



King's Research Portal

DOI:

[10.1038/nrneurol.2017.191](https://doi.org/10.1038/nrneurol.2017.191)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Jungbluth, H., Treves, S., Zorzato, F., Sarkozy, A., Ochala, J., Sewry, C., Phadke, R., Gautel, M., & Muntoni, F. (2018). Congenital myopathies: Disorders of excitation-contraction coupling and muscle contraction. *Nature Reviews Neurology*, 14(3), 151-167. <https://doi.org/10.1038/nrneurol.2017.191>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Heinz Jungbluth¹⁻³, Susan Treves⁴⁻⁵, Francesco Zorzato⁴⁻⁵, Anna Sarkozy⁶, Julien Ochala⁷,
Caroline Sewry⁶, Rahul Phadke⁶, Mathias Gautel², Francesco Muntoni⁶

The congenital myopathies – inherited disorders of excitation-contraction coupling and muscle contraction

¹Department of Paediatric Neurology, Neuromuscular Service, Evelina's Children Hospital, Guy's & St. Thomas' Hospital NHS Foundation Trust, London, UK; ²Randall Division of Cell and Molecular Biophysics, Muscle Signalling Section, and; ³Department of Clinical and Basic Neuroscience, IoPPN, King's College, London, UK; ⁴Departments of Anesthesia and Biomedicine Basel University and Basel University Hospital, Hebelstrasse 20, 4031 Basel, Switzerland; ⁵Department of Life Sciences, General Pathology section, University of Ferrara, Via Borsari 46, 44100 Ferrara, Italy; ⁶The Dubowitz Neuromuscular Centre, Developmental Neurosciences Programme, UCL Great Ormond Street Institute of Child Health & Great Ormond Street Hospital for Children, 30 Guilford Street, London, WC1N 1EH, United Kingdom; ⁷Centre of Human and Aerospace Physiological Sciences, Faculty of Life Science and Medicine, King's College, London, UK

Address for correspondence:

Prof Francesco Muntoni,
Dubowitz Neuromuscular Centre,
UCL Great Ormond Street Institute of Child Health,
30 Guilford Street,
London WC1N 1EH
United Kingdom

ABSTRACT

The congenital myopathies (CMs) are a group of early-onset, non-dystrophic neuromuscular conditions with characteristic muscle biopsy findings, variable severity and a stable or slowly progressive course. Muscle weakness pronounced in axial and proximal muscle groups is common, whereas the degree of extraocular muscle weakness, cardiorespiratory and distal muscle involvement may implicate specific genes. Based on the predominant muscle biopsy finding, Central Core Disease (CCD), Multi-minicore Disease (MmD), Centronuclear Myopathy (CNM) and Nemaline Myopathy (NM) were the main CMs to be originally reported and still represent the major diagnostic categories. Mutations in more than 20 genes have been identified to date, encoding proteins implicated in skeletal muscle calcium homeostasis, excitation-contraction coupling (ECC), thin/thick filament assembly and interactions, and other mechanisms. Mutations in the skeletal muscle ryanodine receptor (*RYR1*) gene are the most frequent genetic cause, and CCD and MmD (the “core myopathies”) are the most common subgroups. Widespread introduction of next generation sequencing (NGS) has vastly improved mutation detection in large genes such as *RYR1*, nebulin (*NEB*) and titin (*TTN*), and identified novel genetic backgrounds. There is an increasing recognition that the originally described entities represent a partially skewed selection of a much wider phenotypical spectrum, as many patients may show only subtle, non-specific or multiple histopathological features, evading easy categorization. Most of the principal mechanisms have been largely resolved, but the etiology of the pathognomic histopathological features and secondary effects on muscle growth and atrophy pathways remain only poorly understood. Whilst so far management has been mainly supportive, therapy development is reaching the clinical trial stage in some conditions.

INTRODUCTION

The congenital myopathies (CMs) are a genetically heterogeneous group of early-onset muscle conditions characterized by variable degrees of muscle weakness and characteristic structural abnormalities on muscle biopsy. They are almost invariably disorders of disturbed ECC, the process whereby an electrical neuronal impulse is translated into muscle contraction through controlled Ca^{++} release leading to sarcomeric protein activation, or of proteins primarily involved in sarcomeric filament assembly and interaction. Nevertheless, recent findings suggest other less common pathogenic mechanisms. The concept of the CMs was established in the 1950s and 1960s, when the application of histochemical and ultrastructural techniques to diseased muscle identified histopathological features considered to be pathognomonic at the time. Recognition of these features – central cores, multi-minicores, central nuclei, nemaline rods – resulted in the designation of novel disease entities – Central Core Disease (CCD) ¹, Multi-minicore Disease (MmD) ², Centronuclear Myopathy (CNM) ³ and Nemaline Myopathy (NM) ⁴ – that still represent the major diagnostic categories.

Considerable progress has been made concerning the understanding of the phenotypical spectrum, diagnosis and management of the CMs. In addition to primary myopathic features, non-neuromuscular manifestations are observed in several forms, pointing to a role of the defective proteins in non-skeletal muscle tissues ⁵. Muscle imaging, in particular muscle magnetic resonance imaging (MRI), has emerged as a powerful tool for deep phenotyping ⁶. Presentations late in adulthood have now been recognized ^{7,8}, and due to improved standards of care, even patients with severe early-onset forms increasingly transition from paediatric to adult neurology services.

Since the identification of dominant mutations in the skeletal muscle ryanodine receptor (*RYR1*) gene as the cause of Malignant Hyperthermia (MH) in 1991 and CCD in 1993^{9,10}, mutations in more than 20 genes have been identified. Introduction of next generation sequencing (NGS) techniques into routine clinical diagnosis¹¹ has resulted in an improved detection rate of mutations in genes such as *RYR1*, nebulin (*NEB*) or titin (*TTN*), due to their sheer size previously only studied with Sanger sequencing in few patients. These novel techniques have led to the recognition that different mutations in the same gene may give rise to variable histopathological phenotypes, whilst mutations in different genes may cause the same histopathological feature, often due to functional association of the defective proteins. Moreover, it has also become increasingly clear that in many CMs, non-specific or a combination of pathological abnormalities rather than a “pure” muscle pathology picture may be found. A classification based on predominant histopathological and associated clinical features is still practically useful; however, it is also helpful to consider these conditions according to the main underlying disease mechanisms.

In the present review, we will summarize genetic, clinical and pathological features of the major CMs. Common pathogenic mechanisms, diagnostic and current management approaches, and principles of therapy development will be outlined.

CLASSIFICATION AND EPIDEMIOLOGY

Data concerning the precise epidemiology of the CMs are limited, and mostly focused on the originally described major pathological variants, CCD, MmD, CNM and NM; the key characteristics of these entities are detailed below and illustrated in Figure 1.

CCD, initially described in the 1950s¹, and MmD² (also often referred to as the “core myopathies”¹²) derive their name from the histochemical appearance of focally reduced

oxidative enzyme activity, corresponding to myofibrillar changes on ultrastructural examination. Centrally located, well-demarcated cores running along a significant extent of the fibre axis on longitudinal sections are characteristic of CCD, whilst multiple cores of less well-defined appearance and of longitudinally more limited extent define MmD.

The hallmark of CNM is fibres with centralized nuclei, which vary in number and in terms of associated features between muscles and genetic backgrounds. NM (for review, ¹³) is characterized by the presence of numerous nemaline rods that stain red on the Gomori trichrome and are confirmed on EM.

The overall prevalence of these CM variants has been estimated at 1 in 26000 ¹⁴. While originally NM was considered the most frequent form, emerging data suggest that CMs with cores (CCD, MmD) are the most common subgroup. Marked genetic heterogeneity is now acknowledged and detailed in the sections on the major diagnostic categories below. In essence, recent data indicate that *RYR1* is the gene most frequently involved in the CMs, in particular CCD and MmD. Recessive *NEB* mutations and (*de novo*) dominant mutations in *ACTA1* encoding skeletal muscle alpha-actin are the most common known causes of NM, whereas X-linked recessive mutations in *MTM1* encoding myotubularin are believed to be the most common cause of CNM. Mutations in *TTN* are increasingly being recognized and may be implicated in a substantial proportion of currently unresolved CMs, as well as other neuromuscular disorders, including muscular dystrophies ¹⁵. The genes implicated in the CMs are listed in Table 1 and the key clinico-pathological features associated with the most common genetic backgrounds are summarized in Table 2. Characteristic histopathological features are illustrated in Figure 1.

CLINICO-PATHOLOGICAL AND GENETIC FEATURES

Congenital myopathies with cores – CCD, MmD and MH

In view of the pathological and genetic overlap, CCD, MmD (also referred to as the “core myopathies”) and MH are discussed here in a single section.

CCD is most closely linked to dominant *RYR1* mutations, whereas MmD is genetically more heterogeneous, mainly due to recessive mutations in *RYR1*¹⁶⁻¹⁸, *SEPN1* encoding selenoprotein N¹⁹ and, less frequently, *MYH7*²⁰. The histopathological appearance of MmD has also been described in some patients with recessive mutations in *MEGF10* encoding multiple epidermal growth factor 10²¹⁻²⁴. (Mini)cores on muscle biopsy may also be prominent in *TTN*-related myopathies²⁵, often in conjunction with other myopathic and dystrophic features, and may also occur in other neuromuscular disorders.

Clinically, CCD due to dominant *RYR1* mutations (for review,¹²) is usually a relatively mild condition, although early severe presentations, often associated with *de novo* inheritance, are on record²⁶. Extraocular muscles are usually spared and facial, bulbar and respiratory involvement is typically mild. Congenital dislocation of the hips (CDH) and scoliosis are common. Most patients achieve independent ambulation and have a static or only slowly progressive course. Clinical features of predominantly recessively inherited MmD (for review¹²), are more variable. *SEPN1*-related myopathies^{19,27} are characterized by marked weakness, early spinal rigidity, scoliosis and respiratory impairment. Recessively inherited *RYR1*-related core myopathies show a distribution of weakness and wasting similar to the *SEPN1*-related form but have additional extraocular muscle involvement and, with few exceptions, lack the severe

respiratory impairment^{17,18}. Variable combinations of scoliosis, spinal rigidity, multiple, mainly distal contractures and an associated cardiomyopathy may occur in *TTN*- and *MYH7*-related forms^{20,25}. *MEGF10*-related myopathies are associated with a very wide spectrum, ranging from a severe early-onset myopathy with areflexia, respiratory distress and dysphagia (termed EMARDD)^{21,23,24} to adult-onset cases with minicores on muscle biopsy²². Muscle MRI may help to differentiate genetically distinct core myopathies^{28,29}.

