HHS Public Access

Author manuscript

Curr Neurol Neurosci Rep. Author manuscript; available in PMC 2015 July 05.

Published in final edited form as:

Curr Neurol Neurosci Rep. 2012 April ; 12(2): 165–174. doi:10.1007/s11910-012-0255-x.

Congenital Myopathies: An Update

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Abstract

Congenital myopathy is a clinicopathological concept of characteristic histopathological findings on muscle biopsy in a patient with early-onset weakness. Three main categories are recognized within the classical congenital myopathies: nemaline myopathy, core myopathy, and centronuclear myopathy. Recent evidence of overlapping clinical and histological features between the classical forms and their different genetic entities suggests that there may be shared pathomechanisms between the congenital myopathies. Animal models, especially mouse and zebrafish, have been especially helpful in elucidating such pathomechanisms associated with the congenital myopathies and provide models in which future therapies can be investigated.

Keywords

Congenital myopathy; Nemaline rod myopathy; Core myopathy; Central core disease; Multiminicore disease; Centronuclear myopathy; ACTA1; NEB; TMP2; TPM3; TNNT1; Cofilin 2; KTBDB13; RYR1; SEPN1; MTM1; DNM2; BIN1

Introduction

The diagnosis of a congenital myopathy involves a constellation of clinicopathological features typically involving a patient with early-onset weakness together with characteristic histopathological findings on muscle biopsy and normal to slightly elevated creatine

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Disclosure No potential conflicts of interest relevant to this article were reported.

phosphokinase levels. Involvement of the extraocular and/or facial musculature is also common. The three main clinicopathologically defined categories of classical congenital myopathies are nemaline myopathies (NMs), core myopathy, and centronuclear myopathy (CNM). Recent findings suggest that the congenital myopathies are a more diverse group of disorders with varied but overlapping clinical and histologic phenotypes, showing more similarities than anticipated. Increasing evidence suggests that some of the histological features on muscle biopsies can occur on a spectrum that crosses the boundaries of individual genetic entities. Animal models have been especially helpful in elucidating the pathomechanisms of the congenital myopathies. Recent advances suggest that abnormal excitation-contraction coupling may be a common theme in the congenital myopathies, either as a result of malformed contractile filaments in the case of the NMs or disruption of calcium homeostasis at the level of the triad (the smallest functional component of the myofiber that includes the T-tubule and sarcoplasmic reticulum [SR]) in the case of the centronuclear/myotubular and core myopathies.

This review discusses advances leading to this expanded picture of congenital myopathies over the past 3 years, with an emphasis on emerging clinical and histologic phenotypes and genotype-phenotype relationships. We focus on the most common histologic types of congenital myopathies (nemaline, core, and centronuclear), and highlight the broadening spectra of genotypes and overlapping histological phenotypes within each category. We also discuss the recent relevant developments of animal models for elucidating disease mechanisms and preclinical therapeutic possibilities.

Congenital Myopathies with Rods

In biopsies from patients with NM, the muscle cells contain typical rod-like accumulations of Z-disk–derived material [1]. Rods typically are found in the sarcoplasm but may also be intranuclear [2]. Rod formation has been associated with mutations in skeletal muscle α-actin (*ACTA1*) [3], nebulin (*NEB*) [4], tropomyosin 3 (*TPM3*) [5], tropomyosin 2 (*TPM2*) [6], troponin T1 (*TNNT1*) [7], cofilin (*CLF2*) [8], and, most recently, a member of the BTB/Kelch family of proteins (*KBTBD13*) (Table 1) [9••].

Clinically, the NMs are subclassified into severe congenital, intermediate congenital, typical congenital, childhood-onset, and adult-onset forms [10]. The typical presentation consists of proximal weakness, respiratory insufficiency, and prominent facial weakness, most often sparing of the extraocular muscles [10]. The clinical phenotype associated with intranuclear rods may be more severe than that associated with sarcoplasmic rods [11•]. Patients with nebulin-related NM may have distal predominant weakness [12]. Also, some of the genes associated with NM have been associated with distal arthrogryposis (*TPM2* [13], *NEB* [14], and *TPM3* [15]). There is no association between clinical severity and the number of rods observed in a biopsy [16].

