early onset phenotypes are due to pathogenic variants located in the anticodon binding and the catalytic domains of GARS. Affected individuals present at birth or within the first few weeks of life with severe respiratory insufficiency (involvement of the diaphragm could help to differentiate from 5q-SMA), inspiratory stridor (vocal fold palsy), feeding difficulties, hypotonia of lower more than upper limbs, and absent DTR. Tongue fasciculation may be present. Muscle weakness is severe and affects both proximal and distal muscles with a distal-proximal gradient. While patients may acquire the ability to sit independently, limb muscle weakness is progressive. Brain MRI is normal and electrophysiological studies show active denervation

on EMG and severe axonal neuropathy on electroneuronography (ENG). Sensory action potentials are variably affected, supporting the idea of an overlap with CMT2D.

REEP1 (AD)

Autosomal dominant variants in *REEP1*, a gene encoding for a protein that regulates endoplasmic reticulum (ER) and mitochondrial interaction, are a well established cause of spastic paraplegia (SPG31). A splice-site alteration in *REEP1* (c.304-2A>G) was also associated with HMN.⁵³ Interestingly, while HSP causing variants are thought to derive from haploinsufficiency, HMN phenotype may be generated by a toxic gain-of-function. The conservation of the N-terminal half and the inability to trigger nonsense mediated decay of the mutant RNA was unique of this variant. *REEP1*-associated HMN may therefore be a rare condition since only a small fraction of genetic changes are expected to exert similar consequences.

Clinically, the disease is characterized by an onset within the first or second decade of life. Selective hand muscle weakness and atrophy confined to the thenar and first dorsalis interosus muscle (i.e. split hand sign) may be the presenting symptom (HMN5B), but patients can also display lower limb involvement such as pes cavus and peroneal atrophy and weakness causing stepping gait. DTR are absent or diminished in all patients.

BSCL2 (AD)

While recessive variants in the *BSCL2* gene were first identified as the cause of congenital generalized lipodystrophy type 2 (Berardinelli-Seip congenital lipodystrophy type 2), heterozygous variants cause a wide spectrum of conditions ranging from HMN5C, Silver syndrome (HSP17, spastic paraparesis plus marked weakness and atrophy of hand muscles), CMT2⁵⁴ and ALS.⁵⁵ Incomplete penetrance and significant clinical variability have been described even within the same family and the same dominant mutation can manifest with very different phenotypes.^{56,57} Of note, motor neuron 'seipinopathies' are mainly caused by two toxic gain-of-function pathogenic variants (p.N88S; p.S90L) in the *BSCL2* gene.

BSCL2 encodes for the ER resident glycoprotein Seipin. Preclinical studies have demonstrated that toxic mutations in the gene induce unfolded protein response (UPR) and subsequent ER-stress mediated cell death.^{9,58}

Seipinopathies are usually characterized by degeneration of both upper and lower motor neurons. Hence, the finding of pyramidal signs (e.g. from isolated brisk reflexes to increased muscle tone and positive Babinski sign) is not uncommon. Most affected individuals present in the second decade with progressive distal muscle weakness and atrophy affecting upper and lower limbs. However, given that *BSCL2*-related HMN can occasionally first manifests in the upper limbs ('split hand'-type atrophy, sometimes asymmetrical),^{59,60} this condition should go in the differential also with HMN5.

The key message is that there can be extreme intrafamilial variability and the suspicion of *BSCL2* mutations should also rise in presence of a distal neuronopathy associated with pyramidal signs in patients presenting during the first decade of life,^{57,61} or even in cases presenting in the first decade of life with distal weakness of the legs, rather than in the hands, and absent DTRs.⁵⁹

HMN with prominent respiratory impairment

This group includes the recently described phenotype associated with variants in *GARS*, which was discussed above.