Dominant *RYR1*-related CCD is allelic to the ***Malignant Hyperthermia Susceptibility (MHS)*** trait, a pharmacogenetic predisposition to MH, a severe adverse reactions to volatile anaesthetics and muscle relaxants (for review,³⁰), with some CCD-associated *RYR1* mutations also carrying an increased MHS risk. The association with recessive *RYR1*-related MmD is less well-established; however, MmD cases due to compound heterozygosity for dominant MHS *RYR1* mutations are on record^{18,31,32}.

RYR1-related ***King-Denborough syndrome (KDS)*** is an MHS-associated myopathy characterized by dysmorphic facial features, short stature, spinal rigidity, scoliosis and variable histopathological features³³. Another recently recognized myopathy with similar clinicopathological features is ***Native American myopathy (NAM)***, originally described in the Lumbee population of North Dakota and due to homozygosity for a founder mutation (p.W284S) in *STAC3*³⁴.

MHS-associated *RYR1* mutations have now also been identified as a common cause of ***exertional myalgia and rhabdomyolysis (ERM)*** in otherwise healthy individuals with variable muscle biopsy findings³⁵. Of note, exertional myalgia may be prominent in CCD³⁶, where mild to moderate CK elevations (up to 1000 IU/l), unusual in the context of other CMs, are also not uncommon. MHS-associated *RYR1* mutations may also give rise to a ***late-onset axial myopathy*** in previously healthy (or even particularly athletic) individuals^{37,38}.

Centronuclear Myopathy (CNM)

CNM (for review, ³⁹) is associated with X-linked recessive mutations in *MTM1* encoding myotubularin (X-linked myotubular myopathy, XLMTM) ⁴⁰, autosomal-dominant mutations in *DNM2* encoding dynamin 2 ⁴¹ and *BINI* encoding amphiphysin 2 ⁴², and autosomal-recessive mutations in *RYR1* ⁴³, *BINI* ⁴⁴, and *TTN* ⁴⁵. Recessive mutations in *SPEG* have been identified in a small number of families ⁴⁶ and dominant mutations in *CCDC78* ⁴⁷ in one isolated pedigree. Heterozygous missense variants in *MTMR14* (or *hJUMPY*) identified in 2 patients with CNM may represent a genetic modifier of other genetic backgrounds ⁴⁸.

In *MTM1*-related cases, the central nuclei are usually spaced down the long fibre axis, whereas in *DNM2*-related cases they may form chains; in the rare *BINI*-related cases, clusters of central nuclei may occur. A typical feature of *MTM1*-related cases is central areas of enhanced oxidative enzyme activity and a pale peripheral halo. This finding and central nuclei are features shared with congenital myotonic dystrophy. Strictly centralized nuclei are more common than multiple internalized nuclei in the *MTM1*-, *DNM2*- and *BINI*-related forms ^{40,41,44}, whereas the opposite applies to *RYR1*- and *TTN*-related cases ⁴³. A radial distribution of sarcoplasmic strands with staining for NADH-TR and PAS is often seen in *DNM2*-related CNM ⁴¹. “Necklace” fibres are often seen in milder *MTM1*-mutated cases or female carriers ⁴⁹, and, occasionally, *DNM2*-related cases ⁵⁰. In most forms, ultrastructural triad abnormalities are observed ⁵¹.

Clinically, extraocular muscle involvement is the most consistent feature in all forms (for review ⁵²) except the *TTN*-, *SPEG*- and *CCDC78*-related form. The most severe form, XLMTM, typically presents in affected males with profound hypotonia, weakness and

contractures at birth, and associated bulbar and respiratory involvement almost always necessitating ventilation for survival. While the provision of constant respiratory support does improve life-expectancy in XLMTM there are recognized complications in some long-term survivors⁵³, probably related to the ubiquitous role of the defective protein. Dominantly inherited CNM associated with mutations in *DNM2* is frequently a relatively mild condition^{41,54}, although more severe *de novo* cases are on record^{55,56}. Additional characteristic features may include distal weakness, calf muscle hypertrophy, exertional myalgia/fatigue, peripheral or central nervous system involvement, and multisystem features such as neutropenia or cataracts. The peripheral axonal neuropathy CMTDIB is an allelic condition⁵⁷. Recessive and, less frequently, dominantly inherited and milder, *BINI*-related CNM have been reported in few families^{42,44,58}. Recessively inherited CNM due to *RYR1* mutations⁴³ shows considerable clinical overlap with other forms of recessively inherited *RYR1*-related myopathies (see above). Mutations in *TTN* are often associated with dysmorphic facial features, scoliosis, spinal rigidity and contractures⁴⁵, showing some overlap with the Emery-Dreifuss muscular dystrophy (EDMD) and the KDS spectrum. Cardiac involvement has only been reported in the *TTN*- and *SPEG*-related forms.

Nemaline Myopathy (NM)

NM has been associated with mutations in more than 10 genes to date, most commonly recessive mutations in the nebulin (*NEB*) gene^{59,60}, and (*de novo*) dominant mutations in the slow skeletal muscle α -actin (*ACTA1*) gene⁶¹. Dominant mutations in the alpha-tropomyosin (*TPM3*)⁶², the beta-tropomyosin (*TPM2*)⁶³ and the *KBTBD13*⁶⁴ genes, as well as recessive mutations in *ACTA1*⁶⁵, in *TPM3*⁶⁶, *TPM2*⁶⁷ the slow troponin T (*TNNT1*)⁶⁸, cofilin-2 (*CFL2*)⁶⁹, Kelch-repeat and BTB (POZ) domain containing 13 (*KBTBD 13*)⁶⁴, *KLHL40*⁷⁰,

*KLHL41*⁷¹, leiomodlin-3 (*LMOD3*)⁷², myopalladin (*MYPN*)^{73,74} and myosin XVIIIIB (*MYO18B*)⁷⁵ are less common or even limited to single families.

The number and distribution of nemaline rods varies between muscles and patients. Rods are believed to be derived from Z-lines, and may show continuity with Z-lines; they are mainly cytoplasmic but may also be nuclear, in particular in *ACTA1*-related NM⁷⁶ where there may be additional actin accumulation and compensatory expression of cardiac actin. Nemaline rods are usually seen in both fibre types except in patients with *TPM3* mutations, where they are limited to type 1 fibres. Numerous small rectangular rods in fibres with very few myofibrils are a feature of *KLHL40*-related NM⁷⁰.

Clinically, NM is highly variable and conventionally classified by age of onset and severity: Profoundly severe, often lethal cases within the fetal akinesia spectrum have been reported in association with recessive mutations in *KLHL40*⁷⁰, *KLHL41*⁷¹, *LMOD3*⁷² and *MYO18B*⁷⁵ whereas the “typical” congenital form of NM characterized by infantile onset, hypotonia and often disproportionate bulbar involvement is most commonly due to recessive *NEB* mutations⁷⁷. Dominant (frequently *de novo*) *ACTA1* mutations are often associated with severe congenital presentations, but milder cases have been reported^{65,78-80}. *KBTBD13*-gene related NM is an unusual form characterized by progressive proximal and neck weakness, gait abnormalities, poor exercise tolerance and a peculiar slowness of movements⁸¹. Extraocular muscle involvement is only seen in a proportion of cases with *KLHL40*, *KLHL41* and *LMOD3* mutations. An associated cardiomyopathy may be seen in *MYPN*- and *MYO18B*-associated NM^{74,75}. Many forms of NM may show marked distal involvement, and many of the causative genes have also been implicated in distinct distal arthrogryposis (DA) syndromes (for example,⁸²). Muscle MRI may help to distinguish different genetic forms of NM⁸³.

Other congenital myopathies

Recent years have seen an expansion of the phenotypical spectrum of already known CM-associated genes, as well as the description of novel conditions that share some of the clinical and muscle biopsy findings with the better characterized entities without reaching a comparable level of histopathological “purity”. These CMs with non-specific, multiple (structural) and unusual/other features are summarized in the following paragraph.

CMs with non-specific features. Marked *type 1 predominance or uniformity* is common in all CMs and may be the sole presenting feature⁸⁴. Marked type 1 predominance and atrophy has also been reported in one consanguineous family with clinical features of a congenital myopathy and recessive mutations in *HACD1* encoding 3-hydroxyacyl-CoA dehydratase 1⁸⁵; although recessive mutations in the corresponding canine gene *PTPLA* cause a form of CNM in dogs^{86,87}, increased central nuclei were not a feature in *HACD1*-mutated humans. *Congenital fibre type disproportion (CFTD)*, the marked smallness of type 1 fibres compared to type 2 fibres, is another common feature that has been reported in association with mutations in *TPM3*^{88,89}, *RYR1*⁹⁰, *ACTA1*⁹¹, *SEPNI*⁹² and *MYH7*⁹³, with or without additional structural abnormalities.

CMs with multiple (structural) abnormalities, already recognized in the pre-molecular era⁹⁴, have now been largely genetically resolved and are often attributed to already previously identified genetic backgrounds: The common occurrence of cores and rods (“core-rod myopathy”) has been attributed to mutations in *RYR1*, *ACTA1* and *NEB*, whereas the combination of cores and central nuclei is seen with *RYR1*, *TTN*, *CCDC78*, *DNM2* and *SPEG*

mutations. There is also a rapidly increasing number of novel entities that do not readily fit into the conventional classification based on a single predominant histopathological abnormality: ***CACNAIS-related myopathy***⁹⁵ is characterized by marked neonatal hypotonia, generalized weakness pronounced axially and variable extraocular, bulbar and respiratory involvement. *CACNAIS*-related myopathy is due to recessive and dominant mutations in the gene encoding the pore-forming subunit of DHPR in skeletal muscle (Cav1.1), previously associated with dominantly inherited forms of periodic paralysis (and, rarely, MHS phenotypes)^{96,97}. Characteristic histopathological features include SR dilatation, increased internal nuclei and myofibrillar disorganization resembling minicores. Recessively inherited, ***PYROXDI-related CM***⁹⁸ is an early-onset myopathy of moderate severity characterized by slowly progressive generalized weakness, facial and bulbar involvement, and increased internalized nuclei and myofibrillar disorganization on muscle biopsy. ***Hereditary myosin myopathies*** (“myosinopathies”) (for review,⁹⁹) comprise distinct distal arthrogryposis (DA) syndromes due to dominant mutations in *MYH3* and *MYH8* encoding two developmental myosin heavy chain (MyHC) isoforms, as well as CMs of variable onset and severity due to dominant and recessive mutations in *MYH2* and *MYH7*, the latter also implicated in Laing distal myopathy and myosin storage myopathy (MSM). In addition to the variable presence of cores on muscle biopsy, (recessive) *MYH2*-related myopathies¹⁰⁰⁻¹⁰² show marked reduction (or absence) of type 2A fibres^{99,103}, whereas accumulation of slow myosin (“hyaline bodies”) may be seen in some *MYH7*-related cases. Both *MYH7*- and *MYH2*-related myopathies may also show increased connective tissue, internal nuclei, rimmed vacuoles, ring and lobulated fibres^{20,93,99,103}. In the context of overlapping histopathological features, the presence of extraocular muscle involvement may cause diagnostic confusion with recessive *RYR1*-related MmD. Two other conditions combining ocular involvement, contractures within the DA spectrum and features of a CM are recessively inherited ***ECELL1-related CM***¹⁰⁴⁻¹⁰⁸ and

dominantly inherited *PIEZO2-related CM*¹⁰⁹ (also classified as DA5), both associated with cores and increased internal nuclei on muscle biopsy. A recessive *SCN4A-related CM* due to homozygous or compound heterozygous mutations in *SCN4A*¹¹⁰, encoding the α -subunit of the skeletal muscle voltage-gated sodium channel (Nav1.4) and previously associated with dominantly inherited myotonia and periodic paralysis has been recently described associated with a wide spectrum, from severe *in utero* (often early lethal) presentations to neonatal-onset conditions of variable severity. The phenotype is mainly characterised by hypotonia, facial and neck weakness, respiratory and swallowing difficulties and early-onset spinal deformities but interestingly, no clinical or electrophysiological evidence of myotonia. Mutations in the same gene have also been associated with a presentation featuring severe neonatal laryngospasm¹¹¹. Histopathological features are characterized by a combination of increased fibre size variability and variable increases in fatty tissue, but do usually lack more distinct structural abnormalities¹¹⁰. Many of the genetic backgrounds implicated in the CMs – in particular *RYR1*, *TTN* and *DNM2* – may show marked increases in fat and connective tissue, *features mimicking a congenital muscular dystrophy*^{112,113}.

