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Hereditary Myopathies

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Abstract

Hereditary myopathies are inherited disorders primarily affecting the skeletal muscle tissue. These are caused by mutations in different genes-encoding proteins that play important roles in muscle structure and function. Skeletal muscle weakness and hypotonia are typical clinical manifestations in most of hereditary myopathies. Histological features such as fiber type disproportion, myofibrillar disorganization, and structural abnormalities are usually observed in muscle biopsies of non-dystrophic myopathies, while fibrosis, fiber regeneration, wasting, and atrophy are characteristic of dystrophic myopathies. However, similar histopathological features may overlap in different hereditary myopathies. This is how mutations in a same gene can lead to different forms of hereditary myopathies and a same myopathic phenotype can derive from defects in different related genes making difficult a specific diagnosis. In this regard, understanding all aspects of hereditary myopathies can facilitate a better diagnosis and treatment. In this chapter, we offer a review of some of the most prevalent hereditary myopathies, highlighting clinical, histological, and molecular aspects of these muscle disorders.

Keywords: hereditary myopathy, muscle disease, congenital myopathy, muscular dystrophy

1. Introduction

Hereditary myopathies are a heterogeneous group of inherited diseases primarily affecting the skeletal muscle tissue. These are caused by mutations in genes encoding proteins critical for muscle structure and function, with X-linked, autosomal-recessive or -dominant inheritance pattern. Hereditary myopathies include several forms of dystrophic and non-dystrophic disorders with a wide spectrum of genetic, biochemical, histological, and clinical features. A common characteristic

is the presence of hypotonia and progressive or non-progressive muscle weakness. The onset of hereditary myopathies is commonly at birth, although they may become evident later in childhood or adulthood. Clinical severity is variable being the early-onset forms usually more severe [1]. Diagnosis of hereditary muscle diseases involve physical and neurological evaluation, electromyography and nerve conduction studies (EMG and NCS), magnetic resonance imaging, blood tests including creatine kinase levels (CK), which typically rises in muscle damage and histopathological makers in muscle biopsies [1]. Advances in molecular genetics have allowed identifying an increasing number of genes linked to different forms of hereditary myopathies in the last decades. With this, it has become evident that mutations in a same gene can lead to more than one pathological and clinical phenotype as well as the same pathological feature can result from mutations in different genes. Given this overlap in genetic, clinical, and histological features, the use of different approaches is critical for a proper diagnosis.

This chapter aims to summarize clinical, histological, and molecular aspects of some inherited forms of muscle disease, providing a general overview of the most prevalent hereditary myopathies, including congenital, mitochondrial, and metabolic myopathies, myotonia, and muscular dystrophies. The information discussed in this chapter is resumed in **Table 1**.

Hereditary myopathy	Genes/proteins	Mechanism affected	Histopathological features	Clinical features
Non-dystrophic				
Nemalin myopathy	<i>NEB</i> /nebulin <i>ACTA</i> /skeletal muscle alpha-actin <i>TPM3</i> /alpha-tropomyosin-3 <i>TPM2</i> /beta-tropomyosin-2 <i>TNNT1</i> /troponin T1 <i>CFL2</i> /cofilin-2 <i>KBTBD13</i> /Kelch-repeat-and-BTB-domain-containing-13 <i>KLHL40</i> /Kelch-like-family-member-40; KLHL4 <i>KLHL41</i> /Kelch-like-family-member 41 <i>LMOD3</i> /leiomodin-3 <i>MYPN</i> /myopalladin	Structural disorganization of sarcomere units	Rod inclusions	Hypotonia, proximal weakness, respiratory insufficiency in the most severe cases
Core myopathy (Central and multi-minicore)	<i>RYR1</i> /ryanodine receptor <i>SEPN1</i> /selenoprotein N	EC-uncoupling Defects in Ca ²⁺ and redox homeostasis	Cores and/or multiminicores	Hypotonia, proximal weakness, delayed motor milestones and orthopedic complications. Malignant hyperthermia susceptibility
Centronuclear myopathy/ myotubular myopathy (XLMTM)	<i>MTM1</i> /myotubularin <i>DNM2</i> /dynamin-2 <i>BIN1</i> /amphiphysin-2 <i>RYR1</i> /ryanodine receptor channel	Defects in membrane remodeling and intracellular trafficking	Nuclei centralization Necklace fibers	Proximal and distal muscle weakness, delayed acquisition of motor milestones, difficulty to walk

Hereditary myopathy	Genes/proteins	Mechanism affected	Histopathological features	Clinical features
	<i>TTN</i> /titin <i>SPEG</i> /striated muscle preferentially expressed protein kinase			and climb stairs. Facial muscles involvement typically presenting ptosis and ophthalmoplegia. Persistent hypotonia and respiratory muscles failure in the most severe cases of XLMTM.
Congenital fiber-type disproportion myopathy	<i>TPM3</i> /alpha-tropomyosin-3 <i>ACTA</i> /skeletal muscle alpha-actin <i>RYR1</i> /ryanodine receptor channel	Defects in actomyosin interaction Defects in EC-coupling	Prevalence and hypotrofia of type 1 fibers (5-40% smaller than type 2)	Mild to severe weakness mainly in shoulders, upper arms, hips, and thighs musculature and in face muscles; orthopedic complications and joint contractures . Respiratory muscle hypotonia is observed in some cases.
Myosin storage myopathy	<i>MYH7</i> /slow-skeletal/ β -cardiac myosin heavy chain	Defects in myosin folding Impaired sarcomere thin filament assembly	Hyalin bodies	Hypotonia, proximal muscle weakness, delayed acquisition of motor milestones, respiratory insufficiency secondary and cardiac involvement may occur in some cases.
Mitochondrial myopathy	Cytochrome b/cytochrome c oxidase Q10 Coenzyme <i>TK2</i> /thymidine kinase <i>POLG1</i> /polymerase gamma 1	Dysfunction of the respiratory chain and energy production	Sub-sarcolemmal and intermyofibrillar accumulation of mitochondria; "ragged blue/red fibers"	Typically are multisystem disorders with predominant involvement of muscles and nerves. Myalgia, fatigue, exercise intolerance, proximal and distal muscle weakness and slowly progressive paresis of the extra ocular muscles. Marked hypotonia, respiratory muscle weakness and

Hereditary myopathy	Genes/proteins	Mechanism affected	Histopathological features	Clinical features
				feeding difficulty in most severe cases.
Metabolic myopathy (glycogen storage disease)	<i>GAA</i> /lysosomal enzyme α -glucosidase <i>AGL</i> /glycogen-debranching enzyme <i>PYGM</i> /myophosphorylase	Defects in glycogen hydrolysis and energy production	Basophilic/PAS positive vacuoles cytosolic inclusions	Generalized muscle weakness and hypotonia, fatigue and exercise-induced myalgia, cardiac and respiratory failure in most severe cases
Metabolic myopathy (lipid storage disease)	<i>SLC22A5</i> /carnitine transporter <i>OCTN2</i> <i>ETF</i> /electron-transfer flavoprotein <i>ETFH</i> /ETF-dehydrogenase <i>PNPLA2</i> /adipose triglyceride lipase	Fatty acid dysmetabolism and defects in energy production	Increased number and size of lipid droplets and neutral-lipid containing vacuoles inside muscle fibers	Hypotonia, muscle weakness and cardiomyopathy systemic disorders are often observed including encephalopathy, hepatomegaly, hypoglycemia, and metabolic acidosis
Congenital myotonia	<i>CIC1</i> /skeletal muscle chloride channel	Reduced chloride conductance Enhanced sarcolemmal excitability	Predominance and hypotrophy of type 2 fibers, increased endomysial connective tissue and tubular aggregates are usually observed	Myotonia, myalgia, transient episodes of generalized weakness and muscular hypertrophy
Paramyotonia congenita	<i>SCN4A</i> /alpha-subunit of the skeletal muscle sodium channel	Abnormal persistent sarcolemmal sodium currents	-	Early-onset generalized weakness and "myotonic discharges" and extreme sensitivity to cold
Dystrophic				
Myotonic dystrophy (DM1/DM2)	<i>DMPK</i> /myotonin-protein-kinase (CTG repeat expansion) <i>ZNF9</i> /zinc finger 9 (CCTG repeat expansion)	Deregulation of RNA-binding proteins, toxic nuclear foci and impair gene expression	Central nuclei, type 1 fiber atrophy, regenerating fibers, fibrosis and adipose deposition. Atrophic type 2 fibers with pyknotic nuclear clumps are specifically observed in DM2	Muscle wasting, progressive weakness, myotonia, cataracts, and multi-organ involvement affecting heart, brain, and endocrine system
Duchenne and Becker muscular dystrophy	<i>DMD</i> /dystrophin	Defects in DGC , mechanical stress during muscle contraction, sarcolemmal damage and	Muscle fiber necrosis, regeneration, fibrosis and atrophy, nuclei internalization, Inflammatory	Early-onset dystrophy, delayed acquisition of motor milestones and rapid progression of muscle weakness