The disease genes associated with NM encode components of the thin filament part of the contractile apparatus, and NMs are thus considered diseases of the thin filament. Overall, they represent diseases in which mutations disrupt the ability of the myofiber to generate adequate force during contraction. While numerous studies have supported these

conclusions, the most comprehensive data are provided from recent discoveries in *ACTA1*-related and *NEB*-related congenital myopathies (see below).

ACTA1-Related Myopathies

Mutations in skeletal muscle α-actin cause primarily sporadic autosomal-dominant NM, and are associated with a range of congenital myopathies that additionally include congenital fiber-type disproportion (CFTD) and core-rod, cap, and zebra body myopathies [3, 11•]. ACTA1 is the primary protein component that polymerizes to form the thin filaments in the functioning myotube [3].

Attempts to establish consistent genotype-phenotype correlations in *ACTA1*-related myopathies have been largely inconclusive, and mutations associated with classic NM are scattered throughout the gene [11•]. While there is no consistent relationship between the location of *ACTA1* mutations and the severity of disease [11•, 17, 18], there is some recent evidence suggesting that mutation location is correlated with histopathological appearance. *ACTA1* mutations have been associated with both cytoplasmic and intranuclear rods [11•, 19], while intranuclear rods are most often associated with mutations of p.Val165 [11•]. Mutations that cause CFTD are preferentially found within tropomyosin-interacting sites on the surface of the protein [20]. This is an interesting relationship, given that *TPM3* mutations appear to cause CTFD more commonly than NM [20].

Acta1 transgenic and knock-in mouse models have provided a means for gaining further insight into pathophysiology and possible treatments of *ACTA1*-related myopathies. Transgenic mouse models of dominant *ACTA1* mutations show that, as in human disease, increased disease severity is associated with decreased levels of functional protein [21••]. Studies of overexpression of alternate actin isoforms in *Acta1* knockout mice show that cardiac actin [22] but not cytosolic actin [23] is capable of improving the functional phenotype of the *Acta1* knockout mice. Because of an observed association of muscle hypertrophy with milder disease, *Acta1* (His40Tyr) knock-in mice were exposed to hypertrophy-promoting factors (FHL1 and IGF1) and this resulted in increased body weight, improved mobility, and decreased rod pathology [20]. Based on suggestive data from a small clinical cohort study [24], Nguyen et al. [25] examined the effect of L-tyrosine administration to the same knock-in mouse model. Promisingly, the L-tyrosine treatment resulted in improved mobility and decreased rod pathology on muscle biopsy.

NEB-Associated Myopathies

Mutation in the nebulin gene causes recessively inherited NM [4]. Other than mode of inheritance, *NEB*-related NM is difficult to distinguish from other rod myopathies. While thigh muscle groups are diffusely affected in *ACTA1*-related myopathies, they are relatively spared in *NEB*-related myopathy [26]. Muscle MRI shows more prominent involvement in the distal lower leg muscles in these patients, especially in the ankle dorsiflexors [26]. There is also evidence for histological overlap between *NEB*-related myopathy and core myopathy, as a patient with *NEB* mutations was discovered to have core-rod myopathy [27••]. However, the m pattern was similar to that observed in patients with *NEB*-related NM as opposed to patients with core myopathy alone [27••].

Studies of myocytes in vitro and vertebrate models provide further insights into the molecular mechanism underlying weakness in *NEB*-associated myopathy. Quantification of nebulin expression in patient biopsies reveals a possible correlation between the quantity of nebulin expression and the severity of disease [14]. Studies of myotubes in vitro suggest that nebulin plays an important role in mediation of actin filament stability [28]. In *Neb* knockout mice, nebulin-deficient myofibers have decreased thin filament length and decreased generation of maximal tension in the setting of supramaximal calcium levels [29–31]. These findings are in keeping with what has been observed in patient myofibers [32•, 33]. A recently described zebrafish mutant with a recessive *nebulin* mutation shares the common features observed in both the mouse models of nebulin and patient-derived myotubes [34]. Thus, it seems that nebulin absence/deficiency leads to shortened thin filaments resulting in defective cross-bridge kinetics and submaximal force generation during muscle contraction.