CMs with unusual or other features: Some of the genes associated with NM - *TPM2*, *TPM3*, *ACTA1*, *NEB* and *MYPN* – have also been implicated in rare myopathies with unusual histopathological features, Cap myopathy and Zebra body myopathy^{73,114-116}. *STIM1- and ORAI1-related CMs* (for review,¹¹⁷) due to dominant gain-of-function mutations result in either tubular aggregate myopathy (TAM), a slowly progressive myopathy with variable extraocular muscle involvement, exertional myalgia and variable calf hypertrophy, or York platelet and Stormorken syndromes, related disorders with a CM, pupillary and platelet abnormalities, and variable multisystem involvement that form a clinical continuum. Recessive inheritance of loss-of-function mutations in *ORAI1* and *STIM1* lead to variable combinations of a severe combined immunodeficiency, ectodermal dysplasia and a CM, a combination reported already in the

pre-molecular era in association with minicores on muscle biopsy¹¹⁸. The “*triadin knockout syndrome*” due to compound heterozygosity for *TRDN* (null) mutations is a recessive cardiac arrhythmia syndrome with variable clinical and histopathological features of a CM, the latter characterized by focal dilation and degeneration of the lateral SR cisternae^{119,120}; the highly variable penetrance of the myopathy associated with this entity remains however currently unaccounted for. Mutations in *TRIM32*, *TRIM54* and *TRIM63* (encoding an ubiquitin E3 ligase and muscle-specific RING finger proteins MuRF3 and 1, respectively) have been associated with LGMD2H, sarcotubular myopathy (*TRIM32*), microtubular abnormalities and myosin-containing inclusions (*TRIM54* and *TRIM63*¹²¹), illustrating the increasingly fluid boundaries between the CMs and other neuromuscular disorders, in particular myofibrillar, protein aggregation and vacuolar myopathies.

PATHOGENESIS

The vast majority of the proteins implicated in the CMs have been associated with primary or secondary defects of muscle excitation-contraction coupling (ECC), intracellular calcium homeostasis and disturbed sarcomeric assembly and function (illustrated in Figure 2); other mechanisms are currently emerging.

ECC, muscle contraction and relaxation

Excitation-contraction coupling (ECC) is the process whereby an electrical signal generated by a neuronal action potential is converted into a chemical gradient, i.e. an increase in myoplasmic Ca⁺⁺, leading to muscle contraction. The two main players of skeletal muscle ECC are the ryanodine receptor sarcoplasmic reticulum (SR) Ca⁺⁺ release channel (RyR1)

and the voltage sensing L-type Ca^{2+} channel dihydropyridine receptor (DHPR) (Figure 2). RyR1 is located on the SR junctional face membrane and the DHPR is located on the plasmalemma and transverse tubules, a plasmalemmal invagination running deep into the muscle fibre. ECC is extremely rapid, occurring within a few milliseconds, and relies on a highly defined subcellular architecture, with each DHPR positioned opposite a RyR1, and with every other RyR1 tetramer facing four DHPRs arranged in a characteristic checkerboard shape called a tetrad.

Apart from their principal regulation through direct interaction with DHPR, RyR1s are also regulated by Ca^{++} and Mg^{++} , and are additionally subjected to post-translational modifications (e.g. phosphorylation, sumoylation and nitrosylation) that affect the channel open probability. The junctional SR membrane contains the RyR1 as well as many other smaller proteins, including the structural proteins triadin and junctin, JP-45, the high capacity, low affinity Ca^{++} binding protein calsequestrin^{122,123} in an area adjacent to RyR1, and others that play a role in the fine regulation of SR Ca^{++} release or in maintaining the structural integrity of the Ca^{++} release machinery^{122,124-131}.

Following Ca^{++} release from the SR, its binding to Troponin C, and direct thin-filament interaction, ***muscle contraction*** occurs in the sarcomere, a structure principally composed of parallel thick and thin filaments. Sarcomeric regulation of contraction involves structural changes in the thin filament complex composed of actin, tropomyosin and troponin, triggered by Ca^{++} binding to troponin. The simplest model for sarcomeric Ca^{++} regulation is based on steric-blocking, where tropomyosin prevents myosin binding to the actin filament to generate force. Ca^{++} binding to troponin triggers a chain of reactions that result in azimuthal movements of tropomyosin around the filament to unmask binding sites on actin for myosin, the molecular motor and also major component of the thick filament, allowing force

production and motion¹³² All these contractile proteins and related isoforms are differently expressed in slow and fast twitch muscles to fulfil different functional demands¹³².

Termination of the contraction cycle and muscle relaxation is then achieved by RyR1 closure and by activation of the sarco/endoplasmic reticulum Ca⁺⁺ ATPase (SERCA), the protein component responsible for pumping the Ca⁺⁺ back into the SR¹³³. SERCA activity can be modulated by two small regulatory proteins, sarcolipin and phospholamban¹³⁴⁻¹³⁶.

Although skeletal muscle ECC can occur in the presence of extracellular Ca⁺⁺ in the nM range, there is a wide consensus that Ca⁺⁺ **entry from the extracellular space** is essential to ensure prolonged muscle activity. Two main mechanisms of Ca⁺⁺ entry have been identified in skeletal muscle, (i) excitation-coupled Ca⁺⁺ entry (ECCE) via DHPR which is activated by a train of action potentials or prolonged membrane depolarisation, and (ii) store-operated Ca⁺⁺ entry (SOCE) via STIM1 and Ora1 which is triggered by ER/SR store depletion¹³⁷⁻¹⁴¹.

ECC and Ca⁺⁺ homeostasis abnormalities

Amongst the **primary defects** of ECC and Ca⁺⁺ homeostasis, mutations in ***RYR1*** are the most common cause^{7,18,142,143}. Based on functional studies utilizing cellular and animal models [for review¹⁴⁴]¹⁴⁵, excessive Ca⁺⁺ release and lower RyR1 activation thresholds are consequences of dominantly inherited MHS-associated *RYR1* mutations, whereas both SR calcium store depletion with resulting increased cytosolic calcium levels (“leaky channel” hypothesis) and disturbed EC coupling (“EC uncoupling hypothesis”) have been proposed for dominantly inherited CCD¹⁴². Based on limited studies performed so far, quantitative reduction of RyR1 channels is a more likely mechanism than a qualitative RyR1 dysfunction in recessive *RYR1*-related myopathies¹⁴⁶⁻¹⁴⁸. (Secondary or primary) reduction of the Cav1.1 protein is seen in both recessive *RYR1*- and *CACNA1S*-related CMs^{95,146}, the latter also showing disturbed ECC and, consequently, reduced

depolarization-induced SR Ca⁺⁺ release in myotubes and mature muscle fibres. *STAC3*, the gene homozygously mutated in NAM, targets Cav1.1 to the T-tubules and thus also participates in voltage-induced Ca⁺⁺ release^{149,150}. A similar mechanism is likely to be involved in the recently described “*triadin* knockout syndrome”¹¹⁹, although the basis for the highly variable penetrance of skeletal muscle features in this condition is currently uncertain. Distinct alterations in store operated Ca⁺⁺ influx have been described with dominant mutations in *STIMI* and *ORAI1*, resulting in increased resting Ca⁺⁺ levels due to constitutively active molecules mediating Ca⁺⁺ influx independently of SR Ca⁺⁺ levels^{140,151}; the opposite effect, impaired Ca⁺⁺ influx, is seen with recessive *ORAI1* mutations leading to reduced Orai1 expression¹⁵².

Secondary defects of ECC and Ca⁺⁺ homeostasis have been demonstrated in *SEPNI*-mutated myotubes and in the *SEPNI* KO mouse model^{153,154}, probably due to RyR1 redox modifications. Many of the genes implicated in CNM – *MTM1*⁴⁰, *DNM2*⁴¹, and *BINI*⁴⁴ – code for proteins that have an important role in intricately linked intracellular membrane trafficking pathways and may thus indirectly affect muscle Ca⁺⁺ handling and ECC, probably secondary to abnormalities of triad assembly and the ECC machinery (for review,¹⁵⁵). Although such abnormalities have been demonstrated in mouse models of both *DNM2*- and *MTM1*-related myopathies¹⁵⁶, a recent study on *MTM1*-mutated human myoblasts failed to demonstrate any alterations in ECC and Ca⁺⁺ release, indicating that those alterations may reflect long-term effects *in vivo*¹⁵⁷. Lastly, pathogenicity of *TTN* mutations, although probably multifactorial, is also likely to include several mechanisms implicated in ECC, including calpain-3 mediated RyR1 recruitment to the triad, and obscurin-mediated interactions between the T-tubules, SR and the sarcomere.

Abnormalities of sarcomeric assembly and function

The majority of the genes implicated in NM to date – *NEB*⁵⁹, *ACTA1*⁶¹, *TPM2*¹⁵⁸, *TPM3*⁶² and *TNNT1*⁶⁸ – are involved in thin filament assembly and interactions. Pathogenic mutations in the two most commonly mutated genes, *NEB* and *ACTA1*, have been extensively studied [reviewed in¹⁵⁹]: Mediated through lowered Ca⁺⁺ sensitivity, dominant *ACTA1* mutations exert a dominant negative effect on muscle function, whereas recessive *ACTA1* mutations abolish functional protein expression, with phenotype severity probably reliant on the expression of compensatory proteins such as *ACTC*^{160,161}. Rarely, *ACTA1* may result in enhanced muscle contractility^{162,163}. *NEB* mutations affect the specific role of nebulin in thin filament regulation and force generation¹⁶⁴. The specific effects of various NM-associated mutations on nebulin interactions with actin and tropomyosin¹⁶⁵, thin filament length and force generation¹⁶⁶ has been demonstrated in two recent studies *in vitro*. *MYO18B* recently found to be mutated in one family with a severe form of NM⁷⁵ encodes an unconventional myosin with a more general role in sarcomeric assembly and maintenance^{167,168}.