Hereditary myopathy	Genes/proteins	Mechanism affected	Histopathological features	Clinical features
		abnormal Ca ²⁺ homeostasis	response and elevated serum levels of CK are typically observed	that usually leads to wheelchair needing.
LGMD1	<i>MYOT</i> /myotilin <i>LMNA</i> /lamin A/C <i>CAV3</i> /caveolin3 <i>DNAJB6</i> <i>DES</i> /desmin <i>TNPO3</i> /transportin3 <i>HNRPDL</i>	Defects in sarcomere integrity, nuclear maintenance and gene regulation among others	Muscle fiber necrosis, regeneration, fibrosis and atrophy, nuclei internalization, Inflammatory response and elevated serum levels of CK are typically observed	Proximal and distal weakness, calf hypertrophy, cramps associated to exercise and respiratory and cardiac involvement in some cases
LGMD2	<i>CAPN3</i> /calpain3 <i>DYSF</i> /dysferlin alpha-sarcoglycan beta-sarcoglycan gamma-sarcoglycan delta-sarcoglycan <i>TCAP</i> /teletonin <i>TRIM32</i> <i>FKRP</i> /fukutin-related-protein <i>POMT1</i> /O-mannosyl-transferase 1 <i>FKTN</i> /fukutin <i>POMT2</i> /O-mannosyl-transferase 2 <i>POMGnT1</i> /O-linked-mannose beta-1,2-N-acetylglucosaminyltransferase 1 <i>DAG1</i> /dystroglycan gene <i>TTN</i> /titin <i>ANO5</i> /anoctamin5 <i>PLEC1</i> /plectin <i>DES</i> /desmin <i>TRAPPC11</i> /transport protein particle complex 11 gene <i>GMPPB</i> /GDP-mannose pyrophosphorylase B <i>ISPD</i> /isoprenoid synthase domain containing <i>GAA</i> /lysosomal enzyme acid α-glucosidase <i>LIMS2</i> / <i>PINCH2</i> /senescent cell antigen-like-containing domain protein 2 gene <i>POPDC1</i> /Popeye-domain-containing 1 <i>TOR1AIP1</i> /lamina-associated polypeptide 1B <i>POGLUT1</i> /O-glucosyltransferase 1	Defects in sarcomere organization and maintenance, defects in DGC function and sarcolemmal repair, impaired intracellular trafficking , among others	Raising in serum CK, nuclei internalization wasting and regeneration of muscle fibers, inflammatory infiltrates in some cases	Progressive weakness and atrophy of the shoulder and pelvic girdle musculature with cardiac and respiratory muscles involvement in some cases

Hereditary myopathy	Genes/proteins	Mechanism affected	Histopathological features	Clinical features
Congenital muscular dystrophies	<i>LAMA2</i> /merosin/laminin- α 2 chain <i>COL6A1</i> / <i>COL6A2</i> / <i>COL6A3</i> /collagen 6A <i>POMT1</i> /O-mannosyl-transferase 1 <i>POMT2</i> /O-mannosyl-transferase 2	Defects in DGC function and cell matrix integrity	Variation of fiber size, whorled and split fibers, nuclei internalization increase of connective and adipose tissue	Generalized hypotonia and predominantly proximal weakness, joint contractures, cardiomyopathy, respiratory failure and central nervous system involvement, retinal and brain malformations in the most severe cases
Facioscapulohumeral muscular dystrophy	<i>DUX4</i> /double homeobox 4	Toxic "gain of function" of the normally repressed transcriptional regulator DUX4	Dystrophic features including fibrosis, muscle fiber hypertrophy, central nucleation and endomysial inflammation	Slowly progressive asymmetric and descending weakness, initially affecting face (facio), scapula (scapulo) and upper arms (humeral), followed by weakness of the distal lower extremities and pelvic girdle
Emery-dreifuss muscular dystrophy	<i>EMD</i> /emerin <i>LMNA</i> /lamin A/C	Nuclear envelope defects, impair in gene expression, cell signaling and chromatin architecture	Dystrophic features such as fiber size disproportion, nuclei internalization, increase of endomysial connective tissue, necrosis and regeneration are usually observed. Reduced expression of emerin or lamin A/C in muscle, fibroblasts or blood	Slowly progressive muscular weakness, joint contractures, spine rigidity and heart disease

Table 1. Genetic, histological, and clinical aspects of hereditary myopathies.

2. Congenital myopathies

Congenital myopathies are genetic neuromuscular disorders characterized by typical histopathological alterations including type-1 fibers predominance and hypotrophy and presence of structural abnormalities such as rod-inclusions and cores, among others [1]. Their clinical

course is usually non-progressive or slowly progressive and their prognosis is mainly determined by the involvement of respiratory muscles. Unlike muscular dystrophies, patients with congenital myopathy typically exhibit normal or discretely increased levels of CK [2]. The onset of the disease generally occurs in the neonatal period and it has an estimated incidence of 1:25,000 live births [1].

Clinically, congenital myopathies manifest with heterogeneous features such as generalized weakness, hypotonia, hyporeflexia, and poor muscle bulk. Congenital myopathies also presents with dysmorphic characteristics, secondary to the myopathy such as *pectus carinatum* (a chest malformation characterized by a protrusion of the sternum and ribs), scoliosis, joint-contractures, foot deformities, high-arched palate, and elongated facies [3]. Different mutations in a same gene can cause different phenotypic forms of congenital myopathy, whereas mutations in different genes can induce muscle diseases with overlapping clinical and histological features, making difficult a specific diagnosis. However, based on the histological markers observed in muscle biopsies, congenital myopathies can be divided in five forms: nemaline myopathy, core myopathy, centronuclear myopathy, fiber-type disproportion myopathy, and myosin storage myopathy [1].

2.1. Nemaline myopathy

Nemaline myopathy (NM) is one of the three major types of congenital non-dystrophic myopathies with an estimated incidence of 1:50,000 [4]. Based on the severity and the onset of the disease, NM can be divided in different subtypes ranging from severe forms with neonatal-onset, which is usually lethal in the first months of life, to less severe forms with onset in the childhood or adulthood [5]. Clinically NM courses with hypotonia, weakness of proximal skeletal muscles, including facial and neck flexor muscles that can lead to respiratory insufficiency and death in the most severe cases [4]. Less severe forms of NM exhibit a static or slowly progressive weakness of the distal limbs, trunk, and facial muscles with a delay in the acquisition of motor milestones. Cardiac muscles are usually not affected in NM [4].

Histologically, NM characterizes by the presence of **nemaline-bodies** or small “**rod-like inclusions**.” These are thread-shape structures that stain red or purple by the modified Gömöri’s trichrome staining [1] (**Figure 1**). Rod-inclusions vary from 1 to 7 μm of length and 0.3 to 2 μm of width and, mainly, consist of **actin and alpha-actinin accumulation**, apparently product of an alteration of the ratio of actin-binding proteins and their interaction [6]. At the light microscopy, nemaline bodies appear like clusters localized at the cytoplasm and often at the periphery of the muscle fibers, although they also can be located in the nucleus making difficult to identify. At the ultrastructural level, rod inclusions appear like electron-dense bodies at the Z-bands [1]. The presence of rod-like structures in the sarcomere apparatus difficult the contractibility of muscles. It has been suggested that NM-linked mutations in proteins that compose the sarcomere affect the arrangement of muscle fibers, hindering the typical slid of the fibers during movement, and causing muscles to be unable to efficiently contract [7] (**Figure 2**). However, although the presence of nemaline bodies is required for the diagnosis of NM, they are just a product and are not necessarily the cause of the disease. In this regard, myofibrillar dissociation and smallness appear to be a primary defect causing impaired