Other Rod Myopathies

Recent discoveries of two new genes causing NM highlight an expanding understanding of the overlap between different histological subtypes within the congenital myopathies. The most recent genetic discovery in NM are mutations in *KBTBD13* causing a dominant rod myopathy with cores [9••], referred to as NM type 6. This myopathy is characterized by childhood-onset of slowly progressive weakness of neck and proximal muscle groups, and a slowness of movement that is not common in other congenital myopathies [35]. This slowness of movement, together with core-like structures, may represent a sign of abnormal excitation-contraction coupling. Muscle biopsies show softly defined core areas referred to as “pseudocores” [35], distinct from the sharply demarcated core structures observed in *RYR1* mutations [36, 37] and *NEB* mutations [27••]. The exact role of *KBTBD13* is unknown, but other BTB/Kelch family proteins are involved in regulation of cytoskeleton remodeling, gene transcription, and myofiber assembly [9••].

Mutations in the cofilin gene cause a recessive myopathy with both minicores and rods [8]. The *CFL2* gene encodes a protein that influences actin dynamics though interaction with tropomyosin [38]. Two siblings were described with hypotonia at birth, delayed motor milestones, and inability to run [8]. In contrast to classical NM, these patients have no involvement of facial muscles or distal leg weakness [8].

Together, the identification of *CFL2* and *KBTBD13* mutations in rod myopathy with cores underscores the growing and overlapping list of gene mutations associated with both cores and rods. This list additionally includes *ACTA1* [39], *NEB* [27••], and *RYR1* [36, 37, 40], and suggests the possibility of shared pathomechanisms between the rod and core myopathies. The common pathomechanisms are unknown at this time, but may represent defects in excitation-contraction coupling.

Myopathies with Cores

The core myopathies are characterized by the histopathological finding of areas lacking histochemical oxidative and glycolytic enzymatic activity reflecting an absence of mitochondria [41, 42]. Cores are called unstructured if they contain accumulations of disorganized myofibrillar material. They are referred to as either central cores (running the

length of the myofiber) or minicores (short zones of myofibrillar disorganization that are wider then they are long on a longitudinal section) [41, 42]. Based on these features, patients with core myopathy are traditionally subclassified as having either central core disease (CCD) or multiminicore disease, although this distinction may sometimes be blurred. Clinically, these myopathies manifest with proximal muscle weakness with onset congenitally, in infancy, or in early childhood [43, 44]. Less commonly, there may be bulbar and facial weakness [44]. Core myopathy is thought to be the most common congenital myopathy [45•], but may still be under-recognized because the characteristic histopathological changes may not be present on biopsies at an early age. The genes associated with core myopathies are presented in Table 1.

RYR1-Related Core Myopathies

Myopathies with cores are most commonly associated with mutations in the *RYR1* gene [46], which encodes the skeletal muscle ryanodine receptor. RyR1 is a ligand-gated calcium channel located on the SR, where it functions as a critical regulator of calcium homeostasis and as the channel required for excitation-dependent calcium release during excitation-contraction coupling. Central cores related to *RYR1* mutations are usually identified in type I fibers and the muscle biopsy often shows significant fibroadipose tissue [47]. RYR1 related cores may be described as structured or unstructured depending on the pattern of ATPase activity and the degree of myofibrillary disorganization demonstrated by electron microscopy [44].

Core myopathies caused by *RYR1* mutations can be dominant or recessive. Autosomal-dominant and de novo mutations are usually associated with CCD, and characterized clinically by infantile-onset of static or slowly progressive proximal weakness involving hip and axial muscles [44]. Skeletal deformities are common and may include hip dislocation and foot deformities [48]. Bulbar weakness and respiratory compromise are rare features [38]. Of note, there is a wide range of clinical presentations, especially in relation to age of onset [49].

