BRAIN
REVIEW ARTICLE

Neuromuscular disorders with evidence of both neuropathic and myopathic phenotype

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The landscape of genetic research in neuromuscular diseases is revealing an increasing number of genes capable of manifesting both neuropathic and myopathic phenotypes, sometimes in the same patient. While including these genes in broader next-generation sequencing panels addresses the clinical and neurophysiological challenges posed by overlapping or atypical features, it also introduces complexities in the interpretation of their results.
In this review, we examine genes that can present with a mixed phenotype, classifying them into categories of clinical utility, and propose a clinical-neurophysiological grid algorithm to guide clinicians toward diagnosis. To better understand the molecular and functional connections of the described genes, we conducted a gene set enrichment analysis, which highlighted proteostasis, autophagy, and mitochondrial function as key biological processes shared between neuropathy and myopathy. Our aim is to provide a structured framework for interpreting these dual presentations, highlighting the convergence of pathogenic pathways, and emphasizing the importance of a comprehensive, multifaceted approach in managing such cases.

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Keywords: muscle; nerve; hereditary; pathophysiology; phenotype; mixed

Introduction

'Neuromuscular disorders' (NMDs) causing motor deficits constitute a broad spectrum of diseases in which the primary site of injury lies anywhere between the lower motor neuron and the muscle. Leaving aside the acquired forms, in recent years, we have witnessed unprecedented advancements in the discovery of new causative genes for this class of disorders.

Although the pragmatic boundary between neuropathy and myopathy is useful in clinical practice, certain genes challenge this dichotomy by affecting both muscles and nerves, either through allelic diseases or even within the same patient. The inclusion of newly identified genes in progressively broader genetic panels has facilitated aetiologic identification. However, the careful selection of appropriate panels, along with the interpretation of variants of uncertain significance and false-positive results, remains crucial. The presence of both nerve and muscle involvement may serve as a key diagnostic clue, particularly in settings where targeted genetic panels are more accessible than whole-genome or whole-exome sequencing (WGS/WES), ultimately reducing the time to diagnosis.

Received July 07, 2025. Revised September 11, 2025. Accepted October 05, 2025. Advance access publication October 23, 2025

The diagnostic journey for these patients is often challenging. Nerve and muscle biopsies, though valuable, are not always readily available and are rarely performed in combination. Similarly, advanced imaging techniques are not readily accessible to all patients, underscoring the role of neurophysiological assessments in guiding early diagnosis. However, neurophysiology has inherent limitations that must be considered when evaluating chronic motor neuromuscular disorders. First, when both neurogenic and myopathic motor unit potentials are present within the same muscle, the neurogenic ones are usually more eye-catching, potentially masking an underlying myopathic change. Second, in chronic myopathies, the presence of pseudoneurogenic potentials,[1-3] the reduced recruitment in end-stage muscle disease and the atypical distribution of said alterations can mislead the neurophysiologist into suspecting a neurogenic disorder rather than a myopathy.

In this review, we outline genetic conditions that can manifest as neuropathy, myopathy, or both within the same patient. We categorize these disorders based on whether they affect nerves and muscles equally or show a predominant involvement of one over the other. Using gene set enrichment analysis (GSEA), we highlight shared molecular mechanisms among these genes. Finally, we propose diagnostic algorithms to assist clinicians in navigating the diagnostic pathway efficiently (Figs 1 and 2).

Literature review and methods

A list of genes potentially causative of both myopathic and neuropathic phenotypes was extracted from https://neuromuscular.wustl.edu/. We conducted an in-depth search of peer-reviewed articles in English language on the principal web search engines (PubMed, Scopus, Embase and Web of Science) on these genes and classified them by the level of evidence supporting the genotype/phenotype association and the spectrum of severity.

We used the ClinGen Clinical Genome Resource's Gene-Disease Clinical Validity Framework[4] to assess and score the strength of associations with the neuropathic and myopathic phenotypes. For scoring and classifying gene-phenotype associations, we followed the Gene-Disease Validity Curation Process Standard Operating Procedure version 11.[5] Additionally, we referred to the publicly available ClinGen Gene-Disease Validity Curations to cross-reference our scoring with previously curated data. The severity of the phenotype was rated on a six-point scale, with higher scores indicating greater severity (Table 1). Owing to allelic heterogeneity, some genes were better represented by a range of severity scores rather than a single fixed score.

We conducted GSEA on the list of genes identified using Enrichr[6-8] (https://maayanlab.cloud/Enrichr) and Metascape[9] (https://metascape.org). Pathway and process enrichment analyses were performed using the following ontology sources: KEGG pathways, Gene Ontology (GO) Biological Processes, GO Cellular Components, Reactome gene sets, Canonical pathways, CORUM, WikiPathways and PANTHER pathways. A network of enriched terms was generated via Metascape.[9] A protein network was generated using STRING analysis[10] (Search Tool for the Retrieval of Interacting Genes/Proteins; https://string-db.org/). Markov Cluster Algorithm[11,12] with an inflation parameter = 2 was used to define natural clusters based on the stochastic flow in the protein network. Results were visualized using the Appyter applications, Cytoscape and the STRING web app.

Lastly, we organized these genes according to the subchapters presented in our review. This approach allowed us to compile a comprehensive list of genes associated with neuromuscular and mitochondrial diseases presenting a mixed myopathic and neuropathic phenotype (Tables 2 and 3), providing a solid (albeit not omni-comprehensive) foundation for our review. We also developed a grid-based clinical-neurophysiological diagnostic algorithm (Fig. 1) along with a diagnostic flow chart (Fig. 2), the latter incorporating the extra-muscular characteristics of the described phenotypes.

Genes with strong coexistence of myopathy and neuropathy

These genes are characterized by usual coexistence of myopathic and neuropathic features, which may involve both distal and proximal segments of the limbs. They can be subdivided into genes that typically show a non-length-dependent phenotype (*VWA1*, *BICD2*, *HSPB8*, *DNM2* and *MYH14*), while others tend to present a scapuloperoneal phenotype (*LMNA*, *HSPB3*, *BAG3*). Some typically show contractures (*LMNA*, *DNM2*, *BICD2*).

VWA1

Gene localization and function

VWA1 encodes von Willebrand factor A domain-containing protein 1, an extracellular matrix (ECM) component crucial for maintaining the structural integrity of basement membranes in muscles and the peripheral nervous system through its interactions with perlecan and collagen VI.[13,14]

Classical phenotype

Biallelic pathogenic *VWA1* variants result in a phenotype characterized by a slowly progressive, non-length-dependent weakness in the lower limbs (anterior > posterior muscles), accompanied by foot deformities. Sensory involvement is either absent or minimal, and the onset of symptoms spans a wide age range (from antenatal abnormalities to the sixth decade). In the first described families, instrumental and myopathological findings were indicative of a neuromyopathic process, prompting the nomenclature of hereditary motor neuropathy with myopathic features (HMNMYO).[13] Creatine phosphokinase (CPK) levels are elevated in a minority of individuals. Muscle biopsies reveal increased fibre size heterogeneity and nuclear centralization, accompanied by varying degrees of neurogenic alterations.[13,15]

Expanded phenotype

Recently, Gable *et al.*[16] reported the case of a homozygous frameshift (G25Rfs*74), involving a 3-year-old child presenting with a slowly progressive spastic paraparesis phenotype, characterized by distal spasticity, hyperreflexia and bilateral Babinski sign. Another report described early proximal limb or axial weakness, skeletal deformities and scapular winging, tongue fasciculation and dystonia,[17] further expanding the phenotypic spectrum associated with VWA1.

Pathophysiology and genotype-phenotype correlations

The pathogenic mechanism remains unclear, but interactions with collagen VI and perlecan are likely relevant, considering that pathogenic variants in these genes are a well-known cause for other NMDs, such as congenital myopathies (Bethlem/Ullrich type) and

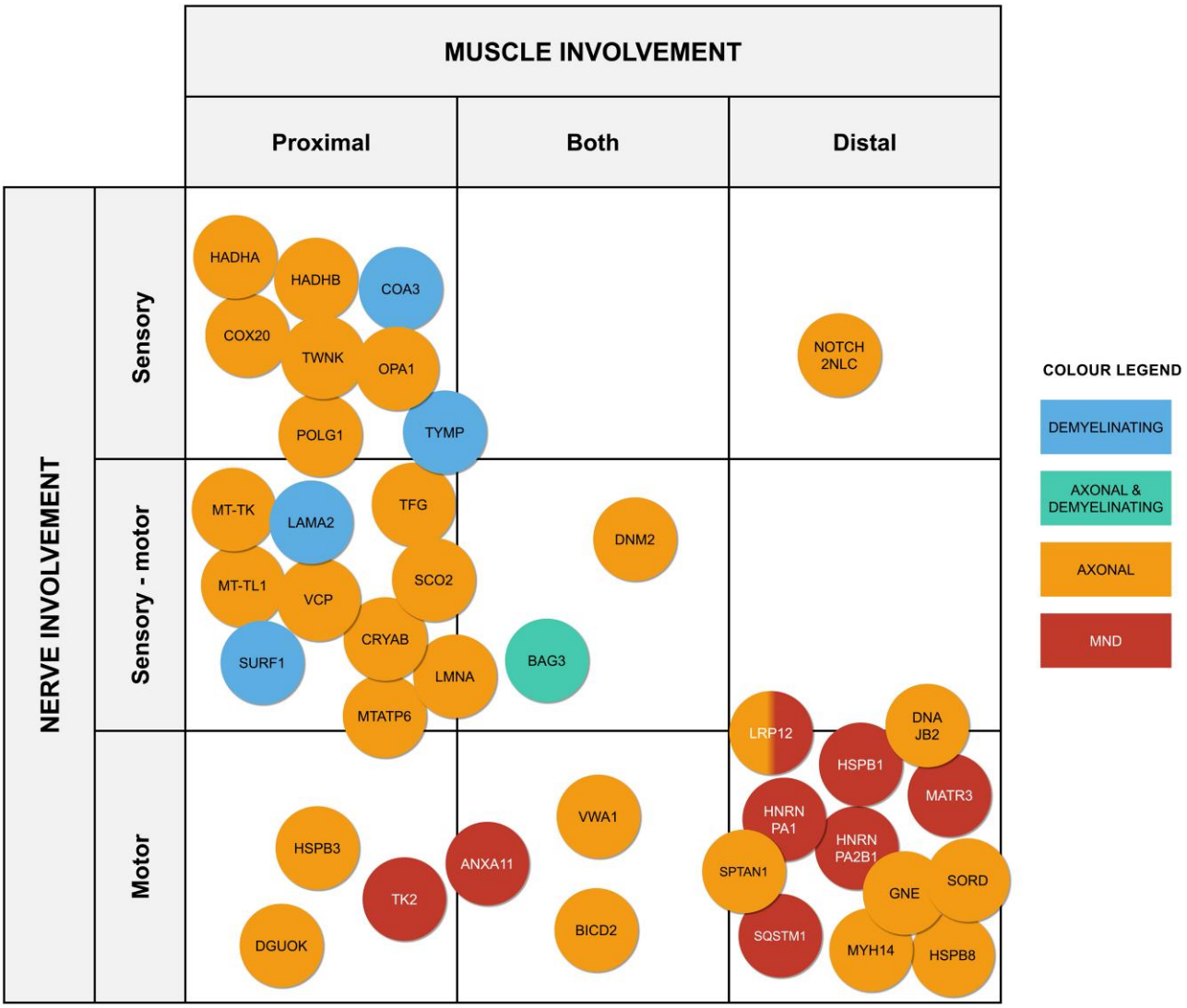

Figure 1 Primary characteristics of neurogenic and myopathic phenotype for genes causing neuropathy and myopathy. Proposed diagnostic grid algorithm based on the clinical and neurophysiological features of neuromuscular involvement. MND = motor neuron disease.