Many of the genes more recently implicated in NM - *KBTD13*, *KLHL40*, *KLHL41* and *LMOD3* – encode a group of Kelch- and associated proteins that are not primary thin filament components but that are involved in muscle quality control processes¹⁶⁹ and may thus affect myofibrillar assembly and function indirectly. Evidence for a direct interaction between *KLHL40*, nebulin and leiomodin 3, respectively, has been recently provided¹⁷⁰. The myosinopathies⁹⁹, disorders of the thick filament, are likely to cause muscle disease by two principal mechanisms, disturbed thick filament interaction and function, and, in particular in *MYH7*-related CMs⁹⁹, aggregation of abnormal protein.

Other pathogenic mechanisms implicated in the CMs

Whilst some of the proteins implicated in the CMs are very specifically involved in ECC and calcium homeostasis, others have (putative) additional roles in and beyond muscle. Selenoprotein N encoded by *SEPN1* is a member of a protein family mediating the various biological effects of selenium and in muscle has been specifically implicated in **myogenesis**, a role shared with MEGF10 mutated in a rarer form of MmD²³, and **redox regulation**^{171,172}. The important role of normally functioning redox regulation for muscle health is also illustrated by the recent identification of recessive mutations in the oxireductase *PYROXDI* as a cause of early-onset congenital myopathies⁹⁸. Reflective of their essential roles in intricately linked intracellular **membrane trafficking** pathways, mutations in the CNM-associated genes *MTM1*, *DNM2* and *BINI* have been associated with a wide range of downstream effects, including defects in mitochondria, the desmin cytoskeleton, satellite cell activation and the neuromuscular junction (for review,¹⁵⁵). Abnormalities of muscle membrane systems have also been described in association with canine *HACD1/PTPLA*-related CNM^{86,87}, a naturally occurring animal model of a non-specific congenital myopathy recently described in humans¹⁷³. The CNM-associated genes *MTM1* and *DNM2* have now also been implicated in pathways that may affect muscle protein turnover and/or **muscle growth and atrophy pathways**: Disturbances of the autophagy pathway have been reported in zebrafish and mouse models of myotubularin deficiency, associated with atrogin upregulation and atrophy¹⁷⁴⁻¹⁷⁶. Abnormalities of autophagosome maturation and autophagic flux have also been described in a mouse model of *DNM2*-related CNM, associated with marked muscle atrophy and weakness¹⁷⁷. Autophagy and other degradation pathways may be also be affected in *TTN*-related CNM, through abrogation of calpain-3 mediated protein turnover with C-terminal truncating *TTN* mutations or its links with the ubiquitin ligase myospryn¹⁷⁸, or through disruption of the link between the kinase domain and the autophagy cargo adaptors Nbr1 and SQSTM1 by M-band disrupting *TTN* mutations²⁵. Intriguingly, the typical

histopathological appearance of CNM has now also been reported in primary disorders of autophagy^{179,180}, further supporting a close link between defective autophagy and abnormal nuclear positioning. A novel epigenetic mechanism involving alterations of muscle specific microRNAs, increased DNA methylation and increased expression of class II histone deacetylases has been recently reported in *RYR1*-related myopathies¹⁸¹ but may also be relevant for other congenital myopathies¹⁵⁷. How mutations in *ECEL1*, *PIEZO2* and *SCN4A* cause specific early-onset CMs is currently uncertain.

DIAGNOSTIC APPROACH

A structured diagnostic approach to the CMs is summarized in¹⁸². Whilst many features on ***clinical assessment*** – weakness and hypotonia pronounced axially – are consistent but non-specific, others, in particular the degree of distal, extraocular muscle, cardiac and respiratory involvement, may indicate specific genetic backgrounds. Useful ***laboratory investigations*** include serum CK levels, typically normal or slightly elevated, and acetylcholine receptor (AChR) antibodies, to exclude autoimmune myasthenic conditions¹⁸³. ***Neurophysiological studies*** including electromyography (EMG) and nerve conduction studies (NCS) are mainly useful for excluding congenital neuropathies, myotonic disorders¹¹¹ or congenital myasthenic syndromes¹⁸⁴. ***Muscle imaging*** (for review⁶), in particular muscle ultrasound (US) as a screening test and muscle magnetic resonance imaging (MRI) for a more detailed assessment, may reveal diagnostic patterns of selective muscle involvement. ***Muscle biopsy*** assessment with a standard panel of histological, histochemical and immunohistochemical stains (for review,¹³) will confirm the specific CM, and exclude distinct conditions with overlapping pathological features such as the congenital muscular dystrophies (CMDs)¹⁸⁵, myofibrillar myopathies (MFMs)¹⁸⁶ and autophagic vacuolar myopathies (AVMs)¹⁸⁷. Electron

microscopy (EM) is very helpful to clarify the pathognomic structural abnormalities seen with light microscopy. Concomitant analysis of multiple CM-associated genes through NGS is rapidly becoming the preferred diagnostic approach. Functional studies will become increasingly relevant for pathogenicity assessment of variants in large genes such as *TTN*, *NEB* and *RYR1*, in which genetic variants of uncertain significance are not uncommon even in healthy control populations.

MANAGEMENT AND THERAPY DEVELOPMENT

Supportive management (outlined in detail in ¹⁸⁸) is based on a multidisciplinary approach: Regular physiotherapy and provision of orthotic support is beneficial to prevent contracture development and to maintain mobility. Dysarthria and feeding difficulties will benefit from regular speech language therapy input; in some cases bulbar involvement and poor weight gain may require gastrostomy insertion. Regular respiratory function monitoring (including sleep studies) and proactive respiratory management (including timely non-invasive ventilation and cough assistance techniques) are mandatory particularly in forms where substantial respiratory involvement, often out of proportion to the degree of limb girdle weakness, is recognized. Regular cardiac monitoring is crucial in CMs with consistently associated cardiomyopathies (in particular *TTN*- and *MYH7*- related forms), but also in individuals where the genetic defect is uncertain. Considering often complex comorbidities, orthopaedic (in particular scoliosis) surgery should be undertaken at a tertiary neuromuscular centre. MHS has to be anticipated in the anaesthetic management of *RYR1*- and *STAC3*-mutated patients and those with unresolved genetic backgrounds.

Already available or currently developed therapies for the CMs detailed below are reviewed in ¹⁸⁹.

Genetic therapies: Due to their enormous size, viral-based gene transfer is unsuitable for most genes commonly implicated in the CMs. However, delivery of *MTM1* through an AAV8-based vector has been demonstrated to improve the clinico-pathological phenotype in *Mtm1*-deficient mice and a canine model of XLMTM^{173,190}. Restoring the mRNA reading frame is in theory applicable to various CMs where nonsense mutations are implicated. Exon skipping has been successfully applied *in vitro* to remove the incorporation of a pseudo-exon in the mRNA of a child with a recessive *RYR1*-related myopathy¹⁹¹. Considering that carriers of truncating *RYR1* mutations are asymptomatic^{191,192}, mutant gene selective silencing may also become feasible therapeutic strategy for dominant *RYR1*-related myopathies in future. Pharmacological suppression of stop codons¹⁹³ with compounds such as PTC124 (Ataluren) is a potential approach in CMs where nonsense mutations are involved, although it is currently uncertain if such an approach will increase normal protein levels sufficiently to restore structural integrity and function, and what the effects on the many loss-of-function variants in the human genome¹⁹⁴ will be. Down- or upregulation of genes acting in related pathways may become particular relevant for different forms of CNM: Recent studies demonstrate that *dynamamin 2 downregulation*¹⁹⁵, or targeting of class II and III PI3 kinases in muscle¹⁹⁶ can rescue the phenotype in XLMTM animal models, suggesting pharmacological modification of intricately linked pathways a potential treatment modality for XLMTM and, possibly, other forms of CNM. Upregulation of cardiac actin may be a therapeutic approach for patients with *ACTA1* null mutations^{197,198}.

Enzyme replacement therapy is currently only relevant to XLMTM due to loss of myotubularin function, where in *Mtm1 KO* mice improvements of contractile function and histopathological features have been observed following short term myotubularin enzyme replacement¹⁹⁹.

Pharmacological therapies potentially applicable to the CMs can be grossly divided into 3

principal approaches: i) direct modification of altered protein function (for example modification of RyR1 release in *RYR1*-related myopathies) or ii) enhancement of thin-thick filament interactions (for example, in some NMs), and iii) those aimed at non-specifically ameliorating downstream effects of the specific gene mutation. *Modification of RyR1 Ca⁺⁺ release* through the specific RyR1 antagonist Dantrolene ²⁰⁰ is the established emergency treatment for MH but has also been effectively used in few patients with *RYR1*-related ERM ^{35,201} and CCD ^{202,203}. Other compounds with the potential to treat excessive SR Ca⁺⁺ release and/or increased SR Ca⁺⁺ leak are the calstabin-stabilizing 1,4-benzothiazepine derivatives JTV519 and S107 (“Rycals”) (for review, ^{204,205}) and the AMPK activator AICAR (or 5-aminoimidazole-4-carboximide ribonucleoside) ^{206,207}, however, safety profiles of these compounds in humans and their roles in *RYR1*-related myopathies associated with reduced rather than enhanced calcium conductance are currently uncertain. *Enhancement of filament interactions* and promotion of force production ^{208,209} (either by slowing the rate of calcium release from troponin C or directly targeting myosin molecules) are potentially valuable for some NMs, however, concerns remain concerning fibre type specificity and/or potential cardiac side-effects of the molecules utilized. *Modification of downstream effect of specific gene mutations* comprises various approaches: Inhibition of myostatin, an important negative regulator of muscle fibre size ²¹⁰, may be applicable to CMs where fibre atrophy is prominent. Based on the observation of increased oxidative stress and a favourable response to these compounds in animal models ^{154,211,212}, antioxidants such as *N-acetylcysteine (NAC)* are currently being investigated in clinical trials concerning *RYR1*- and *SEPNI*-related myopathies. Based on neuromuscular junction/transmission abnormalities in CNM, *RYR1*-related MmD and *KLHL40*-related NM ²¹³⁻²¹⁶, acetylcholinesterase inhibitors have been used with some benefit in a small number of patients. Two other compounds where an apparent benefit was demonstrated in two small open label pilot studies are salbutamol in core

myopathies²¹⁷⁻²¹⁹ and, also supported by pre-clinical data from a relevant animal model²²⁰, L-Tyrosine in NM²²¹. For those disease entities where misfolded proteins or domains play unequivocal primary roles in the disease process (e.g. titin in AR MmD-HD), the development of compounds acting as “chemical chaperones” might bear promise: A pharmacochaperone approach, using the small amphipathic compound 4-phenylbutyrate, was recently shown to alleviate some of the pathological features in a mouse model of *PLEC*-associated epidermolysis bullosa simplex with muscular dystrophy (EBS-MD)²²², although it is uncertain if the observed effect was due to stabilisation of misfolded mutant protein, or its clearance through autophagy induction by the “pleiotropic” drug 4-phenylbutyrate (4PBA)^{223,224}. A beneficial effect of 4PBA has recently also been suggested in a mouse model of a *RYR1*-related myopathy²²⁵. The range of chemical chaperones is increasing rapidly²²⁶, but their effective concentrations (IC₅₀) are often still very low²²⁷, and the development of more target-specific compounds might make this approach more effective and applicable.