Historically, dominantly acting mutations in the *RYR1* gene causing core myopathies localized more commonly to the C-terminal domain of the gene, which encodes the transmembrane and luminal portion of the channel [46], while *RYR1* mutations causing malignant hyperthermia (MH) were usually located in the N-terminal and central regions of protein [50]. However, while this genotype-phenotype correlation still holds true for MH, recent data suggest that dominant CCD mutations in *RYR1* span the length of the gene [49]. Of note, de novo dominant mutations have also been described in individuals with core-rod myopathy [40].

Mutations causing recessive *RYR1*-related myopathy appear to be distributed over the entire sequence of the *RYR1* gene [51]. Histologically, recessive *RYR1* mutations are often associated with multiminicores, which are shorter than classical central cores, lack myofibrillary organization, and are seen in both type I and type II muscle fibers [51, 52]. Recessive mutations are also seen with other histological findings including central nuclei and CFTD [53••, 54].

Recently, Wilmshurst et al. [53••] described a series of 17 patients with *RYR1* mutations and central nuclei on muscle biopsy. Inheritance was autosomal recessive in the majority of patients. There was early infantile presentation with hypotonia and weakness followed by progressive clinical improvement. Extraocular eye muscle involvement was also a prominent feature. Muscle biopsies from all of the patients manifested nuclear centralization/internalization without the presence of central cores commonly associated with *RYR1* mutations. Interestingly, two-thirds of patients demonstrated central cores or minicores on biopsies performed later in life [53••]. An additional seven patients with *RYR1*-related myopathy were described with prominent central nuclei on histopathology [55•]. These patients, particularly those biopsied at older ages, also demonstrated large areas of sarcomeric disorganization on muscle biopsy [55•]. Thus, cores or other core-like areas may develop over time in patients with *RYR1*-related CNM, emphasizing yet another histopathological continuum.

Histological findings may also depend on the muscle sampled, as there is evidence for striking differential muscle involvement in the *RYR1*-related myopathies. Muscle MRI showed relative sparing of the rectus femoris regardless of mode of inheritance and histopathologic subtype [56], and may represent a tool for early diagnosis of myopathies related to *RYR1* mutations. Additional evidence suggests that the gradient of distribution and severity of muscle involvement on muscle MRI may be helpful in differentiating dominant *RYR1*-related disease from recessive RYR1-related disease without ophthalmoparesis [57].

RYR1-related myopathies are thought to result from abnormal excitation-contraction coupling secondary to impaired calcium release in the setting of a defective ryanodine receptor calcium channel. How this defect is related to the histological development of core structures remains unclear. The development of cores was recently studied in an $Ryr1^{Y522S/WT}$ mouse model with MH and mild core myopathy [58]. This mouse had progressive core development with localized mitochondrial damage and subsequent disruption of nearby SR and T-tubule structures, followed by development of early cores with absent mitochondria and shortened sarcomeres [58]. Disruption of the T-tubule system is commonly observed in both core myopathies and centronuclear/myotubular myopathies, which may explain why both cores and central nuclei may be observed in patients with *RYR1* mutations [53••, 58].

A second knock-in mouse models the common and clinically severe CCD mutation p.Ile4898Thr [59•]. Histologically, the diseased mouse muscle undergoes transition from minicores to central cores and rods [59•]. Interestingly, this mutation was recently observed in patients with severe core-rod myopathy [40]. Therefore, additional study of this model may provide key insight into overlap between rod and core myopathies.

SEPN1-Related Core Myopathies

SEPN1 encodes selenoprotein N1, a member of the selenocysteine-containing protein family, which may play a role in intracellular calcium homeostasis and protection against redox-related cellular damage [60]. *SEPN1* gene mutations are associated with multiminicores, which are typically smaller in size than those associated with recessive *RYR1* mutations [47], although there is a large histological spectrum associated with *SEPN1*

mutations that also includes nonspecific myopathic changes, CFTD, and Mallory body-like inclusions [61, 62]. Scoto et al. [63] describe a large case series of patients with *SEPN1*-related myopathies. Clinically, patients with *SEPN1*-related disease manifest with a predominantly axial myopathy with weak neck flexors, spinal rigidity, and scoliosis, as well as prominent respiratory compromise disproportionate to their extremity weakness. The respiratory compromise may be progressive even while limb weakness remains relatively mild and static. The majority of these patients achieve and maintain independent ambulation. Bulbar weakness is reported while extraocular muscle involvement does not seem to occur [63]. There is no relationship between morphological pattern of minicores and the type or localization of *SEPN1* mutations [64].