Schwarz-Jampel syndrome.[14] In the cohort from Deschauer *et al.*,[13] patients with biallelic truncating variants exhibited a predominant myopathic phenotype with neurogenic features. In contrast, Pagnamenta *et al.*[15] identified a relatively common ancestral 10-base pair repeat expansion (G25Rfs*74), predominantly showing neurogenic changes. This genetic variant was estimated to account for up to 1% of unexplained hereditary motor neuropathy (HMN) cases in individuals of European descent.

BICD2

Gene localization and function

BICD2 is an evolutionary homologue of *Drosophila* bicaudal D. Mammals exhibit two paralogues, BICD1 and BICD2.[18] BICD2 is ubiquitously expressed and encompasses five coiled-coil (CC) domains organized into three distinct binding regions that play a pivotal role in mediating interactions with cellular components, including the dynein-dynactin complex, the kinesin motor complex, and the cargo-associated protein RAB6, thereby orchestrating microtubule-mediated transport of directional cargo.[18,19]

Classical phenotype

Pathogenic BICD2 variants typically lead to autosomal dominant spinal muscular atrophy with lower extremity predominance (SMA-LED) or familial spastic paraplegia (FSP). Onset of symptoms occurs during infancy or childhood, although adult-onset cases are documented. The clinical manifestations encompass muscle weakness, atrophy in the lower limbs, ankle and knee contractures and motor neuron-related signs, along with congenital hip dysplasia, foot deformities, lumbar hyperlordosis and scapular winging.[19] Disease progression is generally slow or static, with most patients retaining the ability to walk independently.[20]

Expanded phenotype

Earlier studies suggested a homogeneous phenotype; however, subsequent research has revealed a wide spectrum of disorders associated with BICD2 variants, from nearly asymptomatic presentations to severe, lethal congenital muscular atrophy with arthrogryposis.[21] Muscle biopsies have unveiled a combination of chronic neuropathic and myopathic alterations,[18] while MRI

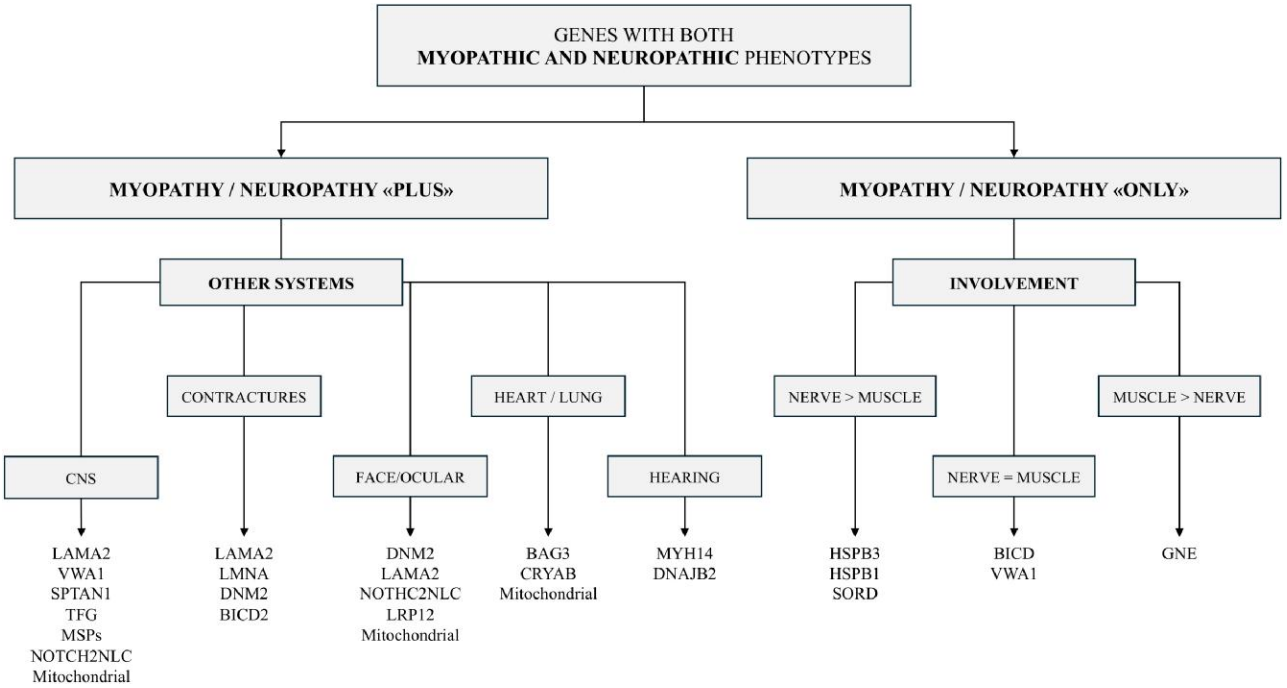

Figure 2 Diagnostic flow chart for gene identification. Disease phenotype categorized on the basis of clinical extramuscular features of involvement.

Table 1 Scoring system used to determine the severity associated with the phenotype

Item	Score
Asymptomatic, only instrumental evidence	0
Symptomatic without significant functional impairment	1
Unable to walk or significant functional impairment occurring >5 years after symptom onset	2
Unable to walk or significant functional impairment occurring ≤5 years after symptom onset	3
Unable to walk or significant functional impairment in childhood or impact on survival	4
Death in childhood	5

studies suggest a consistent pattern of fatty infiltrations beginning in vastus lateralis, sartorius and gastrocnemius.[18]

Pathophysiology and genotype-phenotype correlations

BICD2 variants result in Golgi apparatus fragmentation, a hallmark of cells carrying mutated BICD2, suggesting disturbances in protein trafficking and with potential consequences for the development and maintenance of motor neurons. Of note, defective BICD2 protein impairs the transport and release of neurotrophins through the neuromuscular junction (NMJ) from muscles into the axonal terminals, resulting in motor unit degeneration, as revealed by BICD2-null mice.[22] Moreover, a dysferlin and caveolin-3 reduction at the sarcolemma was noted in human muscle biopsies, suggesting their involvement in BICD2-related muscle pathophysiology. Dysferlin, crucial for muscle membrane repair, is transported via kinesins, while caveolin-3 is implicated in dysferlin trafficking to the plasma membrane. Hence, BICD2 variants may impair the transport of exocytotic cargoes containing dysferlin and caveolin-3 along microfilaments, compromising sarcolemma integrity. Patients with *de novo* variants tend to exhibit congenital disease with severe deformities, including arthrogryposis and upper limb involvement, often leading to an early lethal outcome. Variants occurring in the CC1 domain typically result in a milder and more classical phenotype, while variants within CC2 and CC3 may have a higher association with atypical and severe clinical presentations.[23]

HSPB8

Gene localization and function

HSPB8 encodes heat shock protein beta-8, a molecular chaperone that interacts with several other polypeptides involved in antiapoptotic functions, signal transduction, and degradation of misfolded proteins being part of the Chaperone Assisted Selective Autophagy (CASA) complex. This is a selective type of macroautophagy within the autophagy lysosome system that serves to maintain protein stability within myocytes, neurons and other mechanically strained tissue cells.[24] If mechanical tension results in permanent unfolding of filamin, the CASA chaperone complex leads to autophagic degradation of damaged proteins. Variants in this gene have been associated with various allelic disorders, including Charcot-Marie-Tooth (CMT) type 2L,[25] distal HMN (dHMN) type 2A, distal myopathy and motor neuropathy, and a limb-girdle rimmed vacuolar myopathy.

Classical phenotype

The neurogenic phenotype was first described in a CMT2 Chinese family harbouring the K141N variant.[26] It is characterized by the onset of distal sensory-motor symptoms in adolescence to early adulthood. Sensory manifestations are milder, while a minority of patients present with a non-length dependent pattern of muscle weakness and atrophy in lower limbs, resembling a motor neuron disease (MND) or a myopathy rather than a classical CMT. In contrast, dHMN2A families (K141N and K141E) exhibit a steeper disease

Table 2 Overview of genes associated with neuromuscular diseases presenting mixed myopathic and neuropathic phenotypes