CONCLUSIONS AND OUTLOOK

Widespread clinical implementation of NGS has rapidly expanded the genetic and clinico-pathological spectrum of the CMs, which – in addition to the “classical” entities CCD, MmD, CNM and NM – now encompass a wide range of early-onset non-dystrophic neuromuscular disorders with variable combinations of structural defects. CMs due to mutations in *RYR1*, the most common genetic cause, show a continuum with intermittent induced myopathies – MH and (exertional) rhabdomyolysis – in otherwise healthy individuals, whilst there is substantial overlap with the distal arthrogryposis and protein aggregation myopathy spectrum particularly in forms where sarcomeric proteins are implicated. Unravelling the underlying molecular mechanisms has not only advanced the understanding of the CMs but also our

knowledge of normal muscle physiology and homeostasis: Whilst the primary genetic defects and principal pathogenic mechanisms have been largely elucidated, downstream effects on muscle growth and atrophy pathways, the role of (genetic) modifiers and the molecular basis for the common histopathological features remain largely uncertain. Specific therapies utilizing multiple – including genetic, enzyme replacement and pharmacological - approaches are currently being developed, or are already reaching the clinical trial stage, emphasizing the need for comprehensive natural history studies concerning these clinically variable conditions.

FIGURE AND TABLE LEGENDS

FIGURES

Figure 1

Muscle pathology in congenital myopathies, illustrating the key pathological features of the congenital myopathies, central cores, multiple minicores, central nuclei and nemaline rods. *RYR1*-related Central Core Disease (CCD) (a-c), *SEPN1*-related Multi-minicore Disease (MmD) (d-f), Centronuclear Myopathy (CNM) (g-i *MTM1*- and j-l *DNM2*-related), and *ACTA1*-related Nemaline Myopathy (NM) (m-o). Muscle biopsies stained with haematoxylin and eosin (H&E) (a,d,g,j,m), NADH-TR (b,e,h,k), modified Gomori Trichrome (n), slow myosin heavy chain (c,f,i,l), and myosin ATPase pH 4.6 (o). **a)** Child with dominant *RYR1*-related CCD shows myopathic fibre size variation and marked perimysial fatty infiltration. **b)** Most fibres contain a single central or eccentric ‘core’ with a well-delineated zone of diminished or absent oxidative staining; some of these also show a rim of enhanced oxidative staining surrounding the core lesion. **c)** There is uniformity of type I/slow fibres. **d)** Adolescent with recessive *SEPN1*-related MmD shows myopathic fibre size variation and perimysial fatty infiltration. **e,f)** Fibre typing is preserved with predominance of type I/slow fibres, and both type I and type II fibres display foci areas of diminished or absent oxidative staining (multi-minicores) and occasionally larger lesions. **g)** Male neonate with severe X-

linked recessive myotubular myopathy (XLMTM) shows centrally placed nuclei in a large number of fibres. **h)** The majority of fibres display pale peripheral halos and **(i)** type I/slow fibres are predominant. **j)** Adult with *DNM2*-related CNM shows marked increase in central nucleation and perimysial fatty infiltration. **k)** Many fibres display ‘radial strands’ radiating from a centrally placed nucleus. **l)** There is type I/slow fibre predominance and hypotrophy creating fibre size disproportion; central nuclei are present in both fibre types. **m)** Severely affected neonate with *de novo* dominant *ACTA1*-related NM shows myopathic fibre size variation with an appearance of two fibre populations mostly of smaller type I and larger type II fibres (see o). **n)** Numerous thread-like inclusions are seen in both fibre sizes and appear red with the modified Gomori trichrome and eosinophilic with haematoxylin and eosin (m). **o)** Pale stained type I fibres are often more severely affected and atrophic/hypotrophic. Scale bar: (a-f, i-m, o = 100 µm; g,h,n = 10 µm)

Figure 2

Subcellular localization of the main proteins implicated in skeletal muscle excitation-contraction coupling (ECC), thin-thick filament interaction and assembly. Mutations in genes encoding components of the ECC machinery and thin-thick filaments of skeletal muscle are commonly mutated in the congenital myopathies. The transverse tubules are invaginations of the plasma membrane where the DHPR complex (containing STAC3) is located. This membrane compartment faces the sarcoplasmic reticulum (SR) junctional face membrane (JFM), containing the ryanodine receptor calcium release channel (RyR1) as well as JP-45 and the structural proteins triadin and junctin. Calsequestrin bound to calcium forms a mesh-like structure within the lumen of the SR terminal cisternae. JP-45 also interacts with calsequestrin via its luminal carboxy-terminal domain. Calcium release into the cytosol results in sarcomeric shortening through specific interactions between thin-thick

filaments, in particular sliding of actin past myosin filaments. The ECC is terminated through SR calcium re-uptake through SERCA calcium pumps. SERCAs are present in the terminal cisternae as well as the longitudinal SR, and are regulated by phospholamban, myoregulin and sarcolipin. The calcium-bufferring protein sarcalumenin is also located in the longitudinal sarcoplasmic reticulum and terminal cisternae and is also involved in regulating SERCA activity. (Objects not to scale). Image kindly provided by Christoph Bachmann, Departments of Anesthesia and Biomedicine, Basel University Hospital, Basel, Switzerland.

TABLES

Table 1

Genes implicated in the congenital myopathies and related conditions. Genes that are most commonly implicated in the “classical” structural congenital myopathies (and their most commonly associated histopathological features) are highlighted in bold. AD = autosomal-dominant; AR = autosomal-recessive; CM = Congenital myopathy (non-specific); CCD = Central Core Disease; MmD = Multi-minicore Disease; CNM = Centronuclear Myopathy (CNM); XLMTM = X-linked myotubular myopathy; NM = Nemaline Myopathy; CFTD = Congenital Fibre Type Disproportion; KDS = King-Denborough syndrome (KDS); NAM = North American Myopathy (NAM); TAM = Tubular Aggregate Myopathy (TAM); MSM = Myosin Storage Myopathy; DA = Distal Arthrogryposis; EOM = extraocular muscle involvement; CN = central nuclei;

Table 2

Genetic, clinical and pathological features associated with different genetic backgrounds commonly implicated in the congenital myopathies. *RYR1* = skeletal

muscle ryanodine receptor gene; *SEPN1* = selenoprotein N gene; *TTN* = titin gene; *MTM1* = myotubularin gene, *DNM2* = dynamin gene, *NEB* = Nebulin gene, *ACTA1* = skeletal muscle α -actin gene; *KLHL40* = kelch-like family member 40. - = not reported, + = infrequent, ++ = common and +++ = very common. a = right ventricular impairment secondary to respiratory involvement. b = includes both congenital cardiac defects and acquired cardiomyopathies.

References

- 1 Magee, K. R. & Shy, G. M. A new congenital non-progressive myopathy. *Brain* **79**, 610-621 (1956).
- 2 Engel, A. G., Gomez, M. R. & Groover, R. V. Multicore disease. A recently recognized congenital myopathy associated with multifocal degeneration of muscle fibers. *Mayo Clin Proc* **46**, 666-681 (1971).
- 3 Spiro, A. J., Shy, G. M. & Gonatas, N. K. Myotubular myopathy. Persistence of fetal muscle in an adolescent boy. *Arch Neurol* **14**, 1-14 (1966).
- 4 Shy, G. M., Engel, W. K., Somers, J. E. & Wanko, T. Nemaline Myopathy. A New Congenital Myopathy. *Brain* **86**, 793-810 (1963).
- 5 Lopez, R. J. *et al.* An RYR1 mutation associated with malignant hyperthermia is also associated with bleeding abnormalities. *Sci Signal* **9**, ra68, doi:10.1126/scisignal.aad9813 (2016).
- 6 Jungbluth, H. Myopathology in times of modern imaging. *Neuropathol Appl Neurobiol* **43**, 24-43, doi:10.1111/nan.12385 (2017).
- 7 Snoeck, M. *et al.* RYR1-related myopathies: a wide spectrum of phenotypes throughout life. *Eur J Neurol* **22**, 1094-1112 (2015).
- 8 Jungbluth, H. & Voermans, N. C. Congenital myopathies: not only a paediatric topic. *Curr Opin Neurol* **29**, 642-650 (2016).

- 9 Quane, K. A. *et al.* Mutations in the ryanodine receptor gene in central core disease and malignant hyperthermia. *Nat Genet* **5**, 51-55 (1993).
- 10 Fujii, J. *et al.* Identification of a mutation in porcine ryanodine receptor associated with malignant hyperthermia. *Science* **253**, 448-451 (1991).
- 11 Biancalana, V. & Laporte, J. Diagnostic use of Massively Parallel Sequencing in Neuromuscular Diseases: Towards an Integrated Diagnosis. *J Neuromuscul Dis* **2**, 193-203 (2015).
- 12 Jungbluth, H., Sewry, C. A. & Muntoni, F. Core myopathies. *Semin Pediatr Neurol* **18**, 239-249 (2011).
- 13 Dubowitz, V., Sewry, C. A. & Oldfors, A. *Muscle Biopsy: A Practical Approach*. 4th edn, (Saunders, 2013).
- 14 Amburgey, K. *et al.* Prevalence of congenital myopathies in a representative pediatric united states population. *Ann Neurol* **70**, 662-665 (2011).
- 15 Hackman, P., Udd, B., Bonnemann, C. G., Ferreiro, A. & Titinopathy Database, C. 219th ENMC International Workshop Titinopathies International database of titin mutations and phenotypes, Heemskerk, The Netherlands, 29 April-1 May 2016. *Neuromuscul Disord* **27**, 396-407 (2017).
- 16 Jungbluth, H. *et al.* Autosomal recessive inheritance of RYR1 mutations in a congenital myopathy with cores. *Neurology* **59**, 284-287 (2002).
- 17 Jungbluth, H. *et al.* Minicore myopathy with ophthalmoplegia caused by mutations in the ryanodine receptor type 1 gene. *Neurology* **65**, 1930-1935 (2005).
- 18 Klein, A. *et al.* Clinical and genetic findings in a large cohort of patients with ryanodine receptor 1 gene-associated myopathies. *Hum Mutat* **33**, 981-988 (2012).
- 19 Ferreiro, A. *et al.* Mutations of the selenoprotein N gene, which is implicated in rigid spine muscular dystrophy, cause the classical phenotype of multimicore disease:

- reassessing the nosology of early-onset myopathies. *Am J Hum Genet* **71**, 739-749 (2002).
- 20 Cullup, T. *et al.* Mutations in MYH7 cause Multi-minicore Disease (MmD) with variable cardiac involvement. *Neuromuscul Disord* **22**, 1096-1104 (2012).
- 21 Takayama, K. *et al.* Japanese multiple epidermal growth factor 10 (MEGF10) myopathy with novel mutations: A phenotype-genotype correlation. *Neuromuscul Disord* **26**, 604-609 (2016).
- 22 Liewluck, T. *et al.* Adult-onset respiratory insufficiency, scoliosis, and distal joint hyperlaxity in patients with multiminicore disease due to novel Megf10 mutations. *Muscle Nerve* **53**, 984-988 (2016).
- 23 Logan, C. V. *et al.* Mutations in MEGF10, a regulator of satellite cell myogenesis, cause early onset myopathy, areflexia, respiratory distress and dysphagia (EMARDD). *Nat Genet* **43**, 1189-1192 (2011).
- 24 Boyden, S. E. *et al.* Mutations in the satellite cell gene MEGF10 cause a recessive congenital myopathy with minicores. *Neurogenetics* **13**, 115-124 (2012).
- 25 Chauveau, C. *et al.* Recessive TTN truncating mutations define novel forms of core myopathy with heart disease. *Hum Mol Genet* **23**, 980-991 (2014).
- 26 Romero, N. B. *et al.* Dominant and recessive central core disease associated with RYR1 mutations and fetal akinesia. *Brain* **126**, 2341-2349 (2003).
- 27 Scoto, M. *et al.* SEPN1-related myopathies: clinical course in a large cohort of patients. *Neurology* **76**, 2073-2078 (2011).
- 28 Klein, A. *et al.* Muscle MRI in congenital myopathies due to Ryanodine receptor type 1 (RYR1) gene mutations. *Arch Neurol* **68**, 1171-1179 (2011).
- 29 Jungbluth, H. *et al.* Magnetic resonance imaging of muscle in congenital myopathies associated with RYR1 mutations. *Neuromuscul Disord* **14**, 785-790 (2004).

- 30 Rosenberg, H., Davis, M., James, D., Pollock, N. & Stowell, K. Malignant hyperthermia. *Orphanet J Rare Dis* **2**, 21 (2007).
- 31 Zhou, H. *et al.* Characterization of recessive RYR1 mutations in core myopathies. *Hum Mol Genet* **15**, 2791-2803 (2006).
- 32 Kraeva, N. *et al.* Compound RYR1 heterozygosity resulting in a complex phenotype of malignant hyperthermia susceptibility and a core myopathy. *Neuromuscul Disord* **25**, 567-576 (2015).
- 33 Dowling, J. J. *et al.* King-Denborough syndrome with and without mutations in the skeletal muscle ryanodine receptor (RYR1) gene. *Neuromuscul Disord* **21**, 420-427 (2011).
- 34 Horstick, E. J. *et al.* Stac3 is a component of the excitation-contraction coupling machinery and mutated in Native American myopathy. *Nature Commun* **4**, 1952 (2013).
- 35 Dlamini, N. *et al.* Mutations in RYR1 are a common cause of exertional myalgia and rhabdomyolysis. *Neuromuscul Disord* **23**, 540-548 (2013).
- 36 Bethlem, J., van Gool, J., Hulsmann, W. C. & Meijer, A. E. Familial non-progressive myopathy with muscle cramps after exercise. A new disease associated with cores in the muscle fibres. *Brain* **89**, 569-588 (1966).
- 37 Loseth, S. *et al.* A novel late-onset axial myopathy associated with mutations in the skeletal muscle ryanodine receptor (RYR1) gene. *J Neurol* **260**, 1504-1510 (2013).
- 38 Jungbluth, H. *et al.* Late-onset axial myopathy with cores due to a novel heterozygous dominant mutation in the skeletal muscle ryanodine receptor (RYR1) gene. *Neuromuscul Disord* **19**, 344-347 (2009).
- 39 Jungbluth, H., Wallgren-Pettersson, C. & Laporte, J. Centronuclear (myotubular) myopathy. *Orphanet J Rare Dis* **3**, 26 (2008).

- 40 Laporte, J. *et al.* A gene mutated in X-linked myotubular myopathy defines a new putative tyrosine phosphatase family conserved in yeast. *Nat Genet* **13**, 175-182 (1996).
- 41 Bitoun, M. *et al.* Mutations in dynamin 2 cause dominant centronuclear myopathy. *Nat Genet* **37**, 1207-1209 (2005).
- 42 Bohm, J. *et al.* Adult-onset autosomal dominant centronuclear myopathy due to BIN1 mutations. *Brain* **137**, 3160-3170 (2014).
- 43 Wilmshurst, J. M. *et al.* RYR1 mutations are a common cause of congenital myopathies with central nuclei. *Ann Neurol* **68**, 717-726 (2010).
- 44 Nicot, A. S. *et al.* Mutations in amphiphysin 2 (BIN1) disrupt interaction with dynamin 2 and cause autosomal recessive centronuclear myopathy. *Nat Genet* **39**, 1134-1139 (2007).
- 45 Ceyhan-Birsoy, O. *et al.* Recessive truncating titin gene, TTN, mutations presenting as centronuclear myopathy. *Neurology* **81**, 1205-1214 (2013).
- 46 Agrawal, P. B. *et al.* SPEG interacts with myotubularin, and its deficiency causes centronuclear myopathy with dilated cardiomyopathy. *Am J Hum Genet* **95**, 218-226 (2014).
- 47 Majczenko, K. *et al.* Dominant mutation of CCDC78 in a unique congenital myopathy with prominent internal nuclei and atypical cores. *Am J Hum Genet* **91**, 365-37 (2012).
- 48 Tosch, V. *et al.* A novel PtdIns3P and PtdIns(3,5)P2 phosphatase with an inactivating variant in centronuclear myopathy. *Hum Mol Genet* **15**, 3098-3106 (2006).
- 49 Bevilacqua, J. A. *et al.* "Necklace" fibers, a new histological marker of late-onset MTM1-related centronuclear myopathy. *Acta Neuropathol* **117**, 283-291 (2009).

- 50 Liewluck, T., Lovell, T. L., Bite, A. V. & Engel, A. G. Sporadic centronuclear myopathy with muscle pseudohypertrophy, neutropenia, and necklace fibers due to a DNM2 mutation. *Neuromuscul Disord* **20**, 801-804 (2010).
- 51 Toussaint, A. *et al.* Defects in amphiphysin 2 (BIN1) and triads in several forms of centronuclear myopathies. *Acta Neuropathol* **121**, 253-266 (2011).
- 52 Romero, N. B. Centronuclear myopathies: a widening concept. *Neuromuscul Disord* **20**, 223-228 (2010).
- 53 Herman, G. E., Finegold, M., Zhao, W., de Gouyon, B. & Metzzenberg, A. Medical complications in long-term survivors with X-linked myotubular myopathy. *J Pediatr* **134**, 206-214 (1999).
- 54 Bohm, J. *et al.* Mutation spectrum in the large GTPase dynamin 2, and genotype-phenotype correlation in autosomal dominant centronuclear myopathy. *Hum Mutat* **33**, 949-959 (2012).
- 55 Bitoun, M. *et al.* Dynamin 2 mutations cause sporadic centronuclear myopathy with neonatal onset. *Ann Neurol* **62**, 666-670 (2007).
- 56 Jungbluth, H. *et al.* Centronuclear myopathy with cataracts due to a novel dynamin 2 (DNM2) mutation. *Neuromuscul Disord* **20**, 49-52 (2010).
- 57 Zuchner, S. *et al.* Mutations in the pleckstrin homology domain of dynamin 2 cause dominant intermediate Charcot-Marie-Tooth disease. *Nat Genet* **37**, 289-294 (2005).
- 58 Jungbluth, H., Wallgren-Pettersson, C. & Laporte, J. F. 198th ENMC International Workshop: 7th Workshop on Centronuclear (Myotubular) myopathies, 31st May - 2nd June 2013, Naarden, The Netherlands. *Neuromuscul Disord* **23**, 1033-1043 (2013).
- 59 Pelin, K. *et al.* Mutations in the nebulin gene associated with autosomal recessive nemaline myopathy. *Proc Natl Acad Sci U S A* **96**, 2305-2310 (1999).

- 60 Pelin, K. *et al.* Nebulin mutations in autosomal recessive nemaline myopathy: an update. *Neuromuscul Disord* **12**, 680-686 (2002).
- 61 Nowak, K. J. *et al.* Mutations in the skeletal muscle alpha-actin gene in patients with actin myopathy and nemaline myopathy. *Nat Genetics* **23**, 208-212 (1999).
- 62 Laing, N. G. *et al.* A mutation in the alpha tropomyosin gene TPM3 associated with autosomal dominant nemaline myopathy. *Nat Genet* **9**, 75-79 (1995).
- 63 Donner, K. *et al.* Mutations in the beta-tropomyosin (TPM2) gene--a rare cause of nemaline myopathy. *Neuromuscul Disord* **12**, 151-158 (2002).
- 64 Sambuughin, N. *et al.* Dominant mutations in KBTBD13, a member of the BTB/Kelch family, cause nemaline myopathy with cores. *Am J Hum Genet* **87**, 842-847 (2010).
- 65 Laing, N. G. *et al.* Mutations and polymorphisms of the skeletal muscle alpha-actin gene (ACTA1). *Hum Mutat* **30**, 1267-1277 (2009).
- 66 Lehtokari, V. L. *et al.* Identification of a founder mutation in TPM3 in nemaline myopathy patients of Turkish origin. *Eur J Hum Genet* **16**, 1055-1061 (2008).
- 67 Monnier, N. *et al.* Absence of beta-tropomyosin is a new cause of Escobar syndrome associated with nemaline myopathy. *Neuromuscul Disord* **19**, 118-123 (2009).
- 68 Johnston, J. J. *et al.* A novel nemaline myopathy in the Amish caused by a mutation in troponin T1. *Am J Hum Genet* **67**, 814-821 (2000).
- 69 Agrawal, P. B. *et al.* Nemaline myopathy with minicores caused by mutation of the CFL2 gene encoding the skeletal muscle actin-binding protein, cofilin-2. *Am J Hum Genet* **80**, 162-167 (2007).
- 70 Ravenscroft, G. *et al.* Mutations in KLHL40 are a frequent cause of severe autosomal-recessive nemaline myopathy. *Am J Hum Genet* **93**, 6-18 (2013).