Studies in zebrafish and human muscle demonstrate that SepN1 interacts closely with the RyR1and is thereby involved in the regulation of intracellular calcium homeostasis [65]. A mouse *Sepn1* knockout model, while not expressly recapitulating the weakness and histopathology of the human disease, is likely to provide a system for further exploration of the pathogenesis of *SEPN1* mutations [66].

Myopathies with Central Nuclei

CNMs are characterized by excessive internalized/centralized nuclei within myofibers on muscle biopsy without prominent findings of degeneration or regeneration. There may be abnormal patterns on NADH-TR staining, which can be helpful in differentiating different subtypes of CNM. Clinically, the age of onset and pattern of weakness vary depending on the gene involved and the specific mutation. As with the congenital myopathies discussed earlier, there is increasing evidence of histological overlap and recent studies in animal models that have helped to clarify the underlying molecular mechanisms. Genes associated with CNM are summarized in Table 1.

MTM1-Related Centronuclear Myopathy

X-linked CNM or myotubular myopathy is caused by a mutation in the *MTM1* gene coding for myotubularin, a member of the phosphoinositide phosphatase protein family [67]. Phosphoinositides and their regulatory enzymes are primarily involved in the trafficking of membranes and vesicles between subcellular organelle membranes [68].

Myotubular myopathy most commonly presents with severe symptoms starting from birth [69]. Affected male neonates are profoundly hypotonic and weak with significant respiratory failure and feeding problems, often resulting in early mortality. External ophthalmoplegia is common, although it may not be noticeable at birth [69]. Surviving individuals have significant morbidity, including lifelong wheelchair and ventilator dependence. A minority of boys with *MTM1* mutations have a more mild clinical presentation [69]. Mutations are found throughout the gene, and there is limited correlation between genotype and phenotype [70]. However, a few mutations have been observed to cause milder symptomatology [70, 71]. Female carriers are usually asymptomatic, although there are rare reports of unfavorably skewed X-inactivation leading to a severe infantile form [72] or a mild adult-onset form in females [73].

The histopathology of myotubular myopathy has been reviewed by Romero [74]. Myofibers show single, very central nuclei within round fibers, often with a dark central region surrounded by a pale peripheral halo on NADH-TR staining [74]. In muscles of patients with the milder and more slowly progressive forms of *MTM1*-associated myopathy, necklace fibers, which appear as a basophilic ring of internalized, but not necessarily centralized, nuclei aligned beneath the sarcolemma, are a fairly distinct feature [75•].

Recent advances from the study of animal models for myotubular myopathy have provided insight into the molecular mechanism of the disease and have opened avenues for the development of effective treatments. A zebrafish model of myotubular myopathy recapitulated the salient aspects of the human disease and, importantly, identified structural and functional abnormalities in the T-tubule/terminal SR (triad) system [76••]. This study additionally uncovered triad abnormalities in biopsies from patients with *MTM1* mutations. Subsequently, the observations of structural and functional abnormalities in the triad, including defective excitation-contraction coupling and altered calcium homeostasis, have been demonstrated and expanded upon in both murine and canine models of myotubular myopathy [64, 77, 78, 79••]. These studies have led to a conclusion that a major aspect of disease from *MTM1* mutations is due to abnormalities in the excitation-contraction coupling machinery. This pathology is likely caused by the loss of myotubularin function at the triad, as several studies have demonstrated its localization to this structure, although the exact pathomechanisms are still under investigation [64, 76••, 78].