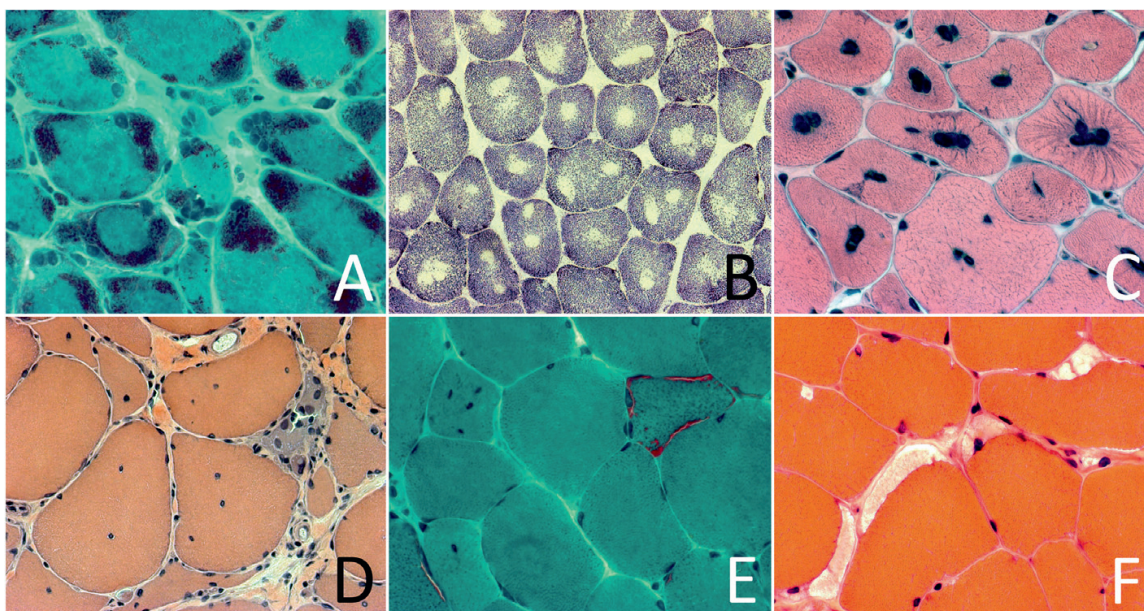


Figure 1. Histopathological markers in hereditary myopathies. (A) Modified Gömöri's trichrome stain showing rods in nemaline myopathy. (B) SDH staining in central core disease due to RYR1 mutations. Note that cores are frequently eccentric and that there are two or more in several fibers. (C) HE staining in a case of DNM2-related centronuclear myopathy. Notice multiple centralized nuclei in some fibers and the radiating strands of intermyofibrillary network. (D) Dystrophic changes in Emery-Dreyfus muscular dystrophy. There is a large variability on the size of the fibers, multiple nuclei internalizations, increase of endomysial connective tissue, and foci of necrosis-regeneration, which define the dystrophic pattern. (E) Modified Gömöri's trichrome stain showing a ragged red fiber in mitochondrial myopathy. (F) HE stain in McArdle's disease. At the subsarcolemmal level large chromophobe vacuoles containing glycogen are shown. Pictures in A and B are courtesy of Dr. Norma B. Romero, Institute of Myology, Paris, France; picture in panel C is courtesy of Prof. Anders Oldfors, University of Gothenburg, Gothenburg, Sweden.

contractility and muscle weakness in NM [5]. Moreover, nemaline bodies can be observed in other myopathies and in muscle degeneration related to aging [6].

NM is caused by mutations in 11 genes encoding proteins that compose or regulate the sarcomere thin filaments. These are **nebulin** (*NEB*) [8], **skeletal muscle alpha-actin** (*ACTA1*) [9], **alpha-tropomyosin-3** (*TPM3*) [10], **beta-tropomyosin-2** (*TPM2*) [11], **troponin T1** (*TNNT1*) [12], **cofilin-2** (*CFL2*) [13], **Kelch-repeat-and-BTB-domain-containing-13** (*KBTBD13*) [14], **Kelch-like-family-member-40** (*KLHL40*) [15], **Kelch-like-family-member 41** (*KLHL41*) [16], **leiomodlin-3** (*LMOD3*) [17] and **myopalladin** (*MYPN*) [18]. Most of these genes encode sarcomeric proteins that are critical for the structural organization and function of the contractile apparatus. Therefore, NM-causing mutations can directly affect these functions, resulting in skeletal muscle weakness. The most frequent mutated gene is **nebulin** (*NEB*) which account for over 50% of the NM cases, all of them inherited in an autosomal-recessive way [8]. **Nebulin** is a giant actin-binding protein whose large size is proportional to the thin filament length. Nebulin C-terminal region is anchored into the Z-disks and its N-terminal extends to the thin filament pointed-end, acting as a "ruler" of the thin filament length for the sarcomere assembly during myofibrillogenesis [19]. A great diversity of nebulin isoforms has been described, which differ among various striated muscles types, developmental stages, and diseases [20]. Most nebulin mutations causing NM result in truncations or internal deletions and in a

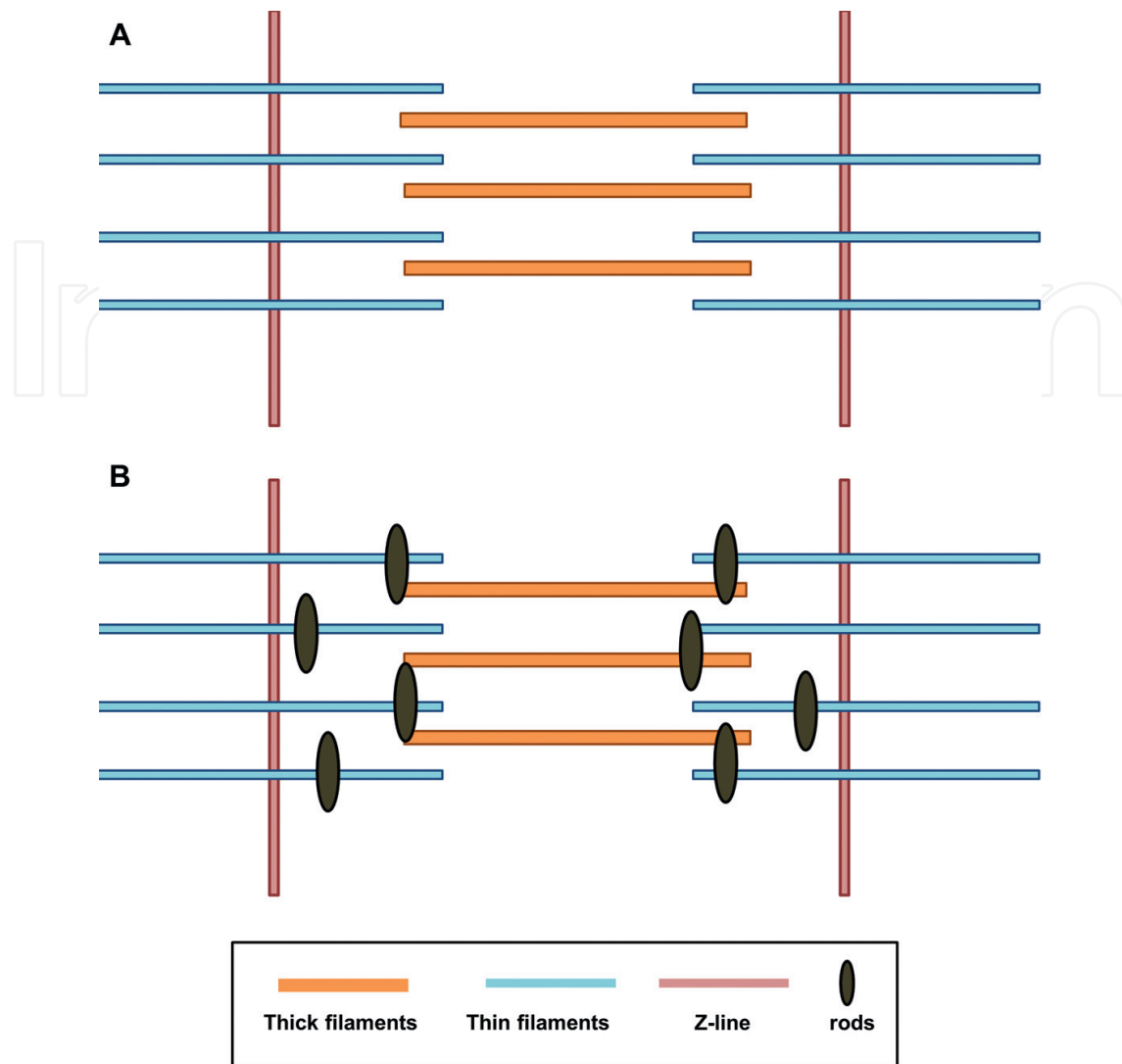


Figure 2. Rod inclusions in the sarcomere. (A) A healthy sarcomere is schematized. (B) Rod inclusions in the sarcomere are schematized. Rods are clustered near to the Z-line in the sarcomere of nemaline myopathy patients, affecting the sarcomere arrangement and hindering contraction.

reduction in the diversity of nebulin isoforms [6, 20], likely shortening thin-filaments length during myofibrillogenesis and disrupting muscle development.

Mutations in *ACTA1* gene are linked to around 20% of the NM cases [9] which are predominantly inherited in an autosomal-dominant way [1]. Mutations in skeletal alpha-actin that cause NM and other congenital myopathies are spread over different domains affecting primary actin functions such as binding and hydrolysis of nucleotide, folding, F-actin polymerization and stability, or its interaction with actin-binding proteins [21, 22].

Less prevalent mutations in *TPM3* and *TPM2* account for approximately 2–3% of the NM cases [1]. Tropomyosins are coiled-coil proteins that polymerize along actin filaments providing stability and regulating the binding of the myosin heads to the thin actin filaments in the sarcomere (cross-bridges), in a Ca^{2+} -dependent way. NM-linked mutations in **beta-tropomyosin-2** have shown to

induce a reduction in actin-affinity and Ca^{2+} sensitivity [23] and to change the position of tropomyosin in the actin filaments, disorganizing the assembly of the actomyosin complex, reducing its ATPase activity and leading to contractile dysfunction [24]. NM-causing mutations in TPM3 have shown to suppress the expression of the slow **alpha-tropomyosin-3** [25], likely deregulating myosin-actin interaction and impairing the force-generating capacity of the sarcomere.