Gene	Class/Pathway	Classical phenotype	E	S	Alt. phenotype	E	S	SP
ANXA11	Stress granules	ALS/FTD	D	4	hIBM	S	2	Y
BAG3	Chaperone	Myofibrillar myopathy	D	2–4	GAN	S	1–2	Y
BICD2	Trafficking	SMALED2/FSP	D	1–5	Distal myopathy	M	1	Y
CRYAB	Chaperone	MFM2	D	2–5	HSMN	M	1–2	N
DNAJB2	Chaperone	HMNR5/AR-CMT2	D	1–3	DVM	L	1–3	Y
DNM2	Membrane	CNM	D	1–4	CMT-IB	D	1–2	N
GNE	Membrane	hIBM	D	2	Neuropathy/MND	L	2	Y
HNRNPA1	RNA-binding	hIBM/PDB/FTD/MND	M	2–4	–	/	/	N
HNRNPA2B1	RNA-binding	hIBM/PDB/FTD/MND	M	2–4	–	/	/	Y
HSPB1	Chaperone	CMT2F/dHMN2B	D	2–4	DVM	M	2	N
HSPB3	Chaperone	dHMN2C/CMT2	D	2	Proximal myopathy	M	1–2	Y
HSPB8	Chaperone	CMT2L/dHMN2A	D	1–2	DVM	S	1–2	Y
LAMA2	ECM	LGMDR23/CMD	D	2–4	Dismyelinating neur.	D	0–1	Y
LMNA	Cytoskeleton	EMD/LGMD	D	2–5	CMT2B1	D	1–3	Y
LRP12	Signalling	OPDM1	M	2–4	ALS/PMA/HMN/CMT	M	1–4	Y
MATR3	RNA-binding	VCPDM/hIBM	D	2	FTD/MND	M	4	N
MYH14	Cytoskeleton	PNMHH	D	1–3	–	–	–	Y
NOTCH2NLC	Corticogenesis	NIID/CMT	S	4	OPDM3/DVM	M	4	Y
SORD	Polyol pathway	AR-CMT2	D	1–2	Distal myopathy	L	1–2	Y
SPTAN1	Cytoskeleton	HMND11	D	0–2	Distal myopathy	L	0–2	Y
SQSTM1	Autophagy	hIBM/PDB	D	2	FTD/MND	M	4	N
TFG	Trafficking	HMSN-P	D	1–2	Vacuolar myopathy	L	0–1	Y
VCP	Autophagy	hIBM/MND/PDB	D	4	CMT2Y	D	1–2	Y
VWA1	ECM	HMNMYO	D	1–2	–	–	–	Y

Summary of the genes linked to neuromuscular diseases characterized by combined myopathic and neuropathic presentations. Columns include the gene names, functional classifications, classical and alternative (Alt.) phenotypes, as well as evidence for association (E) and severity levels (S). The final column (SP) indicates genes for which both myopathic and neuropathic phenotypes are observed in the same patient (Y = yes; N = no). AR = autosomal recessive; CMD = congenital muscular dystrophy; CMT = Charcot-Marie-Tooth; CNM = centronuclear myopathy; D = definitive; dHMN = distal hereditary motor neuropathy; DVM = distal vacuolar myopathy; ECM = extracellular matrix; EMD = Emery-Dreifuss dystrophy; FSP = familial spastic paraplegia; FTD = frontotemporal dementia; GAN = giant axonal neuropathy; hIBM = hereditary inclusion body myopathy; HMNMYO = hereditary motor neuropathy with myopathic features; HMSN-P = hereditary motor and sensory neuropathy with proximal dominant involvement; HSMN = hereditary sensory motor neuropathy; L = limited; LGMD = limb girdle muscular dystrophy; M = moderate; MFM = myofibrillar myopathy; MND = motor neuron disease; neur = neuropathy; NIID = neuronal intranuclear inclusion disease; OPDM = oculopharyngodistal myopathy; PDB = Paget disease of bone; PNMHH = peripheral neuropathy, myopathy, hoarseness and hearing loss; PMA = progressive muscular atrophy; S = strong; SMA = spinal muscular atrophy; SMALED = spinal muscular atrophy with lower extremity predominance; VCPDM = vocal cord and pharyngeal weakness with distal myopathy.

progression leading to complete paralysis and atrophy of all distal leg muscles (beginning with a 'hanging big toe', similar to MYH7 myopathy) and weakness in the thigh muscles occurring within 10 years of symptom onset.[27]

Expanded phenotype

More recently, a distinct distal myopathy (K141E) phenotype was also identified with early weakness in the lower legs (especially the anterior compartment), later spreading to thigh muscles.[28] Muscle biopsies revealed dystrophic features, rimmed vacuolar pathology and myofibrillar aggregates.[28] Neurogenic findings in neurophysiological studies prompted the authors to hypothesize a concomitant motor neuropathy in these patients. C-terminal frameshift variants in the *HSPB8* gene have also been associated with adult onset rimmed vacuolar myopathies, with normal nerve conduction studies.[29] In such cases, muscle involvement patterns vary, ranging from a distal myopathy to a limb-girdle distribution, with or without axial involvement.

Pathophysiology and genotype-phenotype correlations

In the knock-in mouse model, toxic accumulation of mutant HSPB8 combined with an inability to degrade HSPB8-positive aggregates through CASA resulted as one of the key pathogenetic mechanism underlying both the neuropathic and myopathic phenotypes.[30] Considering that disease phenotypes and progression in distal myopathy patients seem to adhere to that of described dHMN patients (these being usually classified as such based on a distal onset and compatible neurophysiology), it can also be speculated that some of the individuals diagnosed with a dHMN may actually suffer from a distal myopathy.

DNM2

Gene localization and function

DNM2 encodes the large GTPase dynamin 2, which belongs to the dynamin family. These proteins function as mechanochemical proteins, hydrolysing GTP to facilitate membrane fission processes.[31] Contrary to DNM1 (expressed in neuronal cells) and DNM3 (expressed in brain, heart, testis and lungs), DNM2 is ubiquitously expressed and participates in several cellular processes, including endocytic pathways, vesicle trafficking, centrosome cohesion and the dynamics of actin and microtubules.[32] However, DNM2 variants are associated with a set of distinct diseases and only affect a limited number of cell types: muscle cells in autosomal dominant centronuclear myopathy (CNM) and Schwann cells and/or peripheral neurons in dominant-intermediate CMT subtype B (CMT-DIB) and axonal CMT2M.

Classical phenotype

Autosomal-dominant CNM is characterized by slowly progressive, mostly symmetric muscular weakness and wasting that affects both proximal and distal muscles.[31] This condition is marked by

Table 3 Overview of genes associated with mitochondrial diseases presenting mixed myopathic and neuropathic phenotypes

Gene	Class/Pathway	Classical phenotype	E	S	Alt. phenotype	E	S	SP
COA3	Complex IV	Complex IV deficiency	D	4–5	SN	L	2–3	Y
COX20	Complex IV	Complex IV deficiency	D	2–4	SN	M	2	Y
DGUOK	mtDNA	MDDS	D	4–5	Neuropathy	M	2–3	Y
HADHA	Beta-oxidation	TFPD	D	2–5	SN	M	1–2	Y
HADHB	Beta-oxidation	TFPD	D	2–5	SN	M	1–2	Y
MT-TK	Mito tRNA	MERRF	D	2–5	Neuropathy	D	1–2	Y
MT-TL1	Mito tRNA	MELAS	D	2–5	Neuropathy	D	1–2	Y
MTATP6	ATP synthase	Leigh syndrome	D	4–5	Neuropathy	D	1	Y
OPA1	Mito fusion	ADOA	D	2	Neuropathy/myopathy	D	1	Y
POLG1	mtDNA	SANDO/PEO	D	2–5	SN	D	1–2	Y
SCO2	Complex IV	Complex IV deficiency	D	4–5	SN/SMA-like forms	D	2–5	Y
SURF1	Complex IV	Leigh syndrome	D	4–5	Demyelinating neur.	S	1–2	Y
TK2	mtDNA	MDDS	D	2–5	FSHD-like myopathy	M	2–3	Y
TWNK	mtDNA	PEO	D	2	IOSCA	D	2–4	Y
TYMP	Nucleotide	MNGIE	D	4	Demyelinating neur.	D	1–2	Y

Summary of the genes linked to mitochondrial diseases characterized by combined myopathic and neuropathic presentations. Columns include the gene names, functional classifications, classical and alternative (Alt.) phenotypes, as well as evidence for association (E) and severity levels (S). The final column (SP) indicates genes in which both myopathic and neuropathic phenotypes are observed in the same patient (Y = yes; N = no). ADOA = autosomal dominant optic atrophy; D = definitive; FSHD = facioscapulohumeral muscular dystrophy; IOSCA = infantile-onset spinocerebellar ataxia; L = limited; M = moderate; MDDS = mitochondrial DNA depletion syndrome; MELAS = mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes; MERRF = myoclonic epilepsy with ragged-red fibres; MNGIE = mitochondrial neurogastrointestinal encephalomyopathy; neur = neuropathy; PEO = progressive external ophtalmoplegia; S = strong; SANDO = sensory ataxic neuropathy, dysarthria, and ophthalmoplegia; SMA = spinal muscular atrophy; SN = sensory neuropathy; TFPD = mitochondrial trifunctional protein deficiency.

centrally located nuclei, radial arrangement of sarcoplasmic strands, and a predominance of type 1 fibre atrophy. It was first identified as a childhood or adolescence-onset disorder characterized by delayed motor milestones and mild–moderate muscular weakness.[33] Subsequent studies expanded the phenotypic spectrum to include essentially all ages and ranges of severity.[32] Facial weakness, ptosis and ophthalmoplegia are common, and taken together, these symptoms present some overlap with NMJ disorders.

Expanded phenotype

In addition to CNM, DNM2 variants are associated with CMT-DIB, with onset in the first or second decade,[34] and occasionally a broader array of presentations, such as an infantile axonal CMT associated with congenital cataracts, ophthalmoparesis and ptosis (CMT2M)[35] and a young adult-onset FSP.[36] In variants occurring in the middle domain, both a neuropathy and a myopathy have been described in the same patient.[37] Moreover, mice carrying the K562E variant, associated with CMT-DIB in humans, present a myopathic phenotype, suggesting that the neuropathy in humans may occasionally overshadow a coexistent myopathy.[38]

Pathophysiology and genotype-phenotype correlations

DNM2-related disorders exhibit strong genotype-phenotype correlations, with variants leading to intermediate CMT clustering at the N-terminal of the pleckstrin homology domain, and variants leading to CNM clustering within the middle domain, pleckstrin homology domain and GTPase effector domain.[31] A defect in clathrin-mediated endocytosis (critical for peripheral nerve myelination) caused by DNM2 variants likely contributes to the pathophysiology observed in CMT-DIB.[31] Conversely, dysregulation of T-tubule biogenesis/maintenance, cytoskeletal remodelling and autophagy have been proposed as potential pathogenic mechanisms in CNM.[32] The role of DNM2 in the development and maintenance of postsynaptic NMJs, particularly in sustaining actin cytoskeletal organization, is of special interest, given that the bulbar and ocular symptoms mimic those of a congenital myasthenia.[39]

MYH14

Gene localization and function

MYH14 encodes a member of the non-muscle myosin heavy-chain II family. This protein plays a regulatory role in cytoskeletal actin dynamics, cell motility, polarity and mitochondrial function.[40] Pathogenic MYH14 variants have been identified previously in patients with non-syndromic hearing loss, as the protein is widely expressed in cochlear tissue.