Additional studies using the murine knockout model and the zebrafish model of myotubular myopathy have suggested new avenues for therapy development. Buj-Bello et al. [78] have successfully demonstrated rescue of both histopathologic abnormalities as well as muscle functional properties by adeno-associated virus-mediated re-expression of *MTM1*, revealing the potential efficacy of gene therapy for the disease. A separate study by Lawlor et al. [80] showed that treatment with an activin inhibitor improves muscle strength and prolongs lifespan of the *Mtm1* knockout mice. Lastly, exposure of the zebrafish myotubular myopathy model to an acetylcholinesterase inhibitor resulted in significantly improved movement [81••]. This, in combination with a case report describing clinical features of a neuromuscular disorder and qualitative improvement with pyridostigmine in a patient with myotubular myopathy [81••], suggests that augmentation of neuromuscular junction function may be an additional viable treatment strategy.

DMN2-Related Centronuclear Myopathy

A subset of individuals with dominant CNM possess mutations in the *DNM2* gene [82]. *DNM2* encodes the dynamin-2 protein, a large GTPase involved in membrane traffic, endocytosis, and interaction with the actin and microtubule filamentous networks [83]. Clinical forms of *DNM2*-related CNM range between mild onset in late childhood or adulthood and severe, early onset [82, 84–86]. Characteristic muscle involvement includes facial and extraocular muscle weakness, and ptosis is frequently present [87]. Extremity weakness is often diffuse, although MRI studies show more prominent involvement of the distal limbs in many patients [88, 89]. In terms of genotype-phenotype correlations, mutations causing severe disease are most commonly found in the pleckstrin-homology and

GTPase effector domains, while more mild disease is associated with middle domain mutations [90].

The characteristic pathology of *DMN2*-related myopathy has also been reviewed by Romero [74]. Muscle fibers demonstrate nuclear centralization and, to a lesser degree, nuclear internalization. A characteristic histopathological feature of *DNM2* mutations is strands radiating from the central nucleus, which are identified with NADH-TR staining on transverse sections. Type I myofiber predominance and hypotrophy are also commonly observed.

Although the specific pathomechanisms underlying *DNM2*-related CNM are still unknown, recent studies have provided insight into the molecular basis of the disease. Two in vitro studies found that CNM-causing mutations can increase Dyn2 GTPase activity and alter the self-assembly properties of Dyn2 polymers [91, 92]. In a knock-in mouse model of *DNM2*-related CNM, subtle alterations in triad organization were reported and there was a significant increase in basal cytosolic calcium [93]. Similarly, Cowling et al. [94] showed that viral overexpression of mutant *Dyn2* in mouse muscle causes substantial T-tubule disorganization resembling the changes seen in models of myotubular myopathy. Unlike MTM1, Dyn2 does not appear to localize to the triad [93, 94], and the relationship between Dyn2 function and triad architecture is still unclear.

BIN1-Related Centronuclear Myopathy

Amphiphysin 2-related CNM is a comparatively rare form of CNM. It is associated with mutations in the *BIN1* gene encoding the protein amphiphysin 2, which binds to DNM2 during clathrin-mediated endocytosis [95]. Clinical features include marked facial weakness, prominent masticatory weakness, external ophthalmoplegia, ptosis, and proximal muscle weakness [96].

Several studies have shown that a muscle-specific iso-form of amphiphysin 2 is important for T-tubule biogenesis [97, 98]. In the initial characterization of *BIN1*-related CNM, Nicot et al. [99] demonstrated that expression of mutant protein disrupted tubule formation in an ex vivo model of T-tubule biogenesis. Amphiphysin 2 localization and triad architecture have been shown to be altered in muscle from patients with *MTM1*, *DNM2*, and *BIN1* mutations, as well as the mouse knockout model for *Mtm1* [100••]. Thus, a potential common mechanism emerges with the known genetic causes of CNM involved in the disruption of triad formation and thus the mediation of excitation-contraction coupling. This then also establishes a pathophysiological link between the centronuclear and core myopathies that is reflected in the shared histological features seen in some RYR1-related myopathies.