Mutations in the *TNNT1* are less likely cause of NM. The **troponin complex** (troponin C, troponin I, and troponin T) blocks the actin-myosin interaction, preventing contraction in resting muscles. Specifically, **troponin T** binds to tropomyosins regulating the interaction of the troponin complex with thin actin filaments. NM causing mutations in *TNNT1* are mainly recessive, and produce loss of the expression of troponin T in skeletal muscles [26] and reduction of tropomyosin-binding affinity [27] likely impairing regulation of the muscle contraction.

Mutations in the *CFL2* gene have shown to cause NM [13]. **Cofilin2** is a skeletal muscle-specific actin-depolymerizing factor, and NM-linked mutations significantly reduce the cofilin2 expression levels affecting actin dynamics likely causing its accumulation in the nemaline bodies [13].

More novel mutations in proteins that form part of the BTB/Kelch family have been linked to several forms of NM. BTB/Kelch proteins are involved in a broad variety of cellular processes including cytoskeleton modulation, gene transcription, ubiquitination, and myofibril assembly. Dominant mutations in **Kelch-repeat-and-BTB-domain-containing-13** (*KBTBD13*) produce a mild form of NM with nemaline rods and core lesions ([14]. Autosomal-recessive mutations in **Kelch-like-family-member-40** (*KLHL40*), which seems to be critical for myogenesis and muscle maintenance, cause a severe form of NM that includes fetal akinesia [15]. Recessive mutations in **Kelch-like-family-member 41** (*KLHL41*) associate with a severe NM phenotype with neonatal death; NM-linked mutations cause destabilization of *KLHL41* structural domains and reduce its protein levels in skeletal muscle [16].

Leiomodin-3 (*LMOD3*) is a skeletal muscle-specific member of the tropomodulin family and colocalizes with sarcomere thin actin filaments. Mutations in *LMDO3* produce a severe form of NM that manifests with absence of fetal movements, generalized hypotonia, and respiratory insufficiency. NM mutations abolish *LMOD3* expression in skeletal muscle tissue of NM patients [17].

Mutations in **myopalladin** have been also recently identified to cause relatively mild forms of NM with slowly progressive muscle weakness [18]. Myopalladin is a sarcomere protein localized at the I-bands and Z-line that interacts with several sarcomeric components, including nebulin, regulating sarcomere assembly [18]. NM-linked mutations in *MYPN* are loss of function mutations that markedly decrease the full-length protein levels likely affecting the maintenance of the sarcomeric organization [18].

2.2. Core myopathy

Core myopathies (CM) are heterogeneous congenital muscle diseases that present with hypotonia and weakness of proximal muscles with a static or slow-progressive clinical course. CM is the most common form of congenital myopathy [28]. Histologically, CM is characterized by the presence of “cores,” large areas of abnormal myofibrillar arrangement and sarcomeric

disorganization, devoid of mitochondria, and oxidative-enzyme activity, which are mainly found in type-1 muscle fibers (**Figure 1**). Cores can be single or multiple; and based on biopsy observations, CM can be classified as **central core disease (CCD)** or **multiminicore disease (MmD)** [28]. In CCD, single cores are centrally or eccentrically located along the longitudinal axis of type 1 muscle fibers (**Figure 1**), while in MmD numerous short core lesions localize diffusely throughout type 1 or type 2 muscle fibers [29]. Cores and rods lesions can occur together in “**core-rod myopathy**,” a variant of NM [30]. Dominant-inherited CCD typically courses with hypotonia and motor developmental delay in the childhood, presenting fetal akinesia in the most severe cases [28]. Most mild forms manifest with myalgia, proximal weakness with hip, girdle, and axial muscles involvement. Orthopedic complications including hips dislocation, scoliosis, and foot deformities are also typical in CCD patients [28]. Clinical manifestations of MmD are highly variable. These range from a severe and most prevalent neonatal form, which include axial muscle weakness, spinal rigidity, respiratory impairment, and cardiac failures [31], to milder forms that course with generalized muscle weakness predominantly affecting pelvic girdle [31].

CCD and MmD are caused by mutations in genes encoding two proteins involved in the excitation-contraction (E-C)-coupling, calcium homeostasis, and redox regulation in muscle fibers, these are the skeletal-muscle **ryanodine receptor (RYR1)** [32] and the **selenoprotein N (SEPN1)** [31]. RyR1 is a functional calcium release channel that plays a critical role in the E-C coupling by releasing calcium from the sarcoplasmic reticulum in response to conformational changes induced by the activation of the voltage-sensing dihydropyridine receptor DHPR [33]. Most mutations in RyR1 gene are autosomal-dominant and associate with a CCD phenotype [34]. Autosomal-dominant mutations in RyR1 mainly localizes in the C-terminal region, which encodes the calcium release channel pore of the ryanodine receptor protein and in the N-terminal region that includes the “foot” structure that interacts with DHPR [35]. An important number of dominant mutations in RyR1 also associate to malignant hyperthermia susceptibility (MHS), a pharmacogenetic predisposition to severe and potentially lethal episodes induced by halogenated anesthetic agents (halothane, isoflurane) and succinylcholine [36]. MHS-linked mutations cause a hyperactive RyR1 channel that release excess of calcium to the sarcoplasm [37], initiating a cascade of events that induce hypermetabolism, increased CO₂ production and O₂ consumption, acidosis, muscle rigidity, tachycardia, and tachypnea among others [36]. Although not all patients with MHS exhibit a muscular affection, the majority of CCD patients are susceptible to malignant hyperthermia. Patients with MmD and centronuclear myopathy also exhibit predisposition to MHS linked to RyR1 mutations [36]. Recessive mutations in RyR1 predominantly associate with MmD and are distributed evenly throughout the gene [35], but can also cause other phenotypes with less well defined cores on muscle biopsy [38]. Different molecular mechanisms related to RyR1 mutations have been suggested to underlay core myopathy. For instance, the “leaky channel hypothesis” suggests that MHS- and CCD-linked mutations confer hypersensitivity to the RyR1 channel, increasing its activity; thus, affecting Ca²⁺ homeostasis by depletion of the intracellular Ca²⁺ stores [39]; CCD-mutations have also shown to impair the Ca²⁺ permeation through RyR1 channel after activation, affecting the E-C coupling (“E-C uncoupling hypothesis”) [40] and MmD-linked mutations have been associated with a reduction of the RyR1 protein expression levels [41].

Additionally to RyR1-related forms, mutations in SEPNI associate with approximately 50% of the cases of the most prevalent form of MmD [28]. Selenoprotein-N is a sarcoplasmic glycoprotein implicated in several processes including antioxidant defenses and calcium homeostasis [42]. This is part of the selenoproteins family, which characterize for containing selenocysteine aminoacids (Sec). Incorporation of Sec to the polypeptide chain in selenoproteins occurs due to a “redefinition” of the stop-codon UGA during translation, which requires a Sec insertion sequence (SecIS) in the non-translated 3'UTR region and a Sec redefinition element (SRE) located adjacent to the UGA codon. Myopathy causing mutations in SEPNI affects the Sec insertion efficiency, decreasing the expression of selenoprotein-N, and leading to a deficiency of the protein [43]. Mutations in SEPNI have been also pointed as causative of congenital muscular dystrophy with rigid spine (RSMD), a rare neuromuscular disorder characterized by early spine stiffness and respiratory deficiency [44].

2.3. Centronuclear myopathy

Centronuclear (CNM) myopathy is a heterogeneous group of congenital myopathies clinically manifested by myalgia, fatigability and progressive weakness and atrophy of distal skeletal muscles [45]. Histological markers of the disease are the presence of abnormally high number of muscle fibers with a central rather than peripheral nuclei distribution (**Figure 1**), predominance, and atrophy of type 1 fibers, and a radial arrangement of the sarcoplasmic strands on oxidative stains [45]. Different forms of CNM have been described according to the inheritance pattern and clinical manifestations. The X-linked recessive form, called **myotubular myopathy (XLMTM)**, presents as a severe myopathy with marked hypotonia and generalized muscle weakness in newborn males and exhibit a poor prognosis with the most of patients dying within the first months of life as a consequence of respiratory failure [46]. A late-onset myotubular myopathy has been also reported, which presents with milder symptoms during childhood that worsen after the first or second decade of life and that histologically characterizes by the presence of “**necklace fibers**,” a basophilic ring deposit following the contour of the cell in which myonuclei are aligned [47]. XLMTM is mainly caused by mutations in the *MTM1* gene encoding **myotubularin**, an ubiquitously expressed lipid phosphatase that specifically dephosphorylates phosphatidylinositol-3-phosphate and phosphatidylinositol-3,5-bisphosphate [48]. Myotubularins are implicated in several cell process including endocytosis, membrane trafficking, autophagy, and cytoskeletal dynamics [48, 49] and seem to be critical for skeletal muscle maintenance as shown in *MTM1*-deficient mice [50]. More than 200 different XLMTM-linked mutations in myotubularin have been described to date with most of the mutations predicted to affect its expression and enzymatic activity [51–54]. A mouse model of XLMTM exhibit T-tubules disorganization, a depression in the sarcoplasmic Ca^{2+} release by a reduction in the RyR1 levels and consequent defects in EC-coupling [55].