- 71 Gupta, V. A. *et al.* Identification of KLHL41 Mutations Implicates BTB-Kelch-Mediated Ubiquitination as an Alternate Pathway to Myofibrillar Disruption in Nemaline Myopathy. *Am J Hum Genet* **93**, 1108-1117 (2013).
- 72 Yuen, M. *et al.* Leiomodlin-3 dysfunction results in thin filament disorganization and nemaline myopathy. *J Clin Invest* **124**, 4693-4708 (2014).
- 73 Lornage, X. *et al.* Recessive MYPN mutations cause cap myopathy with occasional nemaline rods. *Ann Neurol* **81**, 467-473 (2017).
- 74 Miyatake, S. *et al.* Biallelic Mutations in MYPN, Encoding Myopalladin, Are Associated with Childhood-Onset, Slowly Progressive Nemaline Myopathy. *Am J Hum Genet* **100**, 169-178 (2017).
- 75 Malfatti, E. *et al.* A Premature Stop Codon in MYO18B is Associated with Severe Nemaline Myopathy with Cardiomyopathy. *J Neuromuscul Dis* **2**, 219-227 (2015).
- 76 Domazetovska, A. *et al.* Intranuclear rod myopathy: molecular pathogenesis and mechanisms of weakness. *Ann Neurol* **62**, 597-608 (2007).
- 77 Ryan, M. M. *et al.* Nemaline myopathy: a clinical study of 143 cases. *Ann Neurol* **50**, 312-320 (2001).
- 78 Feng, J. J. & Marston, S. Genotype-phenotype correlations in ACTA1 mutations that cause congenital myopathies. *Neuromuscul Disord* **19**, 6-16 (2009).
- 79 Witting, N., Werlauff, U., Duno, M. & Vissing, J. Prevalence and phenotypes of congenital myopathy due to alpha-actin 1 gene mutations. *Muscle & nerve* **53**, 388-393 (2016).
- 80 Jungbluth, H. *et al.* Mild phenotype of nemaline myopathy with sleep hypoventilation due to a mutation in the skeletal muscle alpha-actin (ACTA1) gene. *Neuromuscul Disord* **11**, 35-40 (2001).

- 81 Sambuughin, N. *et al.* KBTBD13 interacts with Cullin 3 to form a functional ubiquitin ligase. *Biochem Biophys Res Commun* **421**, 743-749 (2012).
- 82 Davidson, A. E. *et al.* Novel deletion of lysine 7 expands the clinical, histopathological and genetic spectrum of TPM2-related myopathies. *Brain* **136**, 508-521 (2013).
- 83 Jungbluth, H. *et al.* Magnetic resonance imaging of muscle in nemaline myopathy. *Neuromuscul Disord* **14**, 779-784 (2004).
- 84 Sato, I. *et al.* Congenital neuromuscular disease with uniform type 1 fiber and RYR1 mutation. *Neurology* **70**, 114-122 (2008).
- 85 Muhammad, E. *et al.* Congenital myopathy is caused by mutation of HACD1. *Human molecular genetics* **22**, 5229-5236 (2013).
- 86 Maurer, M. *et al.* Centronuclear myopathy in Labrador retrievers: a recent founder mutation in the PTPLA gene has rapidly disseminated worldwide. *PLoS One* **7**, e46408 (2012).
- 87 Walmsley, G. L. *et al.* Progressive Structural Defects in Canine Centronuclear Myopathy Indicate a Role for HACD1 in Maintaining Skeletal Muscle Membrane Systems. *Am J Pathol* **187**, 441-456 (2017).
- 88 Clarke, N. F. *et al.* Mutations in TPM3 are a common cause of congenital fiber type disproportion. *Ann Neurol* **63**, 329-337 (2008).
- 89 Munot, P. *et al.* Congenital fibre type disproportion associated with mutations in the tropomyosin 3 (TPM3) gene mimicking congenital myasthenia. *Neuromuscul Disord* **20**, 796-800 (2010).
- 90 Clarke, N. F. *et al.* Recessive mutations in RYR1 are a common cause of congenital fiber type disproportion. *Hum Mutat* **31**, E1544-1550 (2010).

- 91 Laing, N. G. *et al.* Actin mutations are one cause of congenital fibre type disproportion. *Ann Neurol* **56**, 689-694 (2004).
- 92 Clarke, N. F. *et al.* SEPN1: associated with congenital fiber-type disproportion and insulin resistance. *Ann Neurol* **59**, 546-552 (2006).
- 93 Lamont, P. J. *et al.* Novel mutations widen the phenotypic spectrum of slow skeletal/beta-cardiac myosin (MYH7) distal myopathy. *Hum Mutat* **35**, 868-879 (2014).
- 94 Vallat, J. M. *et al.* Coexistence of minicores, cores, and rods in the same muscle biopsy. A new example of mixed congenital myopathy. *Acta Neuropathol* **58**, 229-232 (1982).
- 95 Schartner, V. *et al.* Dihydropyridine receptor (DHPR, CACNA1S) congenital myopathy. *Acta Neuropathol* **133**, 517-533 (2017).
- 96 Monnier, N. *et al.* Presence of two different genetic traits in malignant hyperthermia families: implication for genetic analysis, diagnosis, and incidence of malignant hyperthermia susceptibility. *Anesthesiology* **97**, 1067-1074 (2002).
- 97 Jurkat-Rott, K. *et al.* A calcium channel mutation causing hypokalemic periodic paralysis. *Hum Mol Genet* **3**, 1415-1419 (1994).
- 98 O'Grady, G. L. *et al.* Variants in the Oxidoreductase PYROXD1 Cause Early-Onset Myopathy with Internalized Nuclei and Myofibrillar Disorganization. *Am J Hum Genet* **99**, 1086-1105 (2016).
- 99 Tajsharghi, H. & Oldfors, A. Myosinopathies: pathology and mechanisms. *Acta Neuropathol* **125**, 3-18 (2013).
- 100 Tajsharghi, H. *et al.* Human disease caused by loss of fast IIa myosin heavy chain due to recessive MYH2 mutations. *Brain* **133**, 1451-1459 (2010).

- 101 Martinsson, T. *et al.* Autosomal dominant myopathy: missense mutation (Glu-706 --> Lys) in the myosin heavy chain IIa gene. *Proc Natl Acad Sci U S A* **97**, 14614-14619 (2000).
- 102 Willis, T. *et al.* A novel MYH2 mutation in family members presenting with congenital myopathy, ophthalmoplegia and facial weakness. *J Neurol* **263**, 1427-1433 (2016).
- 103 Tsabari R, et al. Congenital myopathy due to myosin heavy chain 2 mutation presenting as chronic aspiration pneumonia in infancy. *Neuromuscul Disord* S0960-8966(17)30176-1. (2017)
- 104 McMillin, M. J. *et al.* Mutations in ECEL1 cause distal arthrogyrosis type 5D. *Am J Hum Genet* **92**, 150-156 (2013).
- 105 Dieterich, K. *et al.* The neuronal endopeptidase ECEL1 is associated with a distinct form of recessive distal arthrogyrosis. *Hum Mol Genet* **22**, 1483-1492 (2013).
- 106 Shaaban, S. *et al.* Expanding the phenotypic spectrum of ECEL1-related congenital contracture syndromes. *Clin Genet* **85**, 562-567 (2014).
- 107 Todd, E. J. *et al.* Next generation sequencing in a large cohort of patients presenting with neuromuscular disease before or at birth. *Orphanet J Rare Dis* **10**, 148 (2015).
- 108 Bayram, Y. *et al.* Molecular etiology of arthrogyrosis in multiple families of mostly Turkish origin. *J Clin Invest* **126**, 762-778 (2016).
- 109 Coste, B. *et al.* Gain-of-function mutations in the mechanically activated ion channel PIEZO2 cause a subtype of Distal Arthrogyrosis. *Proc Natl Acad Sci U S A* **110**, 4667-4672 (2013).
- 110 Zaharieva, I. T. *et al.* Loss-of-function mutations in SCN4A cause severe foetal hypokinesia or 'classical' congenital myopathy. *Brain* **139**, 674-691 (2016).

- 111 Singh, R. R. *et al.* Mutations in SCN4A: a rare but treatable cause of recurrent life-threatening laryngospasm. *Pediatrics* **134**, e1447-1450 (2014).
- 112 Bharucha-Goebel, D. X. *et al.* Severe congenital RYR1-associated myopathy: the expanding clinicopathologic and genetic spectrum. *Neurology* **80**, 1584-1589 (2013).
- 113 Schessl, J. *et al.* MRI in DNM2-related centronuclear myopathy: evidence for highly selective muscle involvement. *Neuromuscul Disord* **17**, 28-32 (2007).
- 114 Clarke, N. F. *et al.* Cap disease due to mutation of the beta-tropomyosin gene (TPM2). *Neuromuscul Disord* **19**, 348-351 (2009).
- 115 Lehtokari, V. L. *et al.* Cap disease caused by heterozygous deletion of the beta-tropomyosin gene TPM2. *Neuromuscul Disord* **17**, 433-442 (2007).
- 116 Sewry, C. A., Holton, J. L., Dick, D. J., Muntoni, F. & Hanna, M. G. Zebra body myopathy is caused by a mutation in the skeletal muscle actin gene (ACTA1). *Neuromuscul Disord* **25**, 388-391 (2015).
- 117 Lacruz, R. S. & Feske, S. Diseases caused by mutations in ORAI1 and STIM1. *Ann N Y Acad Sci* **1356**, 45-79 (2015).
- 118 Gordon, C. P. & Litz, S. Multicore myopathy in a patient with anhidrotic ectodermal dysplasia. *Can J Anaesth* **39**, 966-968 (1992).
- 119 Engel, A. G., Redhage, K. R., Tester, D. J., Ackerman, M. J. & Selcen, D. Congenital myopathy associated with the triadin knockout syndrome. *Neurology* **88**, 1153-1156 (2017).
- 120 Altmann, H. M. *et al.* Homozygous/Compound Heterozygous Triadin Mutations Associated With Autosomal-Recessive Long-QT Syndrome and Pediatric Sudden Cardiac Arrest: Elucidation of the Triadin Knockout Syndrome. *Circulation* **131**, 2051-2060 (2015).