Conclusions

Congenital myopathies are a group of muscle disorders largely defined by their histopathological appearance, but more recently have been expanded to include varied and overlapping phenotypes as well as genotypes where a single histological appearance can be caused by mutations in multiple genes and mutations in a single gene can result in multiple

phenotypic and histological presentations. In addition, distinct histopathological features, once thought to be defining for a given subtype, can be observed in the same patient associated with variable genetic diagnoses. These overlapping histopathological features reinforce the concept of overlapping pathophysiological mechanisms. Disruption of excitation-contraction coupling and control of the skeletal muscle contractile apparatus are now emerging as the most important pathophysiological consequences in the majority of the common subtypes. Animal models, especially zebra-fish and mouse knockout models, have been crucial in generating this broader understanding of the molecular pathophysiology and will provide excellent models for understanding more about genotype-phenotype relationships and the development of new treatments.

Acknowledgments

CGB's research is supported by the Intramural Research Program of the National Institute of Neurological Disorders and Stroke, National Institutes of Health, JD is supported by an NIH K08 award (NIH1K08AR054835). We apologize to researchers whose work could not be cited due to this reviews restrictions in length and focus.

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Table 1

Genes associated with congenital myopathies

Myopathy		Inheritance	Gene	Protein	Suspected protein function	Associated histologies	Vertebrate models
Nemaline rod myopathy		De novo/ dominant, rarely recessive	*ACTA-1* [101]	Skeletal muscle α-actin	Primary protein of thin filament	Sarcoplasmic rods Intranuclear rods CFTD Caps Zebra bodies Cores and rods	Mouse: Tg*Acta1(D286G)* [21••], KI *Acta1(H40Y)* [25], Knockout [22]
		AR	*NEB* [101]	Nebulin	Actin-binding protein, regulates thin filament length	Sarcoplasmic rods Cores and rods	Mouse: Knockout [29–31] Zebrafish: *neb* [34]
		AR or AD	*TPM3* [101]	Tropomyosin 3	Actin-binding protein, involved in cross-bridging	Sarcoplasmic rods CFTD	Mouse: Tg*Tpm3(M9R)* [105]
		AD	*TPM2* [101]	β-Tropomyosin 2	Actin-binding protein, involved in cross-bridging	Sarcoplasmic rods Caps	
		AR	*TNNT1* [101]	Slow skeletal muscle troponin	Actin-binding protein, involved in cross-bridging	Sarcoplasmic rods	
		AR	*CFL2* [101]	Cofilin 2	Tropomyosin-binding protein	Cores and rods	
		AD	*KBTBD13* [9••]	BTB/Kelch family member	Cytoskeleton modulation, myofibril assembly	Cores and rods	
Core myopathy	Central core disease	AD	*RYR1* [102]	Ryanodine receptor 1	Skeletal muscle sarcoplasmic reticulum calcium channel	Central cores Central nuclei Cores and rods	Mouse: KI*Ryr1(Y522S)* [58], KI*Ryr1(I4895T)* [59•]
		AR	*RYR1* [102]	Ryanodine receptor 1	Skeletal muscle sarcoplasmic reticulum calcium channel	Central cores Central nuclei Central nuclei and cores CFTD	
	Minicore disease	AR	*SEPN1* [102]	Selenoprotein N1	Selenocysteine-containing protein	Multiminicores	Mouse: Knockout [66] Zebrafish: *sepN* [65]
		AR	*RYR1* [102]	Ryanodine receptor 1	Skeletal muscle sarcoplasmic reticulum calcium channel	Minicores and central nuclei	Zebrafish: *ryr* [106]
Centronuclear myopathy		X-linked	*MTM1* [103]	Myotubularin	Phosphoinositide phosphatase	Central nuclei	Mouse: Knockout [78, 79••, 80••] Zebrafish: Knockdown [76] Canine: Spontaneous [77]
		AD	*DNM2* [104]	Dynamin 2	Protein GTPase	Central nuclei	Mouse: KIDnm2(R465W) [93]
		AR	*BIN2* [104]	Amphiphysin	BAR domain protein, regulates T-tubule biogenesis	Central nuclei	
		AR	*RYR1* [102]	Ryanodine receptor 1	Skeletal muscle sarcoplasmic reticulum calcium channel	Central nuclei	

AD autosomal dominant; *AR* autosomal recessive; *CFTD* congenital fiber-type disproportion.