Neuromuscular phenotype

The R941L variant is associated with a complex childhood-onset phenotype known as peripheral neuropathy, myopathy with mild CPK elevation, hoarseness and hearing loss (PNMHH). This phenotype was initially observed in four families from Korea, characterized by predominantly distal weakness in the lower limbs without significant sensory impairment, and a more occasional involvement of the proximal thigh.[41] In most patients, hearing loss occurred after the onset of muscle weakness. Myopathology and neurophysiology of affected individuals showed a mixed motor neuropathic and myopathic phenotype. Notably, electron microscopy frequently revealed subsarcolemmal accumulation of enlarged mitochondria with paracrystalline inclusions. More recently, the R941L variant has been linked to adolescent-onset axonal sensory-motor neuropathy in two families from Canada and the USA.[42,43] In these cases, there was no consistent evidence of a coexisting myopathy, although the proband of the American family exhibited a mild myopathic EMG pattern in the proximal thigh muscles.

Pathophysiology and genotype-phenotype correlations

The involvement of nerves and muscles seen only with the R941L variant may result from a dominant-negative effect of the mutated

protein on mitochondrial fission, particularly at the axon periphery.[42] Impaired retrograde transport or autophagic removal of mitochondria at the axon tip may be particularly relevant to the peripheral neuropathy phenotype. Interestingly, myopathic changes were most evident in some of the Korean patients, while Canadian and American patients (who underwent only EMG without muscle biopsy) did not consistently show these changes.[40] Nonetheless, the motor neuropathic phenotype appears to be the most clinically relevant in all described patients, while proximal myopathic changes are more subtle.

LMNA

Gene localization and function

LMNA undergoes alternative splicing to encode lamin A/C proteins, intermediate filament proteins of the nuclear lamina with roles in nuclear assembly, chromatin organization, nuclear membrane maintenance and telomere dynamics. Variants in LMNA are responsible for a plethora of distinct disorders, named laminopathies. More than 500 LMNA variants have been documented, associated with 21 distinct phenotypes.[44] Laminopathies can impact specific tissues, including striated muscles (and the heart's conduction system), peripheral nerves or adipose tissue. Alternatively, they manifest as systemic diseases affecting multiple organs, as seen in premature ageing syndromes (progerias). For this review, we will focus on the neuromuscular phenotypes.

Classical phenotype

LMNA variants have been linked to autosomal Emery-Dreifuss muscular dystrophy (EDMD), presenting with either a dominant (EDMD2) or recessive (EDMD3) inheritance pattern. EDMD2 patients exhibit a scapular-peroneal distribution of weakness, along with contractures and early cardiac involvement (dilatative cardiomyopathy and arrhythmias), usually within the second decade.[45] EDMD3 cases are far less common and present at younger ages with a severe phenotype. A limb-girdle phenotype accompanied by cardiac arrhythmias is also possible, characterized by slower progression and absence of contractures with onset in the third decade.[45] Finally, a congenital muscular dystrophy (CMD-L) characterized by marked axial hypotonia, contractures, spinal rigidity and progressive respiratory insufficiency has been observed in infants and toddlers within the first 2 years of life.

Expanded phenotype

Autosomal recessive axonal neuropathy (CMT2B1) or a mixed neuropathic and myopathic phenotype has been reported in patients harbouring LMNA variants.[46-48] This is consistent with similar axonal pathology observed in LMNA-null mice.[49] While the neuropathic phenotype is infrequent in Western countries, it exhibits a certain prevalence in consanguineous families of North Africa (R298C).[50] In these cases, symptom onset typically occurs during the second decade, with a relatively rapid progression and significant disability at the lower limbs, with foot deformities and proximal lower limb involvement (60%) among the most common features.

Pathophysiology and genotype-phenotype correlations

LMNA variants can result in overlapping syndromes or distinct phenotypes, with single variants potentially affecting different organ systems, suggesting different functional domains are essential for the integrity of different cell lineages. EDMD-causing variants are usually missense and act through a gain-of-function mechanism, while frameshifts result in haploinsufficiency and a milder limb-girdle phenotype.[45] The precise mechanisms behind laminopathies and their phenotypic variability remain unclear, although it is hypothesized that post-translational modifications (e.g. phosphorylation) may play a role in regulating lamin function and therefore influencing cell-specific (e.g. mechanical, oxidative) stress resilience mechanisms.[50] Variants in the rod domain (which more likely disrupt protein structure and its resistance to mechanical stress) predominantly cause striated muscle laminopathies and neuropathies, while variants in the tail domain are generally linked to lipodystrophies and premature ageing syndromes.[50]

HSPB3

Gene localization and function

HSPB3 encodes the smallest member of human heat-shock proteins (HSPs). In contrast with other HSPs, HSPB3 does not homodimerize, but (at least in the muscle) forms heterodimers with HSPB2.[51] The HSPB2/HSPB3 complex provides cellular protection against proteotoxic stress and promotes the stabilization of sarcomeres and cytoskeleton. Additionally, HSPB3 plays a role in muscle differentiation, and, unlike other small HSPs, it does not exhibit induction in response to heat stress. Variants in HSPB3 have been associated with HMN type 2C, CMT2 and myopathy.

Classical phenotype

The initial description of HSPB3-related HMN involved two sisters with a heterozygous variant in the N-terminal domain (NTD) of HSPB3 (R7S), presenting with distal muscle wasting in early adulthood and minimal sensory disturbances.[52] More recently, a variant in the highly conserved α-crystallin domain of HSPB3 (Y118H) was identified in a Korean family with a similar clinical phenotype.[53] However, in this case, clinical and neurophysiological evaluation revealed more pronounced sensory disturbances, suggesting a diagnosis of CMT2.

Expanded phenotype

Dominant HSPB3 variants (L34Ffs*50 and R116P), were associated with myopathic features in two Italian patients: a 70-year-old man with shoulder-girdle weakness and atrophy and a young woman displaying an axonal neuropathy, myalgia and diffuse muscle weakness.[54] Muscle biopsy revealed severe myofibrillar disorganization affecting the Z-disc, abnormal sarcoplasmic reticulum morphology, pluri-segmented nuclei and intermyofibrillar glycogen accumulation.

Pathophysiology and genotype-phenotype correlations

HSPB3 variants are likely pathogenetic through different mechanisms. The R116P, Y118H and frameshift variants disrupt the HSPB2/HSPB3 interface, leading to HSPB3 aggregation and failure to regulate HSPB2.[51] This results in excessive HSPB2 compartments, sequestering lamin A to nuclear foci and disrupting gene expression. Conversely, the R7S variant, located near oligomerization motifs, does not significantly affect HSPB2 interaction and has a mild impact on oligomer formation,[51] therefore its functional consequences remain unclear.

BAG3

Gene location and function

BAG3 encodes a multi-domain co-chaperone protein that represents another critical component of the CASA complex, involved in the cellular protein quality control system. BAG3 is prominently expressed in the Z-disks of skeletal and cardiac muscles and to a lesser extent in other tissues.

Classical phenotype

The classical phenotype (P209L) is that of a severe progressive myofibrillar myopathy that manifests in childhood, along with cardiomyopathy and diaphragm paralysis leading to respiratory insufficiency by the second decade of life.[55] The distribution of muscle weakness can vary, although an initial presentation with toe walking and generalized clumsiness appears to be more frequent. Additionally, a rigid spine may be present as an accessory but suggestive feature. A milder adult-onset myopathic phenotype characterized by distal lower limb weakness and scapular winging was also described (P209Q).[56]

Expanded phenotype

Initial neurophysiological studies suggested, as an associated feature, a predominantly axonal neuropathic phenotype in certain patients, which was subsequently confirmed by nerve biopsies displaying evidence of giant axons.[57] In the classic phenotype, the neuropathy has a limited contribution to the overall severe disability, which is primarily driven by cardiac and muscular involvement.[58] Subsequent reports expanded the clinical spectrum to include an isolated adult-onset sensorimotor axonal neuropathy (P209S)[59] and an isolated childhood-onset demyelinating neuropathy (P209L).[60]

Pathophysiology and genotype-phenotype correlations

In humans, different variants at the P209 site yield distinct myopathic and/or neuropathic phenotypes, underscoring the importance of this residue in the function of BAG3. Individuals with heterozygous P209L variants present with a severe myofibrillar myopathic phenotype with cardiomyopathy and giant axonal polyneuropathy, although cases of isolated demyelinating polyneuropathies have also been reported.[60] It is intriguing that, in mice, the P209L variant does not lead to a cardiac phenotype, suggesting that human cardiomyopathy may arise due to species-specific or genetic background-dependent effects.[61] As mentioned, the P209S variant is associated with sensorimotor axonal neuropathies without cardiomyopathy or respiratory involvement,[59] featuring a variable age of onset, while P209Q results in a milder myopathic phenotype with adult onset. The interaction between BAG3 and HSPB8, along with shared pathological mechanisms between myofibrillar myopathy and hereditary neuropathies—primarily linked to protein misfolding and aggregates—implies a plausible biological connection between the concomitant nerve and muscle impairments in these patients.[62] Regarding the giant axonal phenotype, given the function of both BAG3 and the gigaxonin-associated giant axonal neuropathy (GAN) gene in the degradation of misfolded proteins, it is plausible that loss of BAG3 function and consequent disruption of protein degradation pathways may lead to intra-axonal accumulation of misfolded cytoskeletal proteins.[58]

Genes associated with predominantly myopathic phenotypes that may include neuropathic features

Within this group, we present genes associated with disorders in which myopathic manifestations are usually predominant, although neuropathic signs and symptoms may occur in a subgroup of patients. They include genes linked to disorders that present with proximal motor deficits (*LAMA2*, *CRYAB*), while others have predominantly distal deficits (*GNE*).