A classical autosomal-dominant form of CNM, which accounts about 50% of the CNM cases, is caused by mutations in the *DNM2* gene encoding **dynamamin-2** [56]. The spectrum of dynamamin-2-related CNM severity varies from mild, with late-onset, to severe with neonatal onset [57]. Mild and moderates forms of *DNM2*-related CNM manifests with delayed motor milestones, specially walking and climbing stairs, distal muscle weakness, ptosis, and ophthalmoplegia.

More severe early-onset forms courses with generalized weakness and hypotonia, scoliosis, Achilles tendon contractures, and jaw opening among other symptoms [56]. Dynamin-2 is a large GTP-ase that expresses ubiquitously in different tissues and participates in various intracellular processes including endocytosis, exocytosis, membrane trafficking, and actin cytoskeleton remodeling among others [58–60]. CNM-causing mutations in dynamin-2 are clustered in structural domains involved in dynamin's oligomerization (middle domain) and lipid-binding (PH domain) [57]. These mutations have shown to increase dynamin basal GTP-ase activity and enhance oligomerization [61–63]. The impact of CNM-linked mutations on dynamin-2-dependent processes has not yet been fully understood. In non-muscle cells both, reduction [64, 65] and absence of effect [66] in clathrin-mediated endocytosis has been reported. Skeletal muscles of CNM patients exhibit abnormal cytosolic accumulation of dynamin-2 and other endocytic proteins [67], while impaired actin remodeling and actin-mediated trafficking was reported in a rodent mammalian model of CNM [68].

Mutations in the *BIN1* gene, encoding **amphiphysin 2**, cause an autosomal-recessive form of CNM, which presents with a large clinical variability from severe to moderate phenotypes [46]. Currently, BIN1-related CNM manifests with a delay in the acquisition of motor milestones, difficult to walk, run and climb stairs, diffuse muscle weakness and atrophy and facial involvement including diplegia, ptosis and ophthalmoplegia [56]. Amphiphysin 2 is a ubiquity expressed protein that belongs to the BAR-domain family, which acts as sensor of the membrane curvature [69]. At late stages of the clathrin-mediated endocytosis, amphiphysin2 bind to the invaginated membranes and recruits other proteins to the endocytic machinery including dynamin-2 [70]. CNM-causing mutations in BIN1 localizes in its BAR domain affecting its capabilities to tabulate membranes and in its SH3 domain, producing a partial truncation that eliminates its interaction with dynamin-2. The later suggests that mutations in amphiphysin-2 disrupt the formation and maintenance of the T-tubule network by impairing membrane remodeling, leading to CNM [71].

CNM-causing autosomal-recessive mutations have been also reported in the gene encoding *RyR1* [72, 73] and *TTN* gene, encoding **titin** [74]. Clinically, RyR1-related CNM patients exhibit early hypotonia, motor developmental delay, proximal and proximal, facial and ocular muscle weakness. Histologically, they show a variable prominence of central nuclei, type-1 fiber predominance and a wide range of intermyofibrillary abnormalities [72, 74]. Most CNM-linked mutations in RYR1 result in reduced expression of the ryanodine receptor channel [75] likely suggesting defects in the EC-coupling. **Titin** is a giant protein (the largest one known) important in the contraction of the striated muscle. It connects the Z line to the M line in the sarcomere forming a third filament system important for the structural integrity of the myofibril and for the passive tension in stretched muscle fibers [76]. CNM-causing mutations in titin produce degradation and truncated versions of the protein in patients [74], likely affecting muscle stiffness and contractibility. Mutations in titin also associate with cardiomyopathies [77] and muscular dystrophy [78].

Recently, mutations in the *striated muscle preferentially expressed protein kinase SPEG*, a myotubularin-interacting protein, have been related to myotubular centronuclear myopathy [79, 80]. Mutations in *SPEG* cause phenotype that range from mild forms of CNM with moderate hypotonia and weakness to more severe forms with cardiac involvement [79, 80].

2.4. Congenital fiber-type disproportion myopathy

Congenital fiber-type disproportion myopathy (CFTDM) is defined by an abnormal disproportion between the size of type-1 (slow) and type-2 (fast) muscle fibers, with the type 1 fibers found to be at least 35–40% smaller than the type 2 ones [81]. This is a critical point for the diagnosis since other myopathic conditions manifests with fiber type disproportion. Clinically, CFTDM patients experience mild to severe muscle weakness mainly affecting shoulders, arms, hips, and thighs. Orthopedic affections such as lordosis, scoliosis, and joint contractures are usually observed. Approximately, 30% of CFTDM patients exhibit respiratory muscle hypotonia, requiring breathing assistant. Face muscles can also be affected producing long face, high-arched palate, ptosis, and ophthalmoplegia [1]. Genetically, the most well-established causes of CFTDM are mutations in *TPM3*, *RYR1*, and *ACTA1* genes [81]. Mutations in *TPM3* are the most common cause of CFTDM accounting between 20 and 50% of the diagnosed cases [81, 82]. Almost all *TPM3* mutations associated with CFTDM are dominant missense changes and are predicted to impair the interaction between alpha-tropomyosin and actin [82] likely affecting acto-myosin interaction in the cross-bridges cycle and impairing a proper muscle contraction [83]. Recessive mutations in **RYR1** have shown to cause CFTDM accounting 10–20% of the CFTDM families. The most specific clinical indication of RyR1-related CFTDM is the presence of ophthalmoplegia and a dramatic disproportion in the size of type 1 fibers (being 50–84% smaller than type2 fibers) [84]. CFTDM-causing mutations reduce RyR1 protein expression levels [84], probably impairing channel conductance and EC-coupling. Mutations in *ACTA1* linked to CFTDM are less probable compared to *ACTA1* mutations in nemaline myopathy, and account approximately 5% of the CFTDM patients [85]. How mutations in *ACTA1* produce fiber type disproportion is uncertain since it is equally expressed in both, type 1 and type 2 fibers. The pathological mechanism of *ACTA1*-related CFTDM is also unclear, although it was reported that one mutation in a residue located in the external surface of alpha actin, in which a negatively charged residue is replaced by a non-charged one (D294V), impair actin-tropomyosin association, deregulating acto-myosin interaction, and leading to defects in muscle contraction [86]. Much less frequent causes of CFTDM are mutations in the genes encoding beta-tropomyosin-2 (*TPM2*), beta-myosin (*MYH7*), and selenoprotein-N (*SEPN1*) [81].

2.5. Myosin storage myopathy

Myosin storage myopathy (MSM) is a rare congenital myopathy caused by mutations in the gene encoding the **slow-skeletal/ β -cardiac myosin heavy chain** (*MYH7*), a class II myosin and major component of the thick filaments. It is primarily expressed in heart but also in skeletal muscle type-1 fibers [87]. *In vivo*, myosin forms dimers of myosin heavy chains with two globular heads attached to a coiled-coil region known as the myosin rod. The head region is responsible for myosin's ATPase-activity and actin-binding, while the rod region allows the incorporation of myosin to the thick filaments [88]. *MYH7* mutations are spread along the different myosin's domains and according their location associate with different phenotypes. In this regard, mutations in the N-terminal globular head are linked to cardiomyopathies,

whereas mutations in the C-terminal rod associate to skeletal muscle myopathies such as MSM [89]. MSM-linked mutations in MYH7 have shown to alter myosin folding and stability, impairing sarcomere thick filaments assembly and integrity [88, 90]. MSM clinical phenotypes are highly variable between patients. It presents with childhood or adult-onset forms with static or slowly progressive clinical course. Hypotonia and proximal muscle weakness with delayed motor milestones are common features. Respiratory insufficiency secondary to the myopathy may occur, with the presence or not of cardiac involvement [1]. Histologically, MSM characterizes by the sub-sarcolemmal accumulation of β -myosin in type 1 fibers, which can be observed with hematoxylin-eosin and Gömöri trichrome stains as “**hyaline bodies.**”

3. Mitochondrial myopathies

Dysfunctions of the respiratory chain, responsible for oxidative phosphorylation and ATP energy production in the inner mitochondrial membrane, cause **mitochondrial diseases**. These manifest as multisystem disorders with predominant involvement of muscles and nerves. When skeletal muscle is affected, the term **mitochondrial myopathy** is used. In isolated mitochondrial myopathy without involvement of other tissues, patients can exhibit myalgia, fatigue, exercise intolerance, proximal and distal muscle weakness, and elevated serum CK [91]. Other clinical manifestations include the **chronic progressive external ophthalmoplegia (CPEO)**, in which a slowly progressive paresis of the extra ocular muscles is the most important phenotype [92] and **severe encephalomyopathy of infancy or childhood**, in which brain and skeletal muscle tissue are involved, producing marked hypotonia, respiratory muscle weakness, and feeding difficulty [93]. Mitochondrial myopathies may be caused by mutations in mitochondrial or nuclear DNA. Mitochondrial-DNA encoded **cytochrome b** [91] and **cytochrome c oxidase** [94, 95] are mutated in some forms of isolated mitochondrial myopathy. Mutations in nuclear DNA that produce deficiency of **Coenzyme Q10**, an important electron carrier of the respiratory chain also associate to mitochondrial myopathy [96]. Depletion of mitochondrial DNA in skeletal muscle, secondary to mutations in nuclear genes (mitochondrial depletion syndrome) can also cause mitochondrial myopathy. It mainly affects genes encoding proteins involved in the maintenance of the mitochondrial deoxy-ribonucleotide pool, such as **thymidine kinase (TK2)** [97] or proteins implicated in mitochondrial DNA replication such as the **polymerase gamma 1 (POLG1)** [98]. Histologically, mitochondrial myopathy characterizes by a sub-sarcolemmal and intermyofibrillar **accumulation of mitochondria** in muscle fibers, which responds to compensatory mechanisms due to defects in the energy production. Upon Gömöri trichrome stain, proliferated mitochondria look as bright red masses against the blue background of the myofibers, defining the term “**ragged red fibers**” (**Figure 1**). Staining of succinate dehydrogenase (SDH) and cytochrome c oxidase (COX) are indicative of mitochondrial complexes activity. In SDH-positive biopsies “**ragged blue fibers**” can be observed. Staining pattern with normal fibers mixed with ragged blue/red COX-positive fibers is a histological marker of mitochondrial-DNA-related myopathy [99].