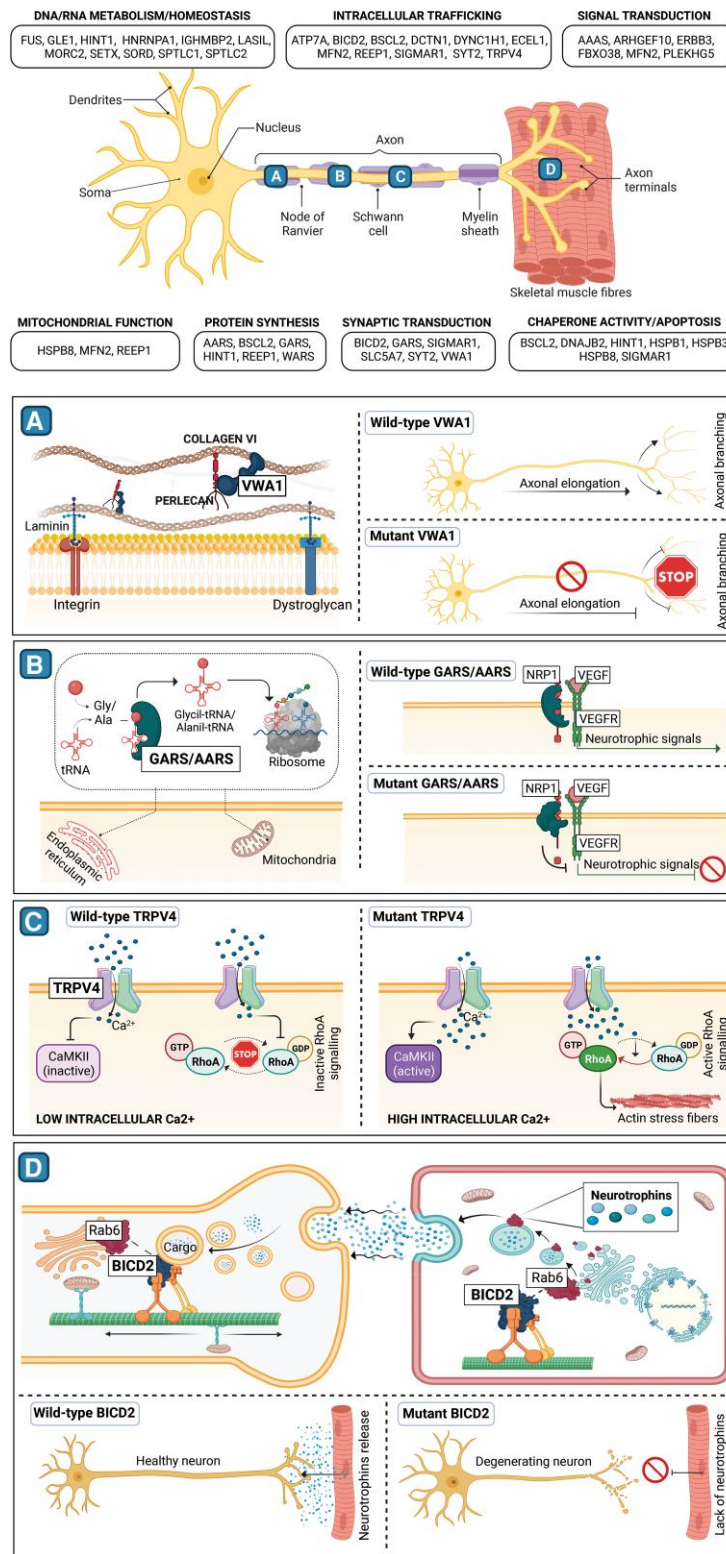


Figure 2 Schematic representation of molecular mechanism involved in neuronopathies. The top section includes a central schematic of motor nerve structure and its interaction with skeletal muscle fibres. Genes associated with neuronopathies, grouped according to their main function, are mentioned in panels surrounding the schematic. (A–D) Aim to show the physiological role of genes recently implicated in these disorders and their presumed pathological mechanism. (A) Mutations in the extracellular protein VWA, that in its wild-type state connects collagen VI and perlecan, affect both axonal elongation and branching. (B) Mutant GARS and AARS tRNA synthetases are thought to impede the release of neurotrophic signals by binding NRP1 protein and thus altering Nrp1/VEGF signalling. (C) The increase of intracellular calcium resulting from the mutant TRPV4 channel activates CaMKII and RhoA signalling, leading to the formation of cytoplasmic actin stress fibers. (D) A defective BICD2 protein impairs both the release of muscle neurotrophins and the neuronal vesicles retrograde transport, resulting in abnormal development of the motor unit and neuronal degeneration.

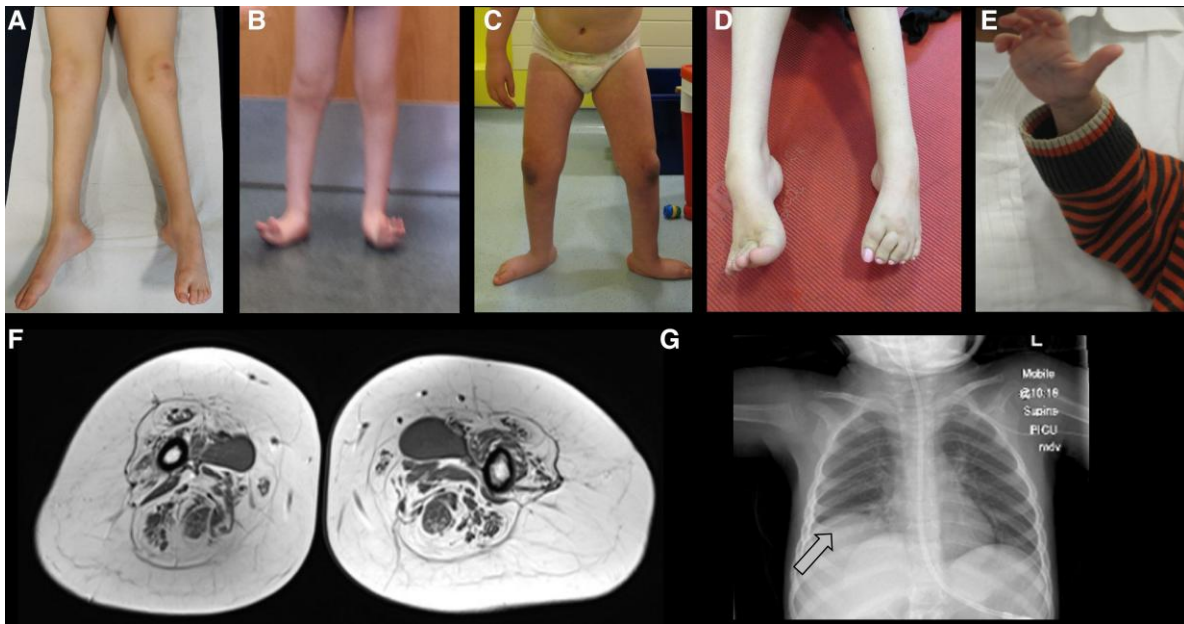


Figure 3 Clinical and radiological features of neuropathies. (A) Distal leg thinning in a patient with MFN2 variant; (B) lower leg atrophy and foot deformities in a patient with BICD2 variant; (C) lower leg atrophy and foot posture in a patient with DYNC1H1 variant. (D) Foot posture in a young adult with TRPV4 variant; (E) photo of hand atrophy (split-hand sign) in a patient with GARS variant; (F) thigh muscle MRI showing islands of muscle, a finding strongly suggestive of neuropathy; (G) X-ray showing diaphragmatic paralysis in SMARD1 (arrow).

IGHMBP2 (AR)

Autosomal recessive variants in the gene encoding for immunoglobulin μ -binding protein 2 (IGHMBP2) are a well established cause of SMARD1. IGHMBP2 is an ATP-dependent helicase, which binds to ribosomes and unwinds RNA and DNA duplexes. Amino acid substitutions causing HMN seem to affect the ATPase and helicase activity rather than the ribosome-binding ability, a pathophysiological mechanism which is supported by the finding of a similar phenotype associated with another helicase (LAS1L).^{62,63}

Relevant clinical differences with 5q-SMA are the involvement of the diaphragm (Fig 3F) within the first weeks of life (this is initially spared in SMA) and the distribution of weakness (distal rather than proximal).^{64,65} A decrease in the number of large myelinated fibres on sural nerve biopsy and slow motor nerve conduction velocities may be observed. The closest phenotypes to SMARD1 are X-linked SMARD2 (LAS1L) and the newly recognized severe phenotype associated with GARS mutations.

Unsurprisingly, the range of possible phenotypes associated with biallelic mutations in IGHMBP2 has increasingly expanded, including sensorimotor polyneuropathy (CMT2S) with onset ranging from <2 years^{66,67} to late childhood,^{68,69} with or without respiratory involvement.⁷⁰ Some cases can even present prenatally with talipes.

Milder cases have been reported also within the HMN spectrum. Specifically, patients may first present with delayed walking evolving into early wheelchair dependency due to progressive severe distal weakness. Respiratory impairment occurs years after the onset of symptoms.^{71,72} Of note, both phenotypes (classic severe and mild) can co-exist in the same family.⁷³ Autonomic disturbances (bladder dysfunction, acute bowel distension), a feature of the severe SMARD1 form, were also reported in a child presenting with CMT2S and in one with the milder HMN phenotype.^{67,72}

The common finding of abnormal sensory conduction velocities and pathological sural nerve biopsies (reduction of the larger

myelinated fibres along different stages of axonal degeneration and atrophy) is in contrast with the definition of a pure motor neuropathy.