LAMA2

Gene location and function

LAMA2 encodes the alpha 2 subunit of the heterotrimeric laminin-211 protein, also referred to as merosin. This protein is specific to certain tissues in the ECM, including skeletal muscles Schwann cells, placental trophoblast, dermis-epidermis junction and myocardium. It plays a central role in the protein scaffold connecting ECM to the cell surface.[63]

Classical phenotype

Pathogenic variants in the *LAMA2* gene cause laminin alpha-2-related muscular dystrophies (LAMA2-RD), a set of autosomal recessive disorders, ranging from severe generalized congenital onset to milder limb-girdle muscular dystrophy appearing later in childhood. Core features of the condition include prevalent upper girdle involvement, elevated CPK levels, and severe head/trunk flexor weakness. Prenatal/neonatal features, such as talipes or mild contractures, are common (approximately 20% of patients at birth).[63]

Expanded phenotype

Neurophysiological evidence of dysmyelinating sensorimotor neuropathy may be incidentally present from early infancy, with conduction velocities progressively decreasing over time, along with a reduction of compound muscle action potential amplitudes.[64] While peripheral neuropathy significantly contributes to the phenotype in mouse models,[64] the extent to which this translates to muscle weakness and disease progression in patients with LAMA2-RD is not fully understood. Apart from muscle weakness, the disease burden in LAMA2-RD is also influenced by respiratory insufficiency, feeding difficulties, joint contractures and scoliosis. Additionally, brain abnormalities, such as structural defects and functional impairments, including epilepsy and intellectual disability, constitute variable and underappreciated features in these patients.[65]

Pathophysiology and genotype-phenotype correlations

Specific merosin receptors have been described so far in peripheral nerves and skeletal muscle, namely integrins and dystroglycan, which activate downstream signalling pathways necessary for tissue function, maintenance and repair.[64,66] While the presence of residual merosin in muscle generally correlates with a milder clinical phenotype, recent findings suggest that CNS abnormalities and the entity of the neuropathy can be uncoupled and are not strictly determined by the type of *LAMA2* gene variants.[64]

CRYAB

Gene location and function

CRYAB encodes αB-crystallin, a small heat shock protein and major structural component of the crystalline lens. It is expressed

throughout various tissues, with the highest concentration observed in the heart and skeletal muscle.[51] In instances of cellular stress, αB-crystallin associate with Z-discs and I-bands, indicative of interactions with client proteins such as desmin and titin.

Classical phenotype

Heterozygous variants in CRYAB are linked to cataracts, cardiomyopathy and myofibrillar myopathy 2 (MFM2). MFM2 typically presents in adulthood with proximal myopathy, although leg muscles involvement is not uncommon. Additional features include facial and bulbar weakness, with respiratory complications from diaphragmatic weakness later in the disease progression, and sudden cardiac death. Muscle biopsies reveal fibre size variation, internal nuclei, fibre splitting and vacuoles, while immunohistochemistry shows protein aggregates of desmin and αB-crystallin.[67] A distinct CRYAB-related disease is fatal infantile hypertonic myofibrillar myopathy, caused by recessively acting CRYAB variants.[51] The disease most severely affects truncal muscles, leading to death in infancy due to respiratory insufficiency. Histopathological changes indicate a severe myofibrillar myopathy, with inclusions originating from Z-discs, along with rimmed vacuoles.

Expanded phenotype

Cortese *et al.*[68] described five patients with the R120G variant in CRYAB associated with cataracts and slowly progressive axonal sensorimotor neuropathy, with slow progression over the years. In three of these patients, some degree of axial and diaphragmatic weakness suggested the coexistence of a myopathic process, although muscle and nerve biopsies were not conducted.

Pathophysiology and genotype-phenotype correlations

Missense variants, particularly at R120 and D109, disrupt dimerization, forming toxic pre-amyloid aggregates. These aggregates exert their pathogenic effects in a desmin-dependent mechanism, which likely explain the muscle-predominant nature of the disease. The other CRYAB variants mainly affect the C-terminal region involved in the chaperone function.[51] Therefore, it is likely that a combination of gain- and loss-of-function mechanisms mediates the pathogenesis in αB-crystallinopathies in muscles and nerves.

GNE

Gene location and function

GNE encodes the bifunctional enzyme known as UDP-*N*-acetylglucosamine (GlcNAc) 2-epimerase/*N*-acetylmannosamine (ManNAc) kinase. This ubiquitous enzyme catalyses the initial two rate-limiting steps in the pathway responsible for producing sialic acid. Sialic acids are monosaccharides located at the terminal portions of sugar chains in glycoproteins and glycolipids, where they regulate numerous biological processes by mediating molecular and cellular interactions.

Classical phenotype

Biallelic GNE variants are associated with the development of an autosomal recessive distal myopathy, previously known as Nonaka distal myopathy or hereditary inclusion body myopathy 2. GNE myopathy presents within the fourth decade of life with distal muscle weakness in the lower limbs, usually resulting in bilateral foot drop. Weakness eventually involves more proximal muscles in upper and lower extremities, leading to the loss of ambulatory function within 20 years from symptom onset. A distinctive feature is the preservation of the quadriceps muscles even in advanced stages of the disease. Argov and Yarom[69] vividly illustrated this in their description of a patient in his sixties, who, despite being confined to a wheelchair, could still extend his knees with his granddaughter seated on his ankles. Some cases may exhibit significant proximal muscle involvement from the onset, particularly in the lower girdle, a feature that may have been under-represented in Western cohorts.[70]

Expanded phenotype

In recent years, GNE variants have also been linked to forms of predominantly motor axonal neuropathy, primarily reported through small case series.[71,72] These patients resemble GNE myopathy patients, and, in fact, an overlapping myopathy was either present or not convincingly ruled out in the diagnostic workup. Additionally, a recessive and slowly progressive phenotype of distal-onset juvenile MND without bulbar signs and quadriceps involvement was described in a consanguineous Turkish family,[73] although a muscle biopsy was not performed.

Pathophysiology and genotype-phenotype correlations

The pathogenic mechanism underlying GNE myopathy likely revolves around reduced sialic acid biosynthesis, leading to hyposialylation of skeletal muscle glycoproteins. However, the exact mechanisms by which these biochemical alterations contribute to muscle weakness and the selective sparing of the quadriceps muscle, remain unclear.[74] Clinical trials investigating the use of ManNAc in GNE myopathy demonstrated increased levels of plasma sialic acid and sarcolemmal sialylation, as well as a slower rate of decline in strength.[75,76] Most variants are missense, suggesting that only an incomplete loss of enzymatic activity results in myopathy. In fact, knocking out the *Gne* gene in mice results in embryonic lethality.[75] From a biological perspective, it is plausible that GNE variants may disrupt axonal function, as research has indicated that GNE plays a role in maintaining neuronal homeostasis in neural crest-derived cell cultures and in heterozygous mice.[77]

Genes associated with predominantly neuropathic phenotypes that may include myopathic features

Within this group, we present genes associated with disorders in which neuropathic manifestations are usually prevalent, but myopathic signs and symptoms may be present in a subgroup of patients. The phenotype is predominantly distal in disorders linked to *HSPB1*, *SPTAN1*, *SORD* and *DNAJB2*, while *TFG* is predominantly proximal.

HSBP1

Gene location and function

HSPB1 encodes heat shock protein 27 (HSP27), which belongs to a well-characterized group of ubiquitously expressed proteins with a key role in the unfolded protein response (UPR). The goal of this pathway is the refolding or degradation of misfolded proteins and aggregates, protecting cells from a diverse range of stressors.[78] HSP27 has also been implicated in axon regeneration, cytoskeleton regulation and maintenance, and microtubule transport.[79]

Classical phenotype

Variants in HSPB1 have been classically associated with CMT2F and dHMN2b. Onset is usually in late adulthood (fifth decade), but earlier presentations have been described.[80] Patients usually show bilateral distal weakness in legs, slowly progressing over 10–20 years to affect arms and limit ambulation. In CMT2F, sensory involvement is generally mild to moderate and usually overshadowed by motor manifestations. A more dramatic, rapidly progressing amyotrophic lateral sclerosis (ALS)-like phenotype has also been reported in some patients with HSPB1 variants.[51,81]

Expanded phenotype

Recently, variants within the highly conserved α-crystallin domain of HSBP1 have been linked to a mixed phenotype characterized by motor neuropathy and distal vacuolar myopathy. In the first reported family, a heterozygous (D129E) variant was found to segregate with late-onset lower limbs weakness without sensory disturbances, with EMG and muscle biopsy revealing a combination of neurogenic and myopathic changes.[82] Another patient exhibiting a similar phenotype but with onset in the second decade of life was also documented, harbouring the homozygous R140G variant within HSPB1.[83]

Pathophysiology and genotype-phenotype correlations

HSPB1 variants impact various protein functions, including thermal stability, structure and interactions with partner proteins. Most HSPB1 variants result in a motor neuropathy phenotype, contrasting with CRYAB variants, which typically cause myopathy.[84] This suggests HSPB1 variants primarily disrupt cytoskeleton integrity and axonal transport.[80] Elevated CRYAB expression in heat-shocked fibroblasts from affected patients suggests that the harmful effects of the myopathic variant may involve interactions with this binding partner.[82] The recent identification of a myopathic phenotype linked to HSPB1 variants is notable, particularly as these affect the α-crystallin domain at a site analogous to CRYAB R120 residue, which is associated with myofibrillar myopathy.[84]

SPTAN1

Gene location and function

The *SPTAN1* gene encodes αII-spectrin, a widely expressed membrane scaffolding protein belonging to the spectrin family.[85] By interacting with actin, spectrins help organize the submembrane cytoskeletal structure in various cell types, contributing to their mechanical properties and elasticity, and playing a role in signalling pathways.[86] Among the six non-erythrocytic spectrin genes, four are linked to neurological disorders, with SPTAN1 associated with the broadest phenotypic spectrum, involving both central and peripheral nervous systems.[87]

Classical phenotype

Heterozygous SPTAN1 variants were initially identified in association with isolated epilepsy, epileptic encephalopathy, and complex neurodevelopmental disorders.[88,89] In 2019, Beijer *et al.*[90] described 12 patients from three families with isolated, juvenile-onset (before the second to third decade), slowly progressive axonal HMN, all carrying heterozygous nonsense variants in SPTAN1. Affected individuals exhibited marked intra- and interfamilial variability, minimal to no upper limb involvement, and nerve conduction studies revealed a purely motor or motor-predominant axonopathy. A subsequent report replicated this association in a Chinese girl presenting with HMN and mild upper motor neuron signs.[91] More recently, monoallelic SPTAN1 variants have also been identified in families with either pure or complex FSP or ataxia.[92]

Expanded phenotype

In 2024, De Winter *et al.*[87] described 20 patients with heterozygous loss-of-function SPTAN1 variants showing a phenotype resembling previously reported HMN cases. However, deep phenotyping led to a reclassification as a mixed neurogenic and myopathic distal disorder. Findings included mildly elevated CPK levels (1.5–2-fold), severe involvement or absence of the extensor hallucis longus on muscle imaging, EMG with predominantly myopathic features and muscle biopsies showing primarily myopathic changes such as internalized nuclei and fibre splitting, alongside clear neurogenic alterations.[87]