4. Metabolic myopathies

Metabolic myopathies result from defects in the metabolism of carbohydrates and lipids that primarily affect skeletal muscle. Defects in energy production are typically manifested by metabolic crisis with generalized muscle weakness, sometimes associated with cardiac and respiratory failure [100]. Metabolic myopathies can be classified as **glycogen storage** and **lipid storage diseases**. Among glycogen storage diseases is **glycogenosis type II (Pompe disease)**, an autosomal-recessive disorder caused by mutations that lead to a deficiency of the **lysosomal enzyme acid α -glucosidase (GAA)**, responsible for catalyze the hydrolysis of glycogen. Deficiency of GAA produces glycogen accumulation and disruption of tissue architecture in different tissues, especially in skeletal muscle [100]. The clinical phenotype of Pompe disease ranges from childhood-onset severe forms to mild adult forms [101]. The most classic childhood form manifests in the first months of life with severe cardiomyopathy, generalized hypotonia and muscle weakness, feeding difficulties, and respiratory failure. The late-onset disease presents with progressive proximal and axial muscle weakness, leading to alteration in the posture and pattern of movements [100]. Enzyme replacement therapy allows diminishing the symptoms although untreated late-onset patients may worsen progressively eventually needing wheelchair and assisted ventilation [102]. Histological markers of Pompe disease are the presence of huge **basophilic vacuoles** inside muscle fibers in childhood-onset forms, and globular **cytosolic inclusions** with acid phosphatase activity in adult-onset forms of the disease [103]. Other glycogen storage diseases affecting glycogen degradation are **glycogenosis type III (Cori disease)**, caused by recessive mutations in the *AGL* gene that lead to **glycogen debranching enzyme** deficiency [104] and **glycogenosis type V (McArdle disease)**, caused by mutations in the *PYGM* gene that cause **myophosphorylase** deficiency [105]. Cori disease patients typically exhibit hypotonia and distal weakness and may present cardiac and hepatic failure [104]. McArdle disease patients presents with fatigue and exercise-induced myalgia. In some cases, patients can exhibit myoglobinuria and acute renal failure due to rhabdomyolysis, as well as higher susceptibility to malignant hyperthermia [106]. Large glycogen-containing vacuoles typically accumulate at the sub-sarcolemmal level in McArdle disease biopsies (**Figure 1**).

Lipid storage myopathies characterizes by abnormal lipid accumulation in muscle fibers due to fatty acid dysmetabolism. Different forms of lipid storage myopathy have been described among them **primary carnitine deficiency (PCD)**, **multiple acyl-CoA dehydrogenase deficiency (MADD)** and **neutral lipid storage disease with myopathy (NLSMD)** [107]. PCD is caused by autosomal-recessive mutations in the *SLC22A5* gene that encodes the **carnitine transporter OCTN2**. Defects in OCTN2 lead to deficiency of carnitine and reduced transportation of long-chain fatty acids to the mitochondrial matrix, producing cytosolic lipid accumulation and a reduction in the ATP production for β -oxidation [107]. Clinically PCD manifests with a wide spectrum of symptoms including hypotonia, muscle weakness, and cardiomyopathy. Histopathological markers include elevated levels of CK and increased number and size of **lipid droplets**, especially in type 1 muscle fibers [107]. MADD is caused by deficiency of **electron-transfer flavoprotein (ETF)** or **ETF-dehydrogenase (ETFH)**, two mitochondrial enzymes that act transferring high-energy electrons produced during the fatty acid β -oxidation by acyl-CoA-dehydrogenases to the respiratory chain. The clinical phenotype of MADD is

highly heterogeneous ranging from neonatal-onset forms that manifest with hypotonia, hepatomegaly, hypoglycemia, and metabolic acidosis and later-onset forms that present with proximal muscle weakness often with hepatomegaly, encephalopathy, and episodic lethargy. Like in PCD, muscle fibers of MAAD patients exhibit increased lipid droplets [107]. NLSDM is caused by mutations in the *PNPLA2* gene, encoding the **adipose triglyceride lipase** implicated in the catabolism of stored triglycerides to glycerol and non-esterified fatty acids [108]. Histopathological markers of the disease include **neutral-lipid containing vacuoles**, stained by oil-red O in neutrophils and monocytes as well as marked **triglyceride storage** and cytoplasmic **lipid droplets** in muscle sections [108]. NLSDM is clinically characterized by, either, childhood- or adult-onset proximal muscle weakness, typically affecting upper limbs, although distal asymmetrical muscle weakness may also occur, as well as elevated CK serum levels and cardiomyopathy in some cases [100].

5. Myotonia

Myotonia is a symptom associated to several neuromuscular disorders characterized by a prolonged contraction or rigidity of the skeletal muscles (delayed relaxation) after voluntary contraction or electrical stimulation. It is present in **congenital myotonia**, **paramyotonia congenita**, and **myotonic muscular dystrophy** among others muscular disorders. **Congenital myotonia** is a non-dystrophic disorder caused by loss-of-function mutations in the skeletal muscle chloride channel *CLC1* resulting in a reduced sarcolemmal chloride conductance [109]. *CLC1* channels are critical players stabilizing resting membrane potential and promoting repolarization. Upon propagation of an action potential along T-tubules, an efflux of potassium ions occur to repolarize membrane potential. Due to the spatial confinement of T-tubules this efflux leads to an increase in extracellular potassium concentration which tends to produce an “after-depolarization” that is dampened by chloride conductance under normal conditions. Mutations in *CLC1* reduce chloride conductance, enhancing the sarcolemmal excitability by accumulation of potassium ions in the transverse tubules [110]. This condition may trigger spontaneous action potentials explaining the persistent muscle contraction observed in myotonic patients. Congenital myotonia is classified in autosomal-dominant **Thomsen’s disease** and autosomal-recessive **Becker’s myotonia**. The first is a moderate form of myotonia with no progressive symptoms, allowing to the patients a relatively normal life expectancy. Becker’s myotonia is an early-onset more severe form of the disease that presents with pronounced myotonia, myalgia, transient episodes of generalized weakness and muscular hypertrophy [110]. Predominance and hypotrophy of type 2 fibers and increased endomysial connective tissue are usually observed in biopsies of congenital myotonia patients. **Paramyotonia congenita** is a non-dystrophic muscular disorder caused by autosomal-dominant mutations in the *SCN4A* gene encoding the pore-forming **alpha-subunit of the skeletal muscle sodium channel (Nav1.4)** [111]. Nav1.4 mutations cause channel gain of function, producing abnormal persistent sodium currents that lead to the myotonic phenotype [111]. Paramyotonia congenita manifests with early-onset generalized weakness and “myotonic discharges” that produce an exacerbated stiffness by repeated muscle contraction.

Patients also exhibit an extreme sensitivity to cold that worsens the symptoms [111]. **Myotonic muscular dystrophy** is the most common cause of muscular dystrophy in adults and results from expression of RNAs that contain expanded nucleotide repeats in the 3' untranslated region of two different genes leading to two forms of the disease. **Myotonic dystrophy type 1 (DM1)** that results from an expansion of **CTG repeats** in the *DMPK* gene encoding **myotonin-protein-kinase** and **myotonic dystrophy type 2 (DM2)** caused by an expansion of **CCTG repeats** in the **zinc finger 9 (ZNF9)** gene. These mutant transcripts form **hairpins**, imperfect double-stranded structure that lead to deregulation of important RNA-binding proteins such as **muscleblind-like protein 1 (MBNL1)**, which are retained in nuclei forming toxic nuclear foci that impair gene expression [112]. Aberrant expansion of nucleotide repeats has shown to deregulate alternative splicing of pre-mRNA for **CIC1 channel**, affecting chloride conductance in skeletal muscle, leading to the myotonic phenotype [113]. Both DM1 and DM2 exhibit an autosomal-dominant inheritance pattern. Clinical presentation includes muscle wasting, progressive weakness, myotonia, cataracts, and multi-organ involvement affecting heart, brain, and endocrine system [112]. DM1 patients manifest more severe myotonia with prominent distal muscle involvement and a severe congenital form with mental retardation. DM1 is characterized by the phenomenon of "**anticipation**," by which the disease has an earlier onset and more severe course in subsequent generations [114]. In DM2 patients, proximal muscles are more affected; exhibiting milder myotonia with no "anticipation" [115]. Histological features in myotonic dystrophy include a high number of **internalized nuclei**, disproportion in fiber diameter with **type 1 fibers atrophy**, **basophilic regenerating fibers**, fibrosis, and adipose deposition. Specifically in DM2 biopsies **atrophic type 2 fibers** with pyknotic nuclear clumps are often observed [112, 116].