HMN that may be associated with vocal cord paralysis (HMN7)

TRPV4 (AD)

Dominantly inherited pathogenic variants in the TRPV4 gene cause different clinical phenotypes spanning from HMN7 to scapuloperoneal SMA, congenital SMA with arthrogryposis,⁷⁴ and autosomal dominant CMT2C.^{75,76} Mutations causing ‘neuronal’ forms usually localize to the intracellular N-terminal domain while other distinct variants give rise to diseases of bone and connective tissue,⁷⁷ fuelling the unsolved conundrum of the reason behind selective vulnerability of specific cell types to mutations happening in ubiquitously expressed genes.⁷⁸

TRPV4 (transient receptor potential vanilloid 4) is a non-selective ion channel preferentially permeable to Ca^{2+} . The mechanisms through which mutations in TRPV4 cause neurodegeneration are still debated but intriguing, given the paucity of ion channels associated with axonal degeneration and the potential for modulatory treatments.

A recent study on *Drosophila* suggested that the primary defect could be the disruption of mitochondrial axonal transport (which has been linked to neurodegeneration in other CMTs) subsequent to the unexpected activation of CaMKII (Ca^{2+} /calmodulin-dependent protein kinase II) due to the increased calcium influx caused in turn by the abnormal functioning of the TRPV4 ion channel.⁷⁹ Another study suggested that neuronal phenotype could specifically derive from the selective disruption of a protein domain involved in the interaction with the small RhoA GTPase, thus allowing RhoA activation and the subsequent formation of actin stress fibers in the cytoplasm^{80,81} (Fig. 2C).

The penetrance of the disease is variable so that not only there are four ‘distinct’ clinical entities, but in the same family affected individuals may present with very different phenotypes. With these premises in mind, the CMT2C phenotype is usually associated with vocal cord paresis, bilateral sensorineural hearing loss, bladder urgency and incontinence, skeletal dysplasia and short stature.⁸²

Vocal cord palsy is not exclusive of CMT2C and has been reported also in 94% of patients presenting with TRPV4-related neuropathy in one case series (17 individuals), thus representing a strong diagnostic clue.⁸³ Of note, vocal cord paralysis may present with congenital stridor or with subtle hoarseness and should not be overlooked. Foot deformity (pes cavus) and kyphoscoliosis develop with time in most cases. Mildly elevated (<500 U/l) CK levels are also a common finding. Interestingly, although initial reports did not mention respiratory insufficiency as a feature of TRPV4-related disease, this was later described in around a quarter of patients, who required the use of non-invasive nocturnal ventilation (BiPAP).⁸³ Scapular winging was reported in close to a half of patients, including individuals not presenting with the scapulo-peroneal type.⁸³ Hearing loss, which can be progressive,⁸⁴ skeletal dysplasia and AMC were reported in <25% of cases. In contrast with *DYNC1H1* and *BICD2* SMALED, talipes at birth is equinovarus rather than calcaneovalgus (Fig. 3D). Distal weakness and wasting are usually seen in both lower and upper limbs, but patients with milder proximal weakness at lower limbs has been also reported. DTR are absent or diminished. Patients usually acquire the ability to walk with support, but not in all cases.

Nerve conduction studies show a slowly progressive, symmetrical, and predominantly distal motor axonal neuropathy (CMAPs are diffusely reduced), sometimes associated with mild sensory involvement. No signs of active denervation are usually seen.

Muscle MRI of lower legs may show initial involvement of the vastus intermedius, vastus lateralis, soleus and medial gastrocnemii muscles. The sparing of biceps femoris and medial gastrocnemius rather than thigh adductors and semitendinosus has been proposed as a differentiating feature compared to SMA-LED.⁸⁵

SLC5A7 (AD)

Heterozygous pathogenic variants in the *SLC5A7* gene on chromosome 2q12 have been associated with HMN7, namely HMN with vocal cord palsy. Interestingly, *SLC5A7* encodes a sodium and chloride dependent high-affinity transporter that mediates the presynaptic uptake of choline for acetylcholine synthesis in cholinergic neurons.⁸⁶

In the original article from Young and Harper,⁸⁷ affected individuals presented in early teens (age 12–14) with hands weakness and/or selective wasting of the thenar eminence. Lower limb weakness occurred usually later, except for one patient who manifested at the age of 11 years with toe walking, and in whom distal UL involvement occurred 10 years later. Other features include pes cavus, hyporeflexia and hoarseness. Importantly, there was variable involvement of one or both vocal cords (but also one patient without vocal cords involvement was reported), a feature that may require early monitoring and intervention.

DCTN1 (AD)

Autosomal dominant variants in the *DCTN1* gene can cause neuropathy. This encodes p150(Glued), the largest of the 10 different polypeptides that constitute the dynactin complex, a crucial macromolecular complex participating in the dynein-driven movement of organelles along microtubules. The spectrum of

neurodegenerative conditions related to *DCTN1* spans from HMN to juvenile ALS and Perry syndrome (rapidly evolving parkinsonism, weight loss, depression and central hypoventilation). *DCTN1*-related HMN was first described in young adults presenting with vocal cord paralysis causing respiratory distress (HMN7B), progressive muscle weakness and atrophy in the hands and facial muscles, and later involvement of LL.⁸⁸

Very recently, a patient with congenital onset harbouring frameshift variant in *DCTN1* gene was reported.⁸⁹ This variant was shown to cause an abnormal distribution of Dynactin 1 within the motor neuron and loss of colocalization with microtubules. The proband presented with talipes and delayed acquisition of independent walking (achieved at 3 years). There was early involvement of the hands (clumsiness, tremor and muscle twitching appearing at the age of 16 years). Distal muscle weakness and atrophy of legs muscles, Achilles tendon contractures and toe varus were evident at the age of 11 years. DTR were brisk but muscle tone was normal. Nerve conduction studies showed a global reduction of CMAPs with normal sensory responses. Sural nerve biopsy was unremarkable.

HMN associated with pyramidal signs

This group includes conditions in which overt pyramidal signs are commonly observed (namely, not only brisk reflexes but also increased muscle tone and extensor plantar response). BSCL2-associated condition was described above.