Pathophysiology and genotype-phenotype correlations

Missense and in-frame variants in the C-terminal domain (CTD) disrupt heterodimerization with β-spectrins, leading to dominant-negative aggregation of αII-spectrin and consequent disruption of neuronal structure and function, as seen in complex neurodevelopmental syndromes.[93,94] In contrast, non-truncating variants outside the CTD associated with FSP and ataxia likely impair α–β spectrin dimerization without inducing toxic aggregation.[92] Finally, most patients with HMN or distal myopathy carry truncating or frameshift variants predicted to undergo nonsense-mediated mRNA decay,[87,90] suggesting haploinsufficiency as the underlying mechanism. A possible bottleneck effect in αII-spectrin availability during PNS development may explain the slow progression observed in later stages of the disease.[87]

SORD

Gene location and function

SORD encodes sorbitol dehydrogenase, the second enzyme in the polyol pathway, a two-step process that converts glucose to fructose via the intermediate sorbitol.[95] The presence of the paralogue SORD2P, a highly homologous but untranslated pseudogene located nearby on chromosome 15, has historically hindered the detection of biallelic SORD variants by next-generation sequencing. Only recently, with improved methods accounting for this pseudogene, was SORD recognized as the most common and potentially treatable cause of autosomal recessive hereditary neuropathy (AR-CMT2).[95]

Classical phenotype

Biallelic variants in SORD cause a mild-to-moderate, motor-predominant (or purely motor) peripheral axonopathy, typically with onset in the second decade.[95,96] Clinically, plantar flexion weakness is usually comparable to dorsiflexion, a finding that is uncommon in other forms of CMT. Males tend to show more pronounced involvement of plantar flexion and a greater degree of progression over time compared to female patients.[95,96]

Expanded phenotype

Massucco *et al.*[97] recently reported a 16-year-old boy presenting with distal lower limb weakness in the absence of sensory abnormalities and a mild elevation of creatine kinase (1.5-fold). Muscle

biopsy of the gastrocnemius revealed scattered angulated fibres, myofibre degeneration and cytoplasmic inclusion bodies positive for desmin and αB-crystallin, findings consistent with a protein surplus myopathy. WES identified biallelic pathogenic variants in SORD.[97]

Pathophysiology and genotype-phenotype correlations

Biallelic loss of function in SORD results in elevated serum sorbitol levels, a well-established biomarker of the disease.[95,96] Disruption of the polyol pathway and subsequent sorbitol accumulation have been implicated in diabetic neuropathy, nephropathy, and retinopathy.[98] In a *Drosophila* model of SORD-related neuropathy, sorbitol accumulation led to synaptic degeneration and progressive motor impairment, both of which were ameliorated by treatment with aldose reductase inhibitors.[95] Additionally, a rat model demonstrated ballooned myelin sheaths, indicative of hyperosmolar stress caused by excess sorbitol.[99]The patient described by Massucco *et al.*[97] carried the two most common pathogenic SORD alleles in compound heterozygosity, suggesting that if muscle involvement is part of the disease spectrum, it is unlikely to be genotype-specific.

DNAJB2

Gene location and function

DNAJ (or Hsp40) co-chaperones stimulate the ATPase activity of Hsp70 proteins via their J domain, facilitating the degradation of client proteins through the ubiquitin-proteasome system (UPS).[100] The *DNAJB2* gene encodes two isoforms with distinct CTDs: the shorter DNAJB2a, which localizes to both the nucleus and cytoplasm, and the longer DNAJB2b, which is anchored to the endoplasmic reticulum (ER) via a geranylgeranyl group. DNAJB2b is the predominant isoform in most tissues, with the notable exception of muscle, where both isoforms are expressed at comparable levels.[101]

Classical phenotype

Biallelic variants in DNAJB2 have been associated with AR-CMT2 or recessive HMN type 5.[102-104] In some cases, additional features such as hearing loss[105] and parkinsonism[105-107] have been reported. Clinical onset typically occurs in the second or third decade, with distal lower-limb weakness.[105-107] Nerve conduction studies usually reveal a severe, length-dependent motor or sensorimotor axonal neuropathy. Most patients lose ambulation by approximately 50 years of age.[105]

Expanded phenotype

Liu *et al.*[108] reported a 29-year-old man with slowly progressive distal lower limb weakness and elevated CPK (428 U/l), in the absence of sensory abnormalities. A biopsy of the tibialis anterior revealed mixed neurogenic and myopathic changes, including rimmed vacuoles and abnormal DNAJB2 immunostaining, with positive signals along the vacuoles and within the sarcoplasm of degenerating fibres. More recently, Sarparanta *et al.*[109] described a dominant neuromyopathy family, in which the proband presented with a late-onset sensorimotor axonal neuropathy and distal myopathy with rimmed vacuoles.

Pathophysiology and genotype-phenotype correlations

Loss of function is thought to be the primary mechanism for DNAJB2-related neuropathy. Biallelic null variants resulted in a marked reduction in mRNA levels and absence of DNAJB2 protein in a patient's skin biopsy, along with phosphorylated transactive response DNA binding protein 43 kDa (TDP-43) and synuclein accumulation.[105] DNAJB2 is known to reduce TDP-43,[110] parkin,[111] and SOD1[104] aggregation, so it is likely that a loss of enzymatic activity could facilitate toxic protein aggregation in neurons. In the dominant family described by Sarparanta *et al.*,[109] the heterozygous variant was predicted to cause a C-terminal extension exclusively in the muscle-expressed DNAJB2a isoform, introducing a transmembrane domain that led to mislocalization of the protein to the ER and accelerated turnover of the wild-type allele. These findings support a combined toxic gain of function and dominant-negative mechanism in this genotype.

TFG

Gene location and function

The tropomyosin-receptor kinase fused gene (*TFG*) encodes a cytoplasmic protein initially identified as a fusion partner leading to the formation of oncogenic products in cancers.[112,113] It is ubiquitously expressed and alternatively spliced into four transcripts, with the full-length form predominantly expressed in the nervous system.[114,115] TFG functions as an octamer, regulating Sec16 in the formation of coat protein complex II vesicles in the ER-Golgi pathway.[112] It also inhibits the UPS and maintains ER homeostasis.[114]

Classical phenotype

A specific TFG variant is linked to hereditary motor and sensory neuropathy with proximal dominant involvement (HMSN-P), a slowly progressive autosomal dominant disorder with onset typically in the forties, characterized by proximal muscle weakness, atrophy and distal sensory disturbances.[115,116] Moderately high CPK levels, cramps, fasciculations and bulbar symptoms are also seen.[114] Neuropathology shows atrophy in ventral and dorsal roots, neuronal loss in the ventral horns, dorsal root ganglia, and hypoglossal and facial nuclei.[117] Immunohistochemistry reveals ubiquitin- and optineurin-positive neuronal inclusions, but not TDP-43,[117] indicating that HMSN-P is fundamentally a motor neuronopathy accompanied by a sensory neuropathy. Tsai *et al.*[118] reported a novel TFG variant in a Taiwanese family with a more typical adult-onset CMT2 phenotype, expanding the gene's phenotypic spectrum. Homozygous variants in TFG have also been implicated in an early-onset FSP, optic atrophy, and peripheral neuropathy with reduced conduction velocities.[119]

Expanded phenotype

The proximal weakness characteristic of HMSN-P and the elevated CPK levels can lead clinicians to suspect a myopathy.[114] Madigan *et al.*[120] described a muscle histology consistent with vacuolar myopathy within the context of a typical HMSN-P clinical presentation, suggesting that myopathy might indeed be part of the HMSN-P spectrum rather than a misdiagnosis.

Pathophysiology and genotype-phenotype correlations

The mechanisms by which TFG variants cause this phenotypic spectrum remain unclear. The P285L variant, associated with HMSN-P, likely enhances UPS inhibition, inducing ER stress through a toxic gain of function.[113,114] In contrast, the G269V variant, linked to CMT2, leads to the formation of aggregates that sequester the wild-type protein, causing disease via a

dominant-negative mechanism.[114,118] Lastly, FSP-causing homozygous R106C variants disrupt TFG oligomerization, leading to alterations in ER architecture.[114,119]

Multisystem proteinopathies

Originally characterized in the context of VCP variants, multisystem proteinopathies (MSPs) represent a growing category of genetic disorders impacting autophagy and related pathways. Non-VCP cases frequently exhibit distal myopathy, with patients often becoming wheelchair-dependent within one or two decades of symptom onset.[121] Muscle histology in these cases largely overlaps with VCP-MSP, and nerve conduction studies may reveal axonal motor or sensorimotor neuropathy. EMG frequently shows a mixed myopathic and neurogenic pattern that suggests the coexistence of MND or motor axonopathy.[121] Given the considerable clinical overlap among non-VCP MSPs, their individual phenotypic features will not be reviewed in detail. Genes like *PFN1* (MSP7) and *OPTN* are also associated with MSP-like phenotypes, though muscular involvement has not been described in these forms and will not be reviewed here.[121,122] Although not formally belonging to the MSPs, LRP12 and NOTCH2NLC will be discussed at the end of this section due to their involvement in a range of clinical phenotypes overlapping with MSPs.