6. Muscular dystrophies

Muscular dystrophies (MD) are a heterogeneous group of neuromuscular disorders that result in progressive weakness and degeneration of skeletal muscles, affecting limbs, axial, and facial muscles. In some forms of the disease, heart and other organs are also affected [117]. The onset of MD is typically in early childhood, although the symptoms can appear in infancy up to middle age or later. The estimated incidence of MD is 1:2000 live births. Histopathological markers of MD are a diffuse **variation in the size of fiber types**, **necrosis** (with or without phagocytosis), **fiber regeneration**, **fibrosis**, and **atrophy**. **Inflammatory response** is present in some forms of MD (**Figure 1**). Elevated serum levels of **CK** are typically observed in MD patients [118]. MD are caused by mutations in genes that encode a wide variety of proteins, including transmembrane and membrane-associated proteins, extracellular matrix proteins, cytoplasmic enzymes, and nuclear envelope proteins [119]. More than 30 different forms of MD have been described, which differ in their genetic background, primarily affected muscles, the age of onset of the symptoms and the degree of weakness and progression. Some of the most common MDs are described below.

6.1. Duchenne and Becker muscular dystrophy

Duchenne and Becker muscular dystrophies are two related X-linked recessive muscle disorders caused by mutations in the *DMD* gene encoding **dystrophin**, a critical component of the **dystrophin-glycoprotein complex (DGC)**, a molecular scaffold that links fiber cytoskeleton to the extracellular matrix, providing mechanical stability to skeletal muscle [119]. Defects in DGC lead to mechanical stress during muscle contraction, producing sarcolemmal damage, abnormal Ca^{2+} homeostasis and consequent fiber necrosis [119]. Duchenne is the most common muscular dystrophy in childhood affecting approximately 1:3500 newborn males [117]. Duchenne-causing mutations usually lead to a pronounced reduction or complete absence of dystrophin, while Becker mutations have a less dramatic effect in dystrophin expression. Occasional muscle fibers positive for dystrophin can be found in about 50% of DMD patients called “revertant fibers,” where dystrophin expresses in discrete domains with a “patchy distribution” that not influence the clinical phenotype [120]. Duchenne patients present early-onset dystrophy, delayed acquisition of motor milestones and a rapid progression of muscle weakness that usually leads them to need wheelchair by adolescence. Becker patients manifest milder symptoms with muscle weakness becoming later in childhood or in adolescence with a much slower progression. Both cases are usually associated with cardiomyopathy [121]. Insulin resistance and other metabolic alterations have also been observed in Duchenne and Becker patients [122].

6.2. Limb-girdle muscular dystrophies

Limb-girdle muscular dystrophies (LGMD) are a heterogeneous group of rare muscular disorders characterized by progressive proximal muscle wasting, predominantly affecting hip and shoulders. Clinical manifestations are broad, ranging from severe forms with rapid onset and progression to slowly progressive late-onset milder forms [123]. According to the inheritance pattern, LGMD can be classified in autosomal-dominant forms (LGMD1) and autosomal-recessive forms (LGMD2). Letters are added consecutively allowing to classify LGMD according to when individual genes were identified [117].

LGMD1 are usually adult-onset mild forms of the disease. Among them, **LGMD1A** is caused by mutations in the *MYOT* gene encoding **myotilin**, a Z-disk associated alpha-actinin-binding protein involved in the structural integrity of sarcomeres [123]. Patients exhibit proximal and distal weakness and occasional respiratory and cardiac involvement. **LGMD1B** is caused by mutations in the *LMNA* gene, encoding the nuclear membrane protein **lamin A/C**, implicated in several roles including mechanical maintenance of the nuclear membrane and gene regulation. Clinical manifestations of this “laminopathy” include proximal weakness, cardiac arrhythmias, and dilated cardiomyopathy [123]. **LGM1C** is caused by mutations in the *CAV3* gene that encodes **caveolin-3**, a muscle-specific sarcolemma protein component of caveolae membranes, specialized lipid rafts involved in plasma membrane maintenance, vesicular trafficking, and signal transduction [124]. Patients exhibit moderate proximal weakness, calf hypertrophy, and muscle cramps associated to exercise [123]. **LGMD1D** is caused by mutations in *DNAJB6*, a

member of the “DNAJ family,” molecular chaperones involved in protein folding. **LGMD1E** associates to mutation in the *DES* gene encoding **desmin**, a component of the intermediate filaments that provides structural support to the sarcomere [123]. **LGMD1F** is caused by mutations in the **transportin 3** gene (*TNPO3*), a nuclear receptor for serine/arginine-rich proteins. Mutations in the RNA-processing protein **HNRPDL** cause **LGMD1G** [123].

Recessive LGMD are more frequent forms of the disease. Among them **LGMD2A** is the most prevalent LGMD worldwide accounting for up to 30% cases and is caused by mutations in the *CAPN3* gene encoding **calpain 3**, a Ca^{2+} -dependent non-lysosomal cysteine protease implicated in sarcomere organization and maintenance in mature muscle fibers. Most of the *CAPN3* mutations result in autolysis and impaired proteolytic activity of calpain 3 [125]. Pathological features of the disease are progressive weakness and atrophy of the shoulder and pelvic girdle musculature, raised levels of serum CK and wasting and regeneration of muscle fibers in biopsy [126]. Recessive mutations in the *DYSF* gene encoding **dysferlin** cause **LGMD2B**. Dysferlin is a ubiquitous transmembrane protein implicated in Ca^{2+} -dependent resealing of the sarcolemma after injury [127]. Dystrophy-causing dysferlin mutations produce a drastic deficiency or complete absence of the protein; however, reduced dysferlin expression can also be observed in other muscular dystrophies secondary to mutations in other related genes [118]. **LGMD2B** account 15–25% of the **LGMD2** cases and presents with slowly progressive proximal weakness that usually begin in the first or second decade of life and eventually lead to wheelchair dependence. Very highly elevated CK serum levels, nuclei internalization, muscle fibers necrosis and regeneration, and inflammatory infiltrates are typically observed. Other typical form of “dysferlinopathy” is **Miyoshi myopathy**, which is an adult-onset, more distal form that mainly affects posterior muscles of legs [117].

LGMD 2C-2F are referred as “**sarcoglycanopathies**” and are caused for loss of function mutations in the genes encoding **alpha**, **beta**, **gamma**, or **delta-sarcoglycans**, respectively. These are transmembrane proteins members of the **sarcoglycan-complex**, critical component of the DGC implicated in connecting cytoskeleton to the extracellular matrix providing mechanical stability to the skeletal muscle [128]. Sarcoglycanopathies have a childhood onset and typically manifest with rapid or slowly progressive proximal weakness involving both, cardiac and respiratory functions [123].

The “**dystroglycanopathies**” group a number of recessive **LGMD (2I, 2K, 2M, 2N, 2O, 2P)** linked to mutations in six genes implicated in the **glycosylation** of **alpha-dystroglycan**, critical component of the DGC: **fukutin-related-protein** gene (*FKRP*) linked to **LGMD2I** [129]; **O-mannosyl-transferase 1** gene (*POMT1*) linked to **LGMD2K** [130]; **fukutin** gene (*FKTN*) associated to **LGMD2M** [131]; **O-mannosyl-transferase 2** gene (*POMT2*) linked to **LGMD2N** [132]; protein **O-linked-mannose beta-1,2-N-acetylglucosaminyltransferase 1** (*POMGnT1*) associated to **LGMD2O** [133] and the **dystroglycan gene** itself (*DAG1*) linked to **LGMD2P** [134]. Abnormal glycosylation of alpha-dystroglycan inhibits its binding to extracellular matrix proteins, impairing skeletal muscle stability. Dystroglycanopathy-causing mutations produce a wide spectrum of dystrophic phenotypes ranging from mild forms such as those observed in **LGMD** to more severe congenital muscular dystrophies (see below) [135].

LGMD2T is caused by mutations in the **GDP-mannose pyrophosphorylase B gene (GMPPB)**, which catalyzes the conversion of mannose-1-phosphate and GTP to GDP-mannose, consequently

causing hypoglycosylation of α -dystroglycan [123]. LGMD2T patients exhibit dystrophy with intellectual disabilities [136]. Mutations in the **isoprenoid synthase domain containing** gene (*ISPD*) also impair dystroglycan glycosylation leading to **LGMD2U** and also to the severe **Walker Warburg syndrome** [137] (see below).