SETX (AD)

Autosomal dominant variants in the senataxin (*SETX*) gene are associated either with HMN with pyramidal signs or with juvenile ALS. Senataxin interacts with several proteins involved in RNA processing, hence suggesting a role in the modulation of transcription.

SETX-related HMN is usually associated with a teen-age onset, and a much slower disease course compared to other forms of juvenile ALS, with survival times extending well into the fourth decade. A predominant upper motor neuron involvement, bulbar sparing and an occasional overlapping sensory ataxia seem to be other characteristic features of this form.⁹⁰ *SPG11*-related cases are similarly indolent, sometimes associated with parkinsonian features, and clinical courses lasting for as long as two decades.⁹¹ Autosomal recessive variants can cause spinocerebellar ataxia with axonal neuropathy.

Other HMN

SIGMAR1 (AR)

The *SIGMAR1* gene encodes an ER chaperone assisting lipid transport from the ER either to plasma membrane or to mitochondria-associated membrane. *SIGMAR1* is essential for the retrograde mitochondrial axonal transport, controls ER calcium efflux and plays an important role in the regulation of ion channels and neurotransmitters release.

Recessively inherited variants in the gene have been first identified as the cause of AR HMN in a cluster of consanguineous families in the Jerash region of Jordan (Rossor *et al.*⁹). The disease manifests between 6 and 12 years of age and is characterized by slowly progressive distal muscle weakness and wasting of lower limbs associated with brisk patellar reflexes (ankle reflexes can be absent) and feet deformities (pes varus). UL involvement usually occurs later and most individuals are independent in everyday life activities in mid-adulthood.^{92,93} Nerve conduction studies

show normal conduction velocities, reduced cMAP amplitudes, normal sensory nerve action potentials, and chronic neurogenic changes on needle EMG. Both neurophysiological and pathological (sural nerve biopsy) sensory investigations are unremarkable.

AAAS (AR)

Recessive variants in the ubiquitously expressed AAAS (Aladin WD Repeat Nucleoporin) gene are a cause of Triple A or Allgrove syndrome, defined by the presence of achalasia, alacrimia, adrenal insufficiency and neurological syndrome. AAAS localizes at the cytoplasmic side of the nuclear pore complex and supports selective nuclear protein import.

Of note, the triad may not be evident in all patients and a progressive neurological syndrome, including predominant motor neuropathy (although sensory-motor are also reported)⁹⁴ with onset in the first decade of life (as early as 1 year).⁵ Other neurological features may include cognitive decline, progressive spasticity, dysautonomia and/or cranial neuropathies.

SORD (AR)

Biallelic pathogenic variants in SORD have been recently identified as a common cause of HMN/CMT2 neuropathy, possibly accounting for ~10% of undiagnosed HMN/CMT2 cases.^{95,96} Close to 70% of described individuals had no familiar history.

SORD encodes the second enzyme of the two-step polyol pathway, in which glucose is converted into sorbitol by aldose reductase, and then oxidized to fructose by SORD. The lack of SORD leads to marked intracellular sorbitol concentrations elevation, with putatively reversible toxic consequences on motor neurons.

The onset is usually in the second/third decade, and the disease manifests as slowly progressive distal weakness and atrophy of both lower and upper limbs, often accompanied by foot deformities (e.g. pes cavus). Proximal strength is preserved. Nerve conduction studies revealed an intermediate reduction of NCV in a quarter of patients and decreased or absent sensory amplitudes in another quarter (reduced vibratory sense was also documented). After two decades from disease onset, the severity of this condition was mild in the vast majority of affected individuals.

A variety of associated signs and symptoms have been reported in some patients, including hand tremor, scoliosis, hearing loss, scapular winging, brisk reflexes, and elevated CK levels. Only two patients presenting within the first decade have been reported thus far.^{95,97}

CMT2 overlap (forms with prevalent CMT2 phenotype)

In this section we will expand the description of those conditions commonly observed in paediatric patients that are usually classified as CMT2, with the caveat that the distinction between HMN and CMT2 is at least blurred.⁷

MFN2 (AD)

Dominantly inherited pathogenic variants in MFN2 are the most common cause of axonal inherited neuropathies (CMT2). Mitofusin2 (MFN2) is a GTPase dynamin-like mitochondrial membrane proteins implicated in mitochondrial dynamics, calcium signalling and axonal trafficking. The phenotypic spectrum is wide but usually characterized by a bimodal age of onset (childhood or early adulthood), slowly progressive gait difficulties with foot drop (in those with onset <10 years, 36% lost ambulation by the fourth decade), and sensory abnormalities of lower limbs (Fig. 3A). In rare cases, neuropathy can be associated with optic atrophy, auditory

impairment, vocal cord palsy or CNS abnormalities.⁹⁸ Sometimes, the disease manifests in the first decade with isolated motor involvement, with progression of distal weakness occurring rapidly within 3–5 years.^{99,100} Talipes at birth has been reported and a distinctive feature that might be observed in these cases is the presence of brisk reflexes.

MORC2 (AD)

Autosomal dominant, missense mutations in MORC2 have been identified as the cause of CMT2Z, an axonal sensorimotor neuropathy with moderately to severely progressive course, characterized by onset in the first two decades of life with typical CMT signs (e.g. gait abnormalities, feet deformity, distal weakness) variably associated with hyporeflexia, hyperreflexia and spasticity, asymmetric weakness, scoliosis, hearing loss (60%), and pigmentary retinopathy.¹⁰¹ In contrast with most CMTs, proximal weakness is commonly seen,¹⁰² a peculiar finding recently described also in CMT2CC (NEFH).¹⁰³ MORC2 is an effector of the epigenetic silencing mediated by the human silencing hub (HUSH). MORC2 mutants have been shown to cause a change in the dimerization dynamics leading to abnormal modulation of HUSH function.¹⁰⁴ Dominant variants have been reported also in a complex neurological disorder characterized by neuropathy, developmental delay, intellectual disability, growth retardation, microcephaly and variable craniofacial dysmorphism.¹⁰⁵ Most importantly for the purpose of this review, MORC2 pathogenic variants were also identified in one patient developing severely (SMA-like) progressive proximal weakness starting from the age of 10 months and leading to complete tetraplegia followed by respiratory insufficiency due to diaphragmatic involvement by the age of 3 years. Electrophysiological studies revealed pure motor neuropathy without sensory involvement. Cranial MRI at 13 months and 4 years demonstrated progressive cerebellar atrophy; cognitive function was abnormal.¹⁰⁶

AARS (AD)