VCP

Gene location and function

The *VCP* gene encodes valosin-containing protein, a ubiquitously and abundantly expressed member of the AAA+ (ATPases associated with diverse cellular activities) family.[123] This chaperone-like protein is implicated in a wide array of functions, including autophagy, protein quality control and mitophagy,[124] among others.[123]

Neuromuscular phenotype

Pathogenic VCP variants cause a complex disorder initially termed hereditary inclusion body myopathy with Paget's disease of bone and frontotemporal dementia (IBMPFD).[125] Subsequent evidence highlighted a wide array of clinical manifestations, including distal myopathy, CMT2Y, familial MND, FSP, parkinsonism and even Huntington's disease.[126,127] This led to the adoption of the broader term 'multisystem proteinopathy 1' (MSP1), as affected tissues exhibit common pathological hallmarks that suggest a shared pathomechanism, related to alterations in autophagy.[123] Muscle histology is characterized by the presence of rimmed vacuoles and tubulofilamentous inclusions positive for ubiquitin, VCP and TDP-43.[128] Most patients seek first neurological evaluation for myopathy, the presenting symptom usually being muscle weakness (predominantly in the lower limbs), sometimes associated with axial involvement. Fifteen per cent of patients also have a clinical sensory-motor axonal polyneuropathy, although a portion of these exhibit intermediate conduction velocities.[127] EMG findings can vary, displaying myopathic, neurogenic, or mixed-type patterns, as well as signs consistent with MND, depending on the most affected system.[127]

Pathophysiology and genotype-phenotype correlations

Most described variants are missense, located primarily in the cofactor-binding NTD, the linker 1 domain and the D1/ATPase domain.[129] A toxic gain-of-function mechanism has been proposed, as the majority of studied variants exhibit increased ATPase activity *in vitro*,[129] and some preclinical studies with VCP inhibitors demonstrated phenotype amelioration.[130,131] However, since some variants do not show increased ATPase activity, a dominant-negative mechanism has also been postulated[123]: pathogenic heterozygous variants in VCP likely affect the active hexameric ring structure, leading to altered affinity for its cofactors, preventing VCP migration to specific organelles (e.g. mitochondria)[132] and/or affecting stress granule dynamics.[133] Although no strict genotype-phenotype correlation has been observed, recent evidence indicates that the R155H variant might be associated with earlier onset, higher rates of axial and scapular involvement, and cognitive impairment,[127] while the R159C variant showed lower rates of Paget disease and a later onset of myopathy.[134] Isolated CMT is rare and has been described in only a few variants.[135-137] The E185K variant has been shown to impair autophagic activity *in vitro* while demonstrating normal ATPase enzymatic activity, suggesting a milder phenotypic expression compatible with isolated polyneuropathy.[135]

HNRNPA2B1 and HNRNPA1 (MSP2 and MSP3)

Variants in HNRNPA2B1 and HNRNPA1 are linked to MSP2 and MSP3, respectively.[138] These genes encode RNA binding proteins (RBPs) involved in RNA metabolism and stress granule formation, in conjunction with TDP-43.[139] Pathogenic variants promote the incorporation of these RBPs into stress granules, leading to cytoplasmic inclusions and cellular degeneration.[138]

SQSTM1 (MSP4)

SQSTM1 variants cause MSP4.[140] The p62/SQSTM1 protein interacts with ubiquitinated proteins and LC3, mediating autophagy. Pathogenic variants, typically in the ubiquitin-associated domain, disrupt this process. Some variants also enhance osteoclast formation by increasing NF-κB activation.[141]

MATR3 (MSP5)

MATR3 variants lead to MSP5.[142,143] Matrin 3, an RNA- and DNA-binding protein, is part of the nuclear matrix. Pathogenic variants result in reduced nucleic acid binding, along with cytoplasmic mislocalization and aggregation.[143]

ANXA11 (MSP6)

ANXA11 variants, recently described in three Brazilian families with ALS and myopathy, cause MSP6.[144] Annexin A11 is a calcium-dependent phospholipid-binding protein, and variants, mostly in the NTD1, impair proper folding. Inclusions positive for annexin A11, p62 and TDP-43 have been observed in muscle tissue.[144]

LRP12

Gene location and function

The *LRP12* gene encodes a low-density lipoprotein (LDL) receptor-related transmembrane protein involved in signal transduction, endocytosis and cell migration. Its cytoplasmic domain directly binds to the intracellular tail of integrin α4, preventing its heterodimerization with the β subunit and inhibiting integrin signalling.[145]

Neuromuscular phenotype

In 2019, Ishiura *et al.*[146] identified CGG repeat expansions in the 5′-untranslated region (UTR) of LRP12 as the cause of oculopharyngodistal myopathy (OPDM), a condition characterized by ptosis, ophthalmoplegia, bulbar involvement and distal muscle weakness, with muscle biopsy typically showing rimmed vacuoles and p62+ inclusions. In 2023, Kume *et al.*[147] reported the same expansion as a rare cause of familial MND (ALS or progressive muscular atrophy). More recently, Hobara *et al.*[148] identified this variant in 44 of 1555 undiagnosed CMT or HMN, ranking it as the fourth most common cause of inherited neuropathy in their cohort, after MFN2, GJB1 and MPZ. These cases were mostly diagnosed as CMT or HMN, with symptom onset around age 40. Neurophysiology showed a distal, axonal, predominantly motor neuropathy. Some degree of overlap with OPDM was seen: CPK was elevated in 94.1% of patients, and a minority exhibited facial (11.1%), bulbar (14.7%) symptoms or ptosis (2.7%). Sural nerve biopsy showed no significant axonal loss, while muscle biopsy revealed predominantly neurogenic changes, although some patients with more than 80 CGG repeats also showed rimmed vacuoles and p62+ inclusions.[148]

Pathophysiology and genotype-phenotype correlations

As in other repeat expansion disorders, the leading hypothesis is a toxic RNA gain-of-function mechanism. Kume *et al.*[147] demonstrated that induced pluripotent stem cell (iPSC)-derived motor neurons from ALS patients with fewer than 100 repeats exhibited nuclear RNA foci and cytoplasmic accumulation of phosphorylated TDP-43, consistent with classic ALS pathology. In contrast, patients with over 100 repeats developed OPDM, and their muscle tissue showed LRP12-RNA-dependent nuclear sequestration of MBNL1, an RBP essential for muscle function.[147] MBNL1 dysfunction has also been implicated in myotonic dystrophy type 1, another distal myopathy caused by toxic repeat expansions.[149,150] Patients with CMT or HMN generally had fewer than 100 repeats, though those with higher repeat counts occasionally showed features overlapping with OPDM,[148] as already discussed.

NOTCH2NLC

Gene location and function

NOTCH2NLC is one of three functional NOTCH2NL paralogues that originated from a partial duplication of NOTCH2 before the last common ancestor of humans, followed by a human-specific 'revival' through ectopic gene conversion involving NOTCH2.[151] The *NOTCH2NL* genes enhance Notch signalling during corticogenesis, promote radial glial cell expansion and delay neuronal differentiation. This function is thought to have played a major role in the evolutionary increase in human cortical size.[151]

Classical phenotype

Pathogenic heterozygous CGG expansions in the 5′-UTR of *NOTCH2NLC* are linked to neuronal intranuclear inclusion disease (NIID), a neurodegenerative disorder that is particularly prevalent in East Asian populations.[152,153] NIID is characterized by significant clinical heterogeneity, with variable combinations of cognitive impairment, autonomic dysfunction, movement disorders and tremor.[152,154] Patients may also experience paroxysmal symptoms, such as episodes of altered consciousness and encephalopathy.[152,154] Diffusion-weighted MRI sequences often reveal typical corticomedullary hyperintensities, known as the 'zigzag edging sign',[155] helping in diagnosis.

Neuromuscular phenotype

While a mild or subclinical axonal sensory-predominant peripheral neuropathy is commonly observed as an accompanying feature in classic NIID phenotypes,[154] NOTCH2NLC has also been implicated in a range of primary neuromuscular conditions. In a study by Liao *et al.*,[156] NOTCH2NLC expansions were identified in 7 of 66 Taiwanese patients with undiagnosed CMT2 who did not exhibit additional NIID-related features, although it is notable that two of these seven patients reported a family history of NIID with cognitive impairment.[156] Pathogenic GGC expansions have also been observed in patients with OPDM type 3[157,158]; a significant subset of these patients also displayed NIID-related features, such as neuropathy and characteristic MRI findings.[157,158] Additionally, Yu *et al.*[159] identified pathological GGC expansions in three unrelated families with distal motor neuropathy and rimmed vacuolar myopathy, in the absence of bulbar or ocular involvement.

Pathophysiology and genotype-phenotype correlations

Several studies have demonstrated that CGG expansion in NOTHC2NLC leads to the production of a neurotoxic polyglycine (polyG) protein that forms p62(SQSTM1)-positive inclusions within the nuclei of neurons, myofibres, Schwann cells, and even in adipocytes, fibroblasts and sweat gland cells[160,161] (highlighting the diagnostic utility of skin biopsies).[162] Moreover, expression of the isolated polyG sequence induced cell death and neurodegeneration in both cell culture and animal models.[160,161]

The phenotypes associated with NOTCH2NLC-CGG repeat expansion likely form a continuum, as indicated by the shared pathological feature of intranuclear inclusions and the variable clinical manifestations observed in affected families. Similar to LRP12, certain correlations between repeat size and phenotype have emerged. Liao *et al.*[156] reported smaller repeat sizes in patients with mild, isolated neuropathy compared to those with more typical phenotypes. At the other end of the spectrum, patients with OPDM3 and weakness-dominant phenotypes often exhibit significantly larger repeat sizes.[157-159] Beyond repeat size, methylation levels of the *NOTCH2NLC* gene appear elevated in asymptomatic carriers,[158] suggesting that epigenetic factors may influence phenotypic expression. Additionally, patients with muscle involvement more frequently show non-GGC repeats in their NOTCH2NLC expansions.[163,164]

Mitochondrial diseases

Mitochondria are essential for ATP synthesis and numerous metabolic pathways. Disruptions in mitochondrial function can severely impact tissues with high energy demands like nerves and muscles. Mitochondrial disorders involve both nuclear and mitochondrial DNA (mtDNA), with mtDNA encoding only a subset of mitochondrial proteins.[165] The effects of mtDNA variants depend on their heteroplasmic distribution across tissues.[165] Red flags for mitochondrial disorders include matrilineal inheritance, white matter abnormalities, ataxia, epilepsy, cognitive impairment, hearing or vision loss, ophthalmoplegia, ptosis, cardiomyopathy, short stature and exercise intolerance. Mitochondrial genes associated with both neuropathy and myopathy are listed in Table 3. For an extensive

description of mitochondrial NMDs we refer readers to relevant reviews.[166-169]

Functional characteristics of genes associated with neuromyopathies

To better understand the functional characteristics of genes implicated in neuromyopathies and to identify shared molecular pathways underlying the dual involvement of nerve and muscle, we performed GSEA on the list of identified genes, as detailed in the 'Methods' section (Fig. 3A and B). Notably, the most enriched terms are related to mitochondrial function and the UPR, suggesting a convergence on pathways involved in cellular stress and energy homeostasis.