LGMD2J is caused by mutations in the gene encoding the giant sarcomeric protein **titin** (*TTN*), mainly clustered in the C-terminal M-line-linked region of the protein, interfering with its structure and function [138]. Mutations in the **anoctamin 5** gene (*ANO5*) cause **LGMD2L**, an adulthood-onset disease that presents with asymmetric muscle weakness, pain after exercise and elevated CK levels [123]. **LGMD2Q**, an early-onset non-progressive form of LGMD is caused by mutations in the gene encoding **plectin** (*PLEC1*) [123], a ubiquitously expressed protein linking actin microfilaments, microtubules and intermediate filaments [139]. Autosomal-recessive mutations in the **DES** gene (see above) determine **LGMD2R**, which may present cardiac involvement [123].

LGMD2S is caused by mutations in the **transport protein particle complex 11** gene (*TRAPPC11*), a transport protein involved in anterograde membrane trafficking from the endoplasmic reticulum (ER) to the ER-to-Golgi; this form shows childhood onset ataxia, and intellectual disabilities [143]. A form of adulthood-onset Pompe's disease has also been classified as **LGMD2V** [123] (see Section 4).

LGMD2W caused by mutations in the LIM and senescent cell antigen-like-containing domain protein 2 gene (*LIMS2/PINCH2*), that regulates cell shape and migration, presents as a childhood-onset LGMD2 with calf and tongue hypertrophy and severe quadriparesis [141].

Mutations in the **Popeye-domain-containing 1** gene (*POPDC1*) alter membrane trafficking and produce **LGMD2X** [142], which associates with atrio-ventricular conduction blockage [144]. Mutations in the torsinA-interacting protein 1 gene (*TOR1AIP1*) encoding the **lamina-associated polypeptide 1B** (*LAP1B*) cause **LGMD2Y** [142, 144]. **LGMD2Z** is caused by mutations in the **POGLUT1** gene [142] encoding **O-glucosyltransferase 1**, an enzyme involved in Notch-posttranslational modification and function, impairing muscle regeneration mediated by Notch. Patients exhibit typical features of LGMD2 and show reduced glycosylation of α -dystroglycan [145].

LGMD2G and **LGMD2H** are the rarest forms of LGMD2. **LGMD2G** is caused by mutations in the **TCAP** gene that encodes **telethonin**, a titin-interacting protein that links titin to other Z-disk proteins supporting sarcomere assembly and muscle stretching [146]. Clinical manifestations include adolescence-onset limb girdle weakness and cardiomyopathy susceptibility [123]. **LGMDH** is a late-onset disease characterized by proximal weakness and atrophy caused by mutations in the **TRIM32** gene encoding a ubiquitous E3 ubiquitin ligase involved in proteasome degradation of multiple targets, including actin [147].

6.3. Congenital muscular dystrophies

Congenital muscular dystrophies (CMD) include a number of neuromuscular disorders with onset at birth or early infancy that manifest with generalized hypotonia, hyperlaxity and predominantly proximal weakness leading to pronounced head drop in most cases. Clinical course is slowly progressive but can evolve to severe retractions leading to skeletal deformations.

Usual cardiomyopathy and respiratory failure are observed and central nervous system involvement in the most severe cases [148]. Histological markers of CMD include abnormal variation of fiber size associated with split fibers, and in some cases with hypercontracted fibers, nuclei internalization and increase of connective and adipose tissue [148]. One of the most common CMD is **merosin-deficient-CMD** caused by mutations in the *LAMA2* gene encoding **laminin- α 2 chain (merosin)** an extracellular matrix protein, major component of the basement membrane whose main function is link the extracellular matrix to the DGC. Mutations in *LAMA2* can result in a total or partial reduction of the protein levels, being the first cases more severe exhibiting progressive respiratory insufficiency, brain involvement and white matter abnormalities [149].

Other common forms of CMD are those related with defects in one of the three genes encoding **collagen 6A** (*COL6A1*, *COL6A2*, *COL6A3*). Collagen 6A is an important component of the extracellular matrix which forms a microfibrillar network that anchors the surface of cells with the interstitial connective tissue playing an important role in mediating cell matrix interactions due to its association with several matrix proteins [150]. Mutations in *COL6A* genes can cause three muscular disorders: **Ulrich-CMD**, **Bethlem myopathy**, and **mysclerosis myopathy**. Ullrich-CMD is a severe syndrome with neonatal onset that presents with hyperlaxity associated with proximal contractures in the spine (kyphosis), elbows, and knees and congenital hip dislocation. Children may never walk or walk and then lose this ability by the end of the first decade due to the progression of contractures and weakness. Respiratory function progressively declines over time leading to night-time respiratory failure and death [151]. Bethlem myopathy is a milder form with autosomal-dominant inheritance characterized by slowly progressive muscle weakness and wasting, distal hyperlaxity, and joint contractures and some patients exhibiting respiratory failures [153]. Mysclerosis myopathy is a rarest form of the disease with autosomal-recessive inheritance characterized by toe walking and calf contractures in childhood, and progressive contractures of all joints in the adult life [151].

Another severe form of CMD is the **Walker-Warburg syndrome**, a “dystroglycanopathy” mainly caused by recessive mutations in *POMT1* and *POMT2* [152]. It manifests with a dystrophic phenotype accompanied by retinal and brain malformations with most of the syndromic children dying in the first 3 years of life due to respiratory failure, seizures, hyperthermia, and ventricular fibrillation [153].

6.4. Facioscapulohumeral muscular dystrophy (FSHD)

FSHD is one of the most prevalent adult muscular dystrophies with an estimated incidence of 1:8000 live births worldwide [154]. It presents with slowly progressive asymmetric and descending weakness, initially affecting face (facio), scapula (scapulo), and upper arms (humeral), followed by weakness of the distal lower extremities and pelvic girdle [155]. Symptoms typically begin during the first or second decade of life [155]. There are no FSHD-specific histopathological markers in biopsy examination but dystrophic features such as fibrosis, muscle fiber hypertrophy, and central nucleation are present. Endomysial inflammation can be observed in up to one-third of FSDH biopsies [156]. Ninety-five percent of cases are inherited in an autosomal-dominant way and associated with a deletion of a key number of D4Z4 macrosatellite repeats in the 4q35 subtelomeric region in the chromosome 4 (**FSHD1**).

The remaining 5% cases (**FSHD2**) have no deletion on chromosome 4q35 and have a variable inheritance pattern [155]. Loss of the D4Z4 repetitive elements leads to decreased methylation and opening up of the chromatin structure, allowing the expression of the *DUX4* gene encoding *double homeobox 4*, a normally repressed transcriptional regulator. As reported by Lemmers and collaborators in 2010, the existence of single nucleotide polymorphisms in the region distal to the last D4Z4 repeat appears to create a poly-adenylation site that activates *DUX4*, leading to a “toxic gain of function” that cause FSHD1 disease [157]. In FSHD2 no deletions, but yet loss of methylation in the D4Z4 region of chromosome 4q35 also lead to *DUX4* abnormal expression [158] suggesting a common pathological mechanism in both FSHD.

6.5. Emery-Dreifuss muscular dystrophy

Emery-Dreifuss muscular dystrophy (EDMD) is an early-onset skeletal myopathy characterized by slowly progressive muscular weakness, joint contractures, spine rigidity, and heart disease [159]. Different types have been described, distinguished by their inheritance pattern in X-linked, autosomal-dominant, and autosomal-recessive forms. Overall prevalence of EDMD is unknown, although X-linked appear to be the most prevalent form affecting an estimated of 1:100,000 individuals [159]. EDMD is classified as a “laminopathy” caused mainly by mutations in the *EMD* gene encoding **emerin** and in the *LMNA* gene encoding **lamin A/C**. While *EMD* mutations associate to the X-linked form of EDMD, *LMNA* mutations are responsible for most of the autosomal cases [159]. Emerin and lamin A/C are important components of the nuclear envelope and defects in these genes could impair diverse functions including gene expression, cell signaling, nuclear structure and chromatin architecture [159, 160]. There are no clear histological markers in EDMD, but dystrophic features such as fiber size disproportion, nuclei internalization, increase of endomysial connective tissue, necrosis, and regeneration are usually observed (**Figure 1**). A reduced expression of emerin or lamin A/C in muscle tissue, fibroblasts or blood can usually confirm the diagnosis of EDMD [161].

7. Conclusions

An incredible large spectrum of hereditary myopathies has been described at date and only some of them have been commented in this chapter. Although hereditary myopathies are cataloged as “rare diseases” due to their relatively low prevalence, the sum of the different forms of hereditary myopathies makes these a relatively common health problem that affect the life quality of patients with complications that can lead to death in the most severe cases. Thanks to the improvement of technology, in the last decade, it has been possible to know a still growing number of genes causative of hereditary myopathies, which contributes to the classification and diagnosis of these disorders. Because defects in the same gene can be the cause of various hereditary myopathies and because the same myopathic phenotype can derive from mutations in different related genes, it is important to know and understand all aspects of the disease to give a successful diagnosis and an adequate management of the symptomatology.

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