Autosomal dominant pathogenic variants in AARS, a gene encoding for alanyl-tRNA synthetase (AlaRS), are a well established cause of CMT2. Like what has been recently demonstrated in GARS, axonal damage seems not to be caused by the loss of enzymatic function, rather from the aberrant interaction between AlaRS and Nrp1,¹⁰⁷ a possible shared disease mechanism among different tRNA synthetases. A single patient presenting at the age of 2 years with frequent falls and a very slow-progressing distal weakness of upper and lower limbs was found to have a phenotype consistent with HMN.¹⁰⁸

Other CMT

In a recent study, we found heterozygous variants in ARHGEF28 (p.Arg475Thr and p.Cys1458Trp) and AGRN causing slowly progressive distal weakness and atrophy in patients who started to have difficulties in walking between the age of 2 and 5 years. In both patients though, electrophysiology revealed the presence of sensory impairment in addition to neurogenic changes on EMG needle examination.⁸

Dominantly inherited pathogenic variants in GBF1 (golgi brefeldin A-resistant guanine nucleotide exchange factor) have been recently identified as causative of a CMT2/HMN phenotype. Whilst the single patient reported with paediatric onset had sensory impairment, we cannot exclude that the clinical spectrum will expand in the forthcoming years.¹⁰⁹

Bansagi and colleagues identified a new heterozygous c.1949G.A, p.(Tyr650Cys) sequence change in ARHGEF10, a gene encoding for a member of the family of Rho guanine nucleotide

exchange factors that are implicated in neural morphogenesis and connectivity and are regulator of small Rho GTPases. The associated phenotype was characterized by talipes and pure motor neuropathy.³ However, no other cases have been reported thus far and in the lack of functional studies there is limited evidence of the causative effect of such variant. Another variant [c.1013G>C; p.(Arg338Thr)] has been associated with a CMT2 phenotype but with decreased conduction velocities; its pathogenicity is also not clearly established.¹¹⁰

A heterozygous variant in MYH14 was reported as causative of a complex phenotype comprising peripheral neuropathy, myopathy, hoarseness (but no vocal cord palsy) and hearing loss in a single large autosomal dominant Korean family. Onset occurred at a median of 10.6 years of age with distal weakness and histopathological and electrodiagnostic studies revealed both chronic neuropathic and myopathic features in the affected patients.¹¹¹ Intriguingly, this study suggested a potential role of myosin heavy chains isoforms also in motor neurons.

Frasquet and colleagues⁵ recently reported on a large cohort of patients presenting with a phenotype consistent with HMN/CMT2 who were evaluated in two tertiary centres in Spain and underwent comprehensive genetic studies. Although limited clinical data are provided, they described two siblings harbouring compound heterozygous mutations (AR) in the FIG4 gene, with onset in childhood and a pure motor, slowly progressive phenotype. FIG4 encodes an enzyme involved in phosphoinositide phospholipid metabolism and has been extensively associated CMT4J, hence a mixed demyelinating/axonal neuropathy. The phenotype of CMT4J varies from severe to milder forms, with both proximal and distal weakness and asymmetric involvement, which may point towards this genetic diagnosis. Lastly, Jacquier and colleagues¹¹² recently reported on a juvenile-onset, pure motor neuropathy associated with pyramidal signs and caused by homozygous variant c.3G>T (p.1Met?) in the COQ7 gene. This finding is intriguing given the potential for treatment with coenzyme Q10.

SMA-LED and HMN with proximal weakness

DYNC1H1 (AD)

Heterozygous mutations in the cytoplasmic dynein heavy chain 1 (DYNC1H1) gene cause SMA-LED type 1 and HMN type 1. DYNC1H1 encodes for the heavy chain 1 of the dynein complex, a ubiquitously expressed motor complex that consists of two heavy chains, two intermediate chains, four light intermediate chains and several light chains. DYNC1H1 is primarily involved in the retrograde axonal transport from the cell terminal to the soma.^{113,114} Other functions include intracellular cargo transport, organelle motility, regulation of the Golgi apparatus, spindle-pole organization, and nuclear migration during mitosis.¹¹⁵

The prototypical phenotype is characterized by congenital or early childhood onset muscle weakness predominantly affecting lower limbs (proximal ≥ distal, especially the hip extensors), distal muscle wasting and feet deformities (Fig. 3C). Non-evolving, proximal (hip/knees) and distal (Achilles' tendon) contractures can be observed in approximately half of patients and scoliosis may develop with time. Brisk DTR can be present in some patients, but these are more often reduced/absent.¹⁰ Around 37% of individuals present at birth with lower limbs malformations (calcaneus valgus talipes; hip dysplasia), 23% present in infancy (motor delay and abnormal gait), and 17% in childhood (gross motor difficulties or frequent falls). Twenty percent of individuals present in adulthood.

With few exceptions, weakness is non-progressing, with most individuals reaching the ability to walk with or without support. Malformation of cortical development (MCD) is seen in >20% of cases (e.g. polymicrogyria, cortical nodularity or gyral over convolution). Cognitive impairment or attention deficit hyperactivity disorder (ADHD) can be observed in up to one third of cases, usually but not exclusively in association with cortical abnormalities.

The spectrum of DYNC1H1-related disorders is expanding and the role of this protein in multiple steps of neurodevelopment is emerging.¹¹⁶ The former includes severe arthrogryposis, isolated intellectual disability, autism, seizures, spastic tetraplegia, MCD plus cataracts and gut dysmotility.¹¹⁷ Although pathogenic variants in specific domains have been associated with distinct phenotypes (e.g. variants in the dynein motor domain with MCD), genotype-phenotype correlation is limited.^{115,118}

Diagnosis of DYNC1H1-related disease is suspected on the basis of clinical presentation and EMG showing motor neuropathy/neuropathy without sensory abnormalities. Muscle MRI may reveal a distinctive pattern of muscle involvement characterized by diffuse alteration of quadriceps muscles associated with the selective sparing and relative hypertrophy of the adductor magnus and/or longus and of the semitendinosus muscles in the thigh, and diffuse lower leg involvement with relative sparing of the anterior-medial muscles.

Muscle biopsy usually demonstrates features compatible with chronic denervation (e.g. fibre-type grouping) but can be occasionally suggestive of congenital myopathy due to the presence of core-like areas, increased internal nuclei and rimmed vacuoles.¹⁰ For this reason, clinical gestalt, neurophysiology and muscle imaging are very useful in differentiating this condition from congenital myopathies.