To explore how these biological processes interact and potentially co-regulate disease mechanisms, we constructed an enrichment network using Metascape (Fig. 3C). This network reveals a functionally organized landscape where interconnected nodes point to key hubs in proteostasis and organelle maintenance and

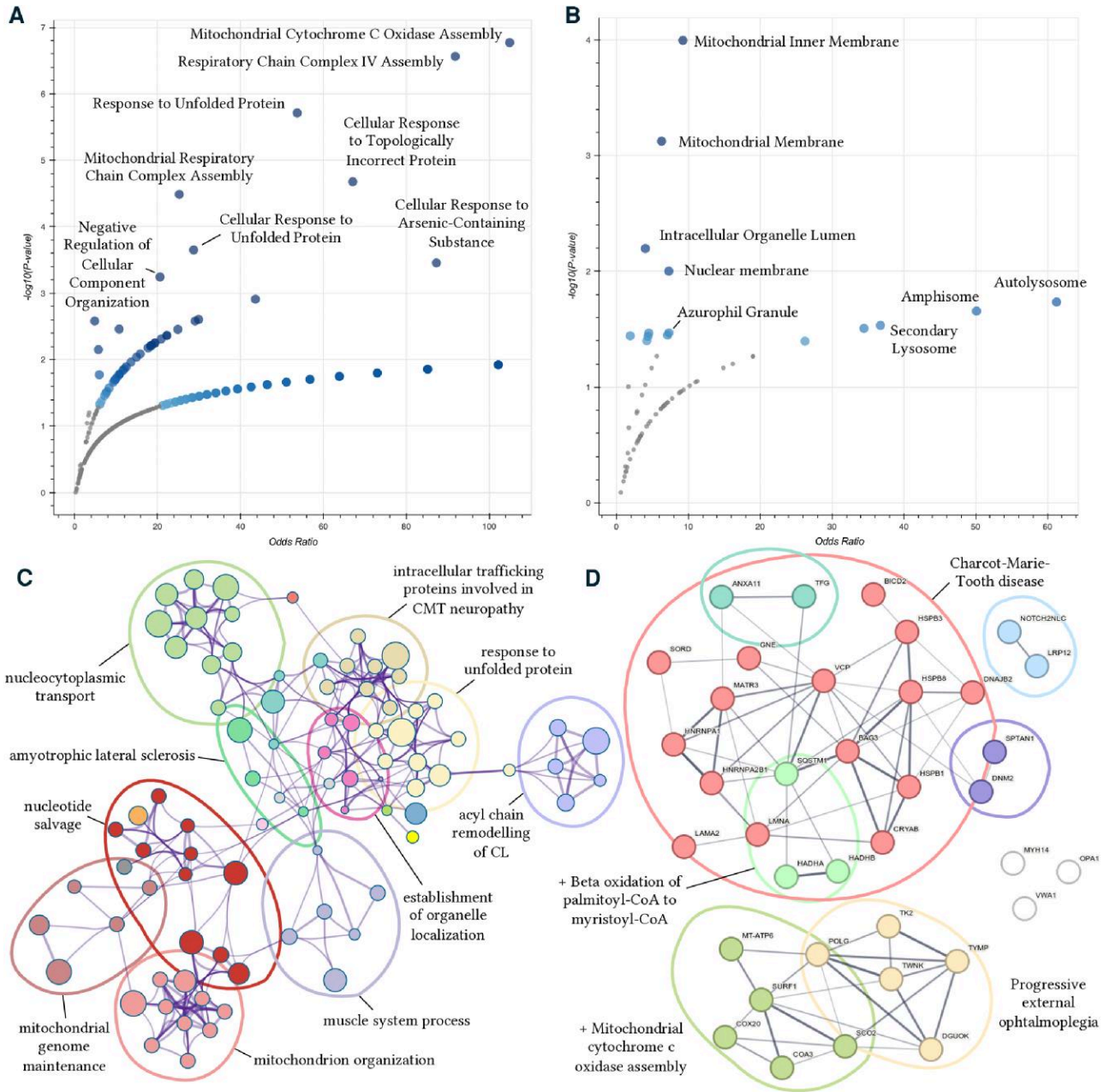

Figure 3 Functional characterization of genes associated with both neuropathy and myopathy. (**A** and **B**) Volcano plots of significantly enriched gene ontology terms related to biological process and cellular component, respectively. Each point represents a single term, plotted by the corresponding odds ratio (*x*-position) and $-\log_{10}$(*P*-value) (*y*-position) from the enrichment results of the input query gene set. The darker-coloured the point, the more significantly enriched the input gene set is for the term. (**C**) shows the network of enriched terms coloured by cluster ID, where node size is proportional to the enrichment score (only major cluster IDs are labelled). (**D**) shows the clustered protein network, with edges indicating both functional and physical interactions between proteins and line thickness indicating the strength of the association (cluster labels, where present, are automatically assigned by STRING). CMT = Charcot-Marie-Tooth.

localization. Furthermore, a clustered protein–protein interaction (PPI) network generated using STRING (Fig. 3D; PPI enrichment $P < 10^{-15}$) provides complementary evidence for functional coherence among the implicated genes. As anticipated, both networks display a densely interconnected core centred around UPR and autophagy, two pathways known to be critical for maintaining neuronal and muscular integrity under stress.

Taken together, these findings underscore a shared vulnerability of muscle and nerve tissues to dysregulated proteostasis and mitochondrial dysfunction, offering a unified framework to interpret the common molecular pathways that contribute to both neuropathy and myopathy.

Discussion

We are at a turning point in the field of neuromuscular disease, as orphan disease-causing genes are close to becoming targetable due to the advent of emerging therapeutic platforms.[170] If most next-generation sequencing panels already include genes with potential for mixed phenotypes in both HMN and myopathies, the shortcomings come at the time of result interpretation, especially in the case of variants of unknown significance.[171] Furthermore, in the context of an ever-growing literature, the likelihood that some reported associations may be spurious remains a concern. Research has already revealed significant overlaps in the genetic basis of various neuromuscular disorders, such as neuropathy, MND and FSP,[172,173] but myopathies have remained relatively distinct in this regard. This review aims to identify, describe and categorize genes that, when mutated, manifest with neuropathic, myopathic or mixed phenotypes.

We focused on clinical, neurophysiological, and pathological perspectives, with particular emphasis on gene-specific pathomechanisms that support these associations.

Some of the genes we identified, such as *VWA1* and *BICD2*, can present a relatively 'pure' neuromyopathic picture, while others, like *HSPB3* and *DNM2*, may cause either a neuropathic or myopathic phenotype. Considering additional clinical features may help refine the list of candidate genes for specific phenotypes (Fig. 2). For example, hearing loss is often associated with MYH14 and DNAJB2, while CNS involvement can be seen with various genes, particularly those related to mitochondrial function, multisystem proteinopathies and LAMA2. Pathogenic variants in LMNA and DNM2 frequently result in contractures, with DNM2 often linked to facial weakness. Variants in BAG3 and CRYAB frequently involve the diaphragm and/or heart.

Finally, we highlighted a common vulnerability to dysregulated proteostasis and mitochondrial function in the neuromuscular axis, which relies on highly specialized, postmitotic cells for transmitting CNS signals to muscle. This process—from synaptic transmission to electromechanical coupling—requires a stable protein architecture, including cytoskeletal elements (e.g. microtubules, neurofilaments, actin and myosin filaments) and synaptic structures. Since proteostasis is crucial for postmitotic cells such as neurons and muscle fibres,[174,175] it is not surprising that many genes implicated in both neuropathies and myopathies are closely associated with UPR and autophagy. Gene variants leading to the production of aberrant or misfolded proteins that accumulate in the ER would trigger ER stress. The UPR is activated to restore homeostasis by halting protein translation, enhancing folding capacity and promoting the degradation of misfolded proteins. However, chronic or overwhelming ER stress—common in these disorders—can lead to maladaptive UPR signalling, contributing to cell dysfunction and death.[176] Notably, this is already a key target for potential therapeutic strategies in both neuropathies/neuronopathies and myopathies.[177-179] Autophagy is another essential biological process for postmitotic cells, playing a critical role in protein turnover, quality control, and maintaining cellular homeostasis and metabolism.[180,181] Both nerves and muscles have high energy demands, primarily relying on mitochondrial oxidative metabolism. Recent research has revealed additional roles for mitochondria beyond ATP production, highlighting key links between these functions, the UPR and autophagy in maintaining cellular health.[182]

Our review may serve as a practical resource for clinicians faced with ambiguous clinical presentations, both in selecting appropriate genetic tests and in interpreting uncertain results. For researchers, it underscores that a single gene can produce distinct phenotypes through different pathogenic mechanisms. For example, mutations in LAMA2 illustrate how the primary alteration (loss of receptor binding) has tissue-specific consequences because different receptors and signalling pathways are involved. In muscle, the absence of laminin-211 leaves dystroglycan and integrin $\alpha7\beta1$ unbound, thereby promoting apoptosis. In nerves, the disrupted interaction with integrin $\alpha6\beta1$ primarily impairs axon defasciculation and, together with dystroglycan, compromises myelination.[64,66] A contrasting scenario is observed in DNM2, where myopathy- and neuropathy-associated mutations appear to exert opposite effects on protein activity: myopathy results from gain-of-function mutations, whereas neuropathy stems from loss-of-function. Remarkably, crossing mouse models of the two conditions produces double-mutant offspring in which the phenotypes partially counterbalance one.[183] Finally, some pathogenic mechanisms act uniformly across cell types. In these cases, pathogenic mechanisms act more uniformly across tissues, as with NOTCH2NLC repeat expansions that generate toxic intranuclear inclusions in both myofibres and Schwann cells.[160,161] Recognizing these diverse and sometimes opposing mechanisms is crucial for designing functional studies that better reflect the complexity of disease.

In conclusion, the genetic and phenotypic complexity of NMDs continues to evolve as advancements in molecular diagnostics and emerging therapies transform this intricate landscape. The convergence of neuropathic and myopathic features, while presenting diagnostic challenges, also opens new windows for understanding the molecular keystones shared across otherwise traditionally antipodal conditions. As we move toward increasingly personalized approaches, the intersection of clinical observation, genetic insight, neurophysiology and pathophysiological understanding will be crucial in refining such diagnoses. Bridging these complexities is not merely a diagnostic necessity but an opportunity to reshape the therapeutic potential in neuromuscular medicine, ultimately driving us closer to effective, targeted interventions for these patients.

Acknowledgements

The authors belong to the EURO-NMD network. The thumbnail image for the online table of contents was generated using Midjourney by artist Stefano Gelibter and is used with permission.

Funding

This work was supported in part by ACMT-Rete Italia, AFM Telethon France (grant no. 24229), and Telethon/UILDM Italy (grant no. GUP21006).

Competing interests

The authors report no competing interests.

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