BICD2 (AD)

Heterozygous pathogenic variants in the bicaudal D cargo adaptor 2 (BICD2) gene cause SMA-LED type 2, which is often clinically indistinguishable from SMA-LED type 1.¹¹ Disease-causing variants map to mutational hot spots in the three coiled-coil domain regions of BICD2, corresponding to crucial interacting regions. BICD2 regulates the dynein-dynactin complex in different cellular processes (N-terminal domain) and functions as cargo adaptor protein (C-terminal domain). In particular, it interacts with dynein and kinesin motors, RANBP2 and RAB6. The latter is an important tissue specific small GTPase that regulates transport and fusion of secretory vesicles.¹¹⁹ The reason why mutations in BICD2 cause neuronal loss is not clear. One hypothesis suggests that the mechanism is neuronal specific and linked to detrimental increased stability of microtubules.¹²⁰ However, a recent work on the *Bicd2*^{-/-} mouse suggested an intriguing alternative explanation: mutations in BICD2 may in fact cause loss of protein function. In normal muscle, BICD2 ensures the correct localization of RAB6 at the trans Golgi surface, which is required for the efficient trafficking of secretory vesicles to the plasma membrane (Fig. 2D). According to the neurotrophin hypothesis,¹¹⁹ during early neurodevelopment a surplus of motor neurons reach the skeletal muscle and compete for muscle-secreted neurotrophic factors for survival. Subsequently, programmed cell-death regulated by neurotrophins follows. Therefore, a reduction in the secretion rate of neurotrophin-containing vesicles (due to RAB6 abnormal localization) may cause an excess of motor neuron death during these early phases of neuronal development.¹²¹ This hypothesis would explain why no progressive motor neuron degeneration occurs, at least in some

patients, and opens to a series of possible novel pathogenic mechanisms involved in congenital motor neuronopathies.

Patients harbouring *BICD2* mutations typically present with delayed motor milestones and contractures, with a subset of individuals also exhibiting arthrogryposis and hip dislocation from birth. While weakness is predominantly observed in lower extremities, upper limb involvement (proximal and/or distal) occurs in ~40–50% of patients, usually later than lower limbs weakness. Up to one-third of patients never achieve ambulation and orthopaedic complications such as joint abnormalities (Fig. 3B), congenital hip dislocation, scoliosis and kyphosis, are frequent.

Respiratory involvement is a feature of severe disease, with 27% of families reported to require some respiratory assistance in a recent review.¹²² In contrast with what initially believed, roughly half of patients showed signs of CNS involvement including brisk reflexes, brain abnormalities, or cognitive impairment. Seizures are infrequent.

Interestingly, although EMG findings are usually neurogenic, in some individuals myopathic features in the context of chronic myopathy have been reported.¹²³

As previously mentioned, pathogenic variants map to all three coiled-coil domains, with no strong genotype-phenotype correlation. An exception is the HSP-like phenotype observed in a family harbouring the p.(R501P) aminoacidic change, which is putatively disrupting the interaction with kinesin-1 (*KIF5A*), a protein which has been involved in HSP (*HSP10*) and CMT.¹²⁴ Lastly, *de novo* variants have been found to be more likely associated with severe disease in terms of congenital onset, respiratory impairment, severity of contractures, brain abnormalities, and lethal outcome, compared to familial cases.

SYT2 (AD)

Dominant missense variants in Synaptotagmin 2 (*SYT2*) have been reported as a rare cause of distal motor neuropathy and myasthenic syndrome, manifesting with stable or slowly progressive distal weakness of variable severity affecting both upper and lower limbs.

SYT2 are integral membrane proteins of synaptic vesicles thought to serve as Ca²⁺ sensors regulating vesicular trafficking and exocytosis. Variants in *SYT2* are thought to have a dominant-negative effect on these processes, although the precise pathophysiological mechanism remains unclear.

After a normal development, the disease manifests during childhood (first decade) with foot deformities (pes cavus and hammer toes) and a variable degree of proximal and distal limb weakness, distal muscle atrophy, muscle fatigue, mild gait difficulties, and reduced or absent DTR. Clinically, the differential diagnosis would include CMT, but sensory studies are normal.¹²⁵

The key feature of this disease is the co-occurrence of impaired presynaptic neuromuscular transmission (Lambert-Eaton like) and a distal motor neuropathy. As such, repetitive stimulation or single fibre EMG should be performed, as patients may benefit by treatment with 3,4-diaminopyridine.¹²⁶

PLEKHG5 (AR)

Autosomal recessive variants in the Pleckstrin homology domain containing family G member 5 gene (*PLEKHG5*) have been reported in a Malian family with a SMA-like phenotype.¹²⁷ *PLEKHG5* is an activator of the nuclear factor kappa-B1 but the pathogenesis has not been elucidated. In the few reported cases the onset was around 2–3 years of age (one sibling with a milder form presented at 11 years and was still ambulant aged 20). The disease course is characterized

by progressive proximal weakness, scoliosis, contractures and respiratory impairment.

VWA1 (AR)

The recent discovery of an autosomal recessive, slowly progressive, non-length dependent, HMN caused by biallelic pathogenic variants in the von Willebrand factor A domain containing 1 (*VWA1*) gene opened up new avenues for investigating the role of extracellular matrix (ECM) components in cell growth and differentiation, particularly with regards to muscle and nerve embryonic development.^{128,129} *VWA1* is a protein interacting with perlecan and Collagen VI and whose putative function is to stabilize ECM structures (Fig. 2A). However, the disease-causing mechanism is not clear.

Disease onset is usually around the age of 2 years, but antenatal abnormalities can be present and adult-onset cases have been reported as well. Congenital or early-onset foot deformities (e.g. talipes, pes cavus, pes equinovarus) are common. With the caveat that only 32 cases have been reported thus far, the first manifestation of this disorder is usually distal (anterior > posterior) LL weakness variably leading to delayed acquisition of independent ambulation, tip-toe walking, Achilles tendon contractures and feet deformities. In contrast with other forms of HMN, atrophy of the distal muscles is not common at the time of diagnosis. Interestingly, recurrent hip and patellar dislocations, which we observed also in other undiagnosed HMN patients and other HMSN, have been reported.¹²⁹ These presenting symptoms slowly evolve in the development of symmetric proximal weakness of lower (but also upper) limbs. Proximal weakness can be either equal, worse or milder than distal involvement. While UL involvement remains mild in the course of the disease, LL involvement can be severe (3/17 individuals lost ambulation in one series), but overall, the progression of the disease was very slow or even non-evolving.

Nerve conduction studies reveal a motor axonal neuropathy (reduction of cMAP) in most cases, usually in presence of normal sensory examination (although clinical sensory disturbances have also been reported). Needle EMG is usually neurogenic but can show a mixed picture of proximal myopathic changes with distal neurogenic abnormalities.

Muscle biopsy results are also variable, with both myopathic and neurogenic changes. One individual presented with paracrystalline inclusions in the mitochondria. CK have been found to be elevated in a minority of individuals (369–1628 IU/l). Muscle MRI of lower limbs showed a rather uniform pattern with predominant affection of the vasti, gastrocnemius and peroneal muscles, with relative sparing of the sartorius, gracilis and soleus muscle.¹²⁸ In those individuals in which brain MRI was performed, this was normal.

In one of the two published series, a founder allele causing a 10-bp expansion at the end of exon 1 (c.62_71dup10;p.G25Rfs*74, NM_022834.5) was found in several families. Notably, patients harbouring a compound heterozygous variants seemed milder than individuals homozygous for the founder mutation. In the broad CMT spectrum, pathogenic variants in *VWA1* may account for up to 1% of cases and new phenotypes are likely to be reported in the future.

Neurogenic arthrogryposis multiplex congenita

AMC is defined by the presence of joint contractures in two or more districts of the body (including jaw, neck and spine) associated with foetal akinesia (reduced foetal movements). The estimated incidence is 1 in 3000–5000 newborn children¹³⁰ and the underlying

acquired or genetic causes are numerous and heterogeneous,¹³¹ with more than 150 causative genes identified thus far.¹³¹ Common AMC causes include maternal events (e.g. myasthenia gravis), amyoplasia (sporadic congenital defect in the development of muscle¹³²), conditions in which we observe a primary central nervous system involvement (e.g. congenital infections, mitochondrial disorders, metabolic disorders) and disorders in which a component of the peripheral nervous system is affected.

Neurogenic arthrogryposis is defined by the presence of AMC and neurogenic changes on EMG. Importantly, such ‘peripheral’ phenotype should include in the differential diagnosis affections of the skeletal muscle (40% of cases are due to congenital myopathies), congenital myasthenic syndromes, severe genetic neuropathies (e.g. new genes such as *CNTNAP1*), congenital muscular dystrophies (e.g. *FKRP*, *FKTN*), and genes causing altered mechanical transduction (e.g. *PIEZO2*). Isolated motor neuron involvement was found to be the cause of 9% of genetically confirmed cases in one large study on >300 individuals presenting with AMC.¹³³

With the caveat that most of case series in the past lacked genetic confirmation, neurogenic AMC without severe foetal phenotype is usually considered a non-progressive condition, and close to half of the patients with LL AMC will acquire independent ambulation despite contractures.¹³⁴

The boundary between neuropathies with congenital onset and a non-progressive course (e.g. *DYNC1H1*, *BICD2*)¹¹⁹ and neurogenic AMC is blurred. The defect that leads to foetal akinesia involves considering a variety of developmental pathways, and complex and yet-to-be elucidated molecular mechanisms. Both in diagnosed and undiagnosed individuals features suggestive of reduced foetal movements such as talipes, hip dislocation, breech presentation and polyhydramnios are common.

Several genes implicated in the embryonic development of central and/or peripheral nervous system (including lower motor neurons, nodes of Ranvier, and myelin) have been associated with lethal congenital contracture syndrome (LCCS) or lethal arthrogryposis with anterior horn cell disease (LAAHD).¹³⁵ The description of such conditions goes beyond our scope (see Beecroft et al.¹³⁵ for a thorough review), but genes such as *GLE1* suggests that the phenotypic spectrum of these very severe forms is ever expanding, with the possibility that milder ‘HMN-like’ phenotypes might be reported in the future.¹³⁶ The peculiar combination of AMC and visceral involvement (gut dysmotility spectrum) could represent a diagnostic clue pointing to known or still unidentified genes (e.g. *ERBB3*).

Of note, neurogenic EMG changes can be also observed in patients presenting with a phenotype consistent with sporadic amyoplasia (see Hall et al.^{132,137} for an extensive review). A hypothesis is that anterior horn damage could be the consequence of vascular compromise happening between the 8th and 12th week of gestation. Hence, the possibility of an ‘acquired’ insult happening at specific stages of uterine life (which could also explain the different involvement of upper and lower limbs) should also be considered.¹³²

Juvenile ALS

ALS is a relentlessly progressive neurological disease belonging to the broader spectrum of motor neuron diseases. It is characterized by a progressive degeneration of upper and lower motor neurons, leading to muscle weakness, respiratory failure and ultimately death, typically occurring 3–5 years after symptoms onset. Despite a classical onset in middle to late life, juvenile forms exist, defined by the occurrence of motor symptoms before the 25th year

of age,¹³⁸ while still respecting the diagnostic criteria for the adult-onset form.¹³⁹

The state-of-the-art working view panel of ALS genes suggest that they cluster in three categories, involving protein homeostasis, RNA homeostasis and trafficking, and cytoskeletal dynamics.¹⁴⁰

Usually, the first symptoms of juvenile ALS manifests in late childhood to adolescence, characterized by progressive muscle weakness, often with an asymmetric distribution, accompanied by atrophy, fasciculations and cramps, pointing to lower motor neurons and their axons as the prime site of pathology. Pyramidal tract signs, such as brisk tendon reflexes and a pathological plantar reflex, are usually present, indicating a concomitant involvement of the central motor tracts. Bulbar involvement may occur as well, including dysarthria, dysphagia, tongue atrophy and hyperactive gag reflex. Emotional lability and inappropriate crying or laughing (pseudobulbar signs) may be present. Cognitive and behavioral functions are seldom involved at the beginning of the disease, but phenotypic variability is almost paradigmatic in this class of disorders, further complicating the already challenging diagnostic process. Neurophysiology can assist the diagnosis, providing evidence of a diffuse lower motor neuron involvement with electromyographic signs of active and chronic denervation.¹⁴¹

Mutations in several genes have been classically associated with juvenile ALS, with both an autosomal dominant pattern of inheritance (*SETX*, *SPTLC1*, *SPTLC2*), and with autosomal recessive inheritance (*ALS2*, *SPG11/spatacsin*, *FUS*, *SIGMAR1*). The presence of overt pyramidal signs, tongue fasciculations and early bulbar involvement should guide the diagnosis in favour of juvenile ALS versus HMN.

FUS (AR/AD)

FUS, encoding for a nuclear-cytosolic shuttling protein with both DNA and RNA binding properties and various functions in RNA metabolism, represents the most frequently mutated gene,¹⁴² accounting for more than 30% of juvenile forms.¹⁴³

As a rule, *FUS* mutated forms tend to be more aggressive, representing the juvenile phenotype closer to the adult form of the disease. These patients have an earlier onset, prominent bulbar involvement, and a premature need for a continuous ventilatory support, usually occurring within 2 years from symptom onset.¹⁴⁴ Some cases may be accompanied by learning difficulties and mental retardation. Atypical presentations may include myoclonus with generalized epileptic discharges,¹⁴⁵ and postural tremor.

Others

Serine palmitoyltransferase, long-chain base subunit 1 (*SPTLC1*)^{146,147} and 2 (*SPTLC2*)¹⁴⁸ and sigma-1 receptor (*SIGMAR1*)¹⁴⁹ mutations have been described in both familial and sporadic forms, characteristically associated with onset from neonatal period to early-childhood, spasticity involving predominantly the lower limbs, followed by diffuse lower motor neurons involvement, and bulbar involvement. Interestingly, *SPTLC1* and *SPTLC2* belong to the serine palmitoyltransferase complex (SPT) and both have been associated with hereditary sensory autonomic neuropathy type 1 (HSAN1). However, in contrast with HSAN, L-serine supplementation might be detrimental in these forms of juvenile ALS due to the unregulated overactivity of SPT.¹⁴⁷

One Japanese case has been associated with a spectrin repeat containing nuclear envelope protein 1 (*SYNE1*) gene mutation, in

the context of a complex phenotype accompanied by cognitive decline and cerebellar ataxia.¹⁵⁰

Lastly, mutations in RNA binding proteins *HNRNPA1* and *HNRNPA2B1*,¹⁵¹ encoding for the heterogeneous nuclear ribonucleoprotein (hnRNP) A1 and B1, have been associated with a spectrum of disorders ranging from ALS, multisystem proteinopathy (MSP),¹⁵² to phenotypes consistent with HMN and/or distal myopathies.¹⁵³ The phenotype is determined by the type of mutation i.e. missense, frameshift.

Discussion

The aim of this review is to convey the biological and clinical complexity underlying a heterogeneous group of conditions that together constitute early onset motor neuronopathies. Over the last decade, several novel genes have been discovered and, intriguingly, phenotypic diversity and variability continue to expand. Most importantly, more than 60% of patients presenting with an HMN-like phenotype still lack a genetic diagnosis. Given the low prevalence of these disorders taken separately, collaborations to gather and deep phenotype similar cases are crucial for an improved and comprehensive understanding of the pathogenesis of these disorders and discovery of novel gene candidates. Interestingly, genes that are thought to be relatively ‘common’ causes of HMN such as *SORD* or *VWA1* have eluded genetic investigations for years.

A key role in determining the success of the diagnostic genetic screening is the choice of the technology used to support the investigation; variants located in complex genomic regions (including genomic rearrangement and triplicated regions) are often missed when relying on the conventional short-read whole genome sequencing, whereas copy number variants in these genomic regions are nowadays more accessible through the advent of the recent long-read whole genome sequencing technology. An example is represented by sorbitol dehydrogenase deficiency (*SORD*). The nonsense *SORD* c.757del variant (rs1042079), which is commonly found either in homozygosity or compound heterozygosity in affected patients, has previously likely escaped short-read analysis due to the presence of the *SORD2P* pseudogene harbouring the same genomic variant. Long-read WGS can distinguish between genes and pseudogenes, hence overcoming limitations of older genetic diagnostics.¹⁵⁴

At the present time, it is difficult to establish a simple diagnostic algorithm for this group of conditions other than based on frequency of individual genetic defects. This should in theory take into consideration the multiple phenotypes associated with the same gene and should also correctly weight the presence or absence of specific findings. Of note, it is also difficult to capture the timing of onset of some peculiar features (Fig. 1B), the absence of which should not exclude a specific diagnosis (for example, respiratory impairment can occur many years after onset in both *IGHMBP2* and *BICD2*-related neuronopathies).

A practical approach could consider the age at which the first signs of the disease manifest (Fig. 1A). This would also reflect the timing at which the *noxa patogena* (e.g. defective embryonic development/axonal pathfinding, response to ageing, bioenergetics failure etc.) intervenes.

The cornerstone upon which a diagnosis of neuronopathy is pursued is the finding of chronic neurogenic changes on EMG, namely high-amplitude polyphasic motor units of long duration. The distribution of neurogenic changes (distal versus proximal), the unexpected presence of active denervation (positive sharp waves and fibrillation potentials), the finding of mixed neurogenic

and myopathic EMG pattern (documented in *BICD2*, *HSPB1*, *HSPB8*, *VWA1*, *GNE*, *AGRN* and *ACTA1*), or the involvement of sensory fibres (SAPs) could all add to the deep phenotyping of these patients. Muscle MRI might represent a supportive tool to guide the differential diagnosis between distal myopathies and neuronopathies (Fig. 3F)¹⁵⁵ and muscle ultrasound can be used in clinics to detect fasciculations. Of note, CK can be elevated.

The molecular mechanisms underlying neuronopathies are heterogeneous and in part still poorly understood. The discovery of *VWA1* and insights on the role played by *BICD2* in mice (specifically its interaction with *RAB6*) highlight the importance of further characterizing axonal pathfinding and the maturation of the motor unit, including the role of ECM components.^{156,157}

While we can group pathomechanisms in broad categories such as disturbed mitochondrial function, impaired axonal transport/intracellular trafficking, abnormal protein synthesis, abnormal RNA/DNA metabolism, abnormal cellular signalling etc. (Table 1 and Fig. 2), there are some cautionary tales. As an example, autosomal dominant variants in both *GARS* and *AARS*, both belonging to the aminoacyl tRNA synthetases family, do not disrupt the enzymatic activity, rather there is increasing evidence suggesting that neuronal damage is caused by the aberrant activation of the *Nrp1/VEGF* signalling pathway.

The precise definition of pathogenic mechanisms, such as the elucidation of the role played by *TRPV4* mutants, should pave the way towards the unmet need for new treatments. Indeed, while several of these conditions have been considered slowly progressive, they can still be severely disabling for patients and disease-related complications have only recently emerged from larger case-series. Longitudinal, multi-centre, natural history data are crucial to anticipate care and identify the rates of disease progression in preparation of future therapeutic trials.

In conclusion, paediatric onset motor neuronopathies are a wide and extremely complex group of disorders, with several genes and phenotypes yet to be uncovered. High phenotypic variability, overlap between different conditions and elusive molecular mechanisms justify caution when establishing fixed categories and should be considered when approaching patients with a consistent clinical presentation.

Acknowledgements

Special thanks and appreciation to the neuromuscular team at the DNC. Figures 1 and 2 were created with BioRender.com.

Funding

No funding was received towards this work.

Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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