- 121 Olive, M. *et al.* New cardiac and skeletal protein aggregate myopathy associated with combined MuRF1 and MuRF3 mutations. *Hum Mol Genet* **24**, 6264 (2015).
- 122 Zhang, L., Kelley, J., Schmeisser, G., Kobayashi, Y. M. & Jones, L. R. Complex formation between junctin, triadin, calsequestrin, and the ryanodine receptor. Proteins of the cardiac junctional sarcoplasmic reticulum membrane. *J Biol Chem* **272**, 23389-23397 (1997).
- 123 Park, H. *et al.* Comparing skeletal and cardiac calsequestrin structures and their calcium binding: a proposed mechanism for coupled calcium binding and protein polymerization. *J Biol Chem* **279**, 18026-18033 (2004).
- 124 Costello, B. *et al.* Characterization of the junctional face membrane from terminal cisternae of sarcoplasmic reticulum. *J Cell Biol* **103**, 741-753 (1986).
- 125 Treves, S. *et al.* Minor sarcoplasmic reticulum membrane components that modulate excitation-contraction coupling in striated muscles. *J Physiol* **587**, 3071-3079 (2009).
- 126 Rios, E. & Gyorke, S. Calsequestrin, triadin and more: the molecules that modulate calcium release in cardiac and skeletal muscle. *J Physiol* **587**, 3069-3070 (2009).
- 127 Guo, W. & Campbell, K. P. Association of triadin with the ryanodine receptor and calsequestrin in the lumen of the sarcoplasmic reticulum. *J Biol Chem* **270**, 9027-9030 (1995).
- 128 Wium, E., Dulhunty, A. F. & Beard, N. A. Three residues in the luminal domain of triadin impact on Trisk 95 activation of skeletal muscle ryanodine receptors. *Pflugers Arch* **468**, 1985-1994 (2016).
- 129 Caswell, A. H., Motoike, H. K., Fan, H. & Brandt, N. R. Location of ryanodine receptor binding site on skeletal muscle triadin. *Biochemistry* **38**, 90-97 (1999).
- 130 Groh, S. *et al.* Functional interaction of the cytoplasmic domain of triadin with the skeletal ryanodine receptor. *J Biol Chem* **274**, 12278-12283 (1999).

- 131 Goonasekera, S. A. *et al.* Triadin binding to the C-terminal luminal loop of the ryanodine receptor is important for skeletal muscle excitation contraction coupling. *J Gen Physiol* **130**, 365-378 (2007).
- 132 Gordon, A. M., Homsher, E. & Regnier, M. Regulation of contraction in striated muscle. *Physiol Rev* **80**, 853-924 (2000).
- 133 Abu-Abed, M., Mal, T. K., Kainosho, M., MacLennan, D. H. & Ikura, M. Characterization of the ATP-binding domain of the sarco(endo)plasmic reticulum Ca(2+)-ATPase: probing nucleotide binding by multidimensional NMR. *Biochemistry* **41**, 1156-1164 (2002).
- 134 MacLennan, D. H., Asahi, M. & Tupling, A. R. The regulation of SERCA-type pumps by phospholamban and sarcolipin. *Ann N Y Acad Sci* **986**, 472-480 (2003).
- 135 MacLennan, D. H. & Kranias, E. G. Phospholamban: a crucial regulator of cardiac contractility. *Nat Rev Mol Cell Biol* **4**, 566-577 (2003).
- 136 Asahi, M. *et al.* Sarcolipin regulates sarco(endo)plasmic reticulum Ca²⁺-ATPase (SERCA) by binding to transmembrane helices alone or in association with phospholamban. *Proc Natl Acad Sci U S A* **100**, 5040-5045 (2003).
- 137 Kurebayashi, N. & Ogawa, Y. Depletion of Ca²⁺ in the sarcoplasmic reticulum stimulates Ca²⁺ entry into mouse skeletal muscle fibres. *J Physiol* **533**, 185-199 (2001).
- 138 Cherednichenko, G. *et al.* Conformational activation of Ca²⁺ entry by depolarization of skeletal myotubes. *Proc Natl Acad Sci U S A* **101**, 15793-15798 (2004).
- 139 Launikonis, B. S. & Rios, E. Store-operated Ca²⁺ entry during intracellular Ca²⁺ release in mammalian skeletal muscle. *J Physiol* **583**, 81-97 (2007).

- 140 Stiber, J. *et al.* STIM1 signalling controls store-operated calcium entry required for development and contractile function in skeletal muscle. *Nat Cell Biol* **10**, 688-697 (2008).
- 141 Peinelt, C. *et al.* Amplification of CRAC current by STIM1 and CRACM1 (Orai1). *Nat Cell Biol* **8**, 771-773 (2006).
- 142 Treves, S., Jungbluth, H., Muntoni, F. & Zorzato, F. Congenital muscle disorders with cores: the ryanodine receptor calcium channel paradigm. *Curr Opin Pharmacol* **8**, 319-326 (2008).
- 143 Hwang, J. H., Zorzato, F., Clarke, N. F. & Treves, S. Mapping domains and mutations on the skeletal muscle ryanodine receptor channel. *Trends Mol Med* **18**, 644-657 (2012).
- 144 Maclennan, D. H. & Zvaritch, E. Mechanistic models for muscle diseases and disorders originating in the sarcoplasmic reticulum. *Biochim Biophys Acta* **1813**, 948-964 (2011). doi:S0167-4889(10)00294-6 [pii]
- 145 Hirata, H. *et al.* Zebrafish relatively relaxed mutants have a ryanodine receptor defect, show slow swimming and provide a model of multi-minicore disease. *Development* **134**, 2771-2781 (2007).
- 146 Zhou, H. *et al.* RyR1 Deficiency in Congenital Myopathies Disrupts Excitation-Contraction Coupling. *Hum Mutat* **34**, 986-996 (2013).
- 147 Zhou, H. *et al.* Epigenetic allele silencing unveils recessive RYR1 mutations in core myopathies. *Am J Hum Genet* **79**, 859-868 (2006).
- 148 Ducreux, S. *et al.* Functional properties of ryanodine receptors carrying three amino acid substitutions identified in patients affected by multi-minicore disease and central core disease, expressed in immortalized lymphocytes. *Biochem J* **395**, 259-266 (2006).

- 149 Nelson, B. R. *et al.* Skeletal muscle-specific T-tubule protein STAC3 mediates voltage-induced Ca²⁺ release and contractility. *Proc Natl Acad Sci U S A* **110**, 11881-11886 (2013).
- 150 Polster, A., Nelson, B. R., Olson, E. N. & Beam, K. G. Stac3 has a direct role in skeletal muscle-type excitation-contraction coupling that is disrupted by a myopathy-causing mutation. *Proc Natl Acad Sci U S A* **113**, 10986-10991 (2016).
- 151 Bohm, J. *et al.* Constitutive activation of the calcium sensor STIM1 causes tubular-aggregate myopathy. *Am J Hum Genet* **92**, 271-278 (2013).
- 152 Volkers, M. *et al.* Orai1 deficiency leads to heart failure and skeletal myopathy in zebrafish. *J Cell Sci* **125**, 287-294 (2012).
- 153 Juryneec, M. J. *et al.* Selenoprotein N is required for ryanodine receptor calcium release channel activity in human and zebrafish muscle. *Proc Natl Acad Sci U S A* **105**, 12485-12490 (2008).
- 154 Arbogast, S. *et al.* Oxidative stress in SEPN1-related myopathy: from pathophysiology to treatment. *Ann Neurol* **65**, 677-686 (2009).
- 155 Jungbluth, H. & Gautel, M. Pathogenic mechanisms in centronuclear myopathies. *Front Aging Neurosci* **6**, 339 (2014).
- 156 Cowling, B. S., Toussaint, A., Muller, J. & Laporte, J. Defective membrane remodeling in neuromuscular diseases: insights from animal models. *PLoS genetics* **8**, e1002595 (2012).
- 157 Bachmann, C. *et al.* Cellular, biochemical and molecular changes in muscles from patients with X-linked myotubular myopathy due to MTM1 mutations. *Hum Mol Genet* **26**, 320-332 (2017).
- 158 Donner, K. *et al.* Mutations in the beta-tropomyosin (TPM2) gene--a rare cause of nemaline myopathy. *Neuromuscul Disord* **12**, 151-158 (2002).

- 159 Wallgren-Pettersson, C., Sewry, C. A., Nowak, K. J. & Laing, N. G. Nemaline myopathies. *Sem Pediatr Neurol* **18**, 230-238 (2011).
- 160 Ravenscroft, G. *et al.* Mouse models of dominant ACTA1 disease recapitulate human disease and provide insight into therapies. *Brain* **134**, 1101-1115 (2011).
- 161 Ravenscroft, G. *et al.* Actin nemaline myopathy mouse reproduces disease, suggests other actin disease phenotypes and provides cautionary note on muscle transgene expression. *PLoS One* **6**, e28699 (2011).
- 162 Jain, R. K. *et al.* Nemaline myopathy with stiffness and hypertonia associated with an ACTA1 mutation. *Neurology* **78**, 1100-1103 (2012).
- 163 Donkervoort, S. *et al.* TPM3 deletions cause a hypercontractile congenital muscle stiffness phenotype. *Ann Neurol* **78**, 982-994 (2015).
- 164 Ochala, J. *et al.* Disrupted myosin cross-bridge cycling kinetics triggers muscle weakness in nebulin-related myopathy. *FASEB J* **25**, 1903-1913 (2011).
- 165 Marttila, M. *et al.* Nebulin interactions with actin and tropomyosin are altered by disease-causing mutations. *Skelet Muscle* **4**, 15 (2014).
- 166 de Winter, J. M. *et al.* Mutation-specific effects on thin filament length in thin filament myopathy. *Ann Neurol* **9**, 959-969 (2016).
- 167 Ajima, R. *et al.* Deficiency of Myo18B in mice results in embryonic lethality with cardiac myofibrillar aberrations. *Genes Cells* **13**, 987-999 (2008).
- 168 Gurung, R. *et al.* A Zebrafish Model for a Human Myopathy Associated with Mutation of the Unconventional Myosin MYO18B. *Genetics* **205**, 725-735 (2017).
- 169 Gupta, V. A. & Beggs, A. H. Kelch proteins: emerging roles in skeletal muscle development and diseases. *Skelet Muscle* **4**, 11 (2014).
- 170 Garg, A. *et al.* KLHL40 deficiency destabilizes thin filament proteins and promotes nemaline myopathy. *J Clin Invest* **124**, 3529-3539 (2014).

- 171 Castets, P. *et al.* Satellite cell loss and impaired muscle regeneration in selenoprotein N deficiency. *Hum Mol Genet* **20**, 694-704 (2011).
- 172 Castets, P. *et al.* Selenoprotein N is dynamically expressed during mouse development and detected early in muscle precursors. *BMC Dev Biol* **9**, 46 (2009).
- 173 Beggs, A. H. *et al.* MTM1 mutation associated with X-linked myotubular myopathy in Labrador Retrievers. *Proc Natl Acad Sci U S A* **107**, 14697-14702 (2010).
- 174 Dowling, J. J., Low, S. E., Busta, A. S. & Feldman, E. L. Zebrafish MTMR14 is required for excitation-contraction coupling, developmental motor function and the regulation of autophagy. *Hum Mol Genet* **19**, 2668-2681 (2010).
- 175 Fetalvero, K. M. *et al.* Defective autophagy and mTORC1 signaling in myotubularin null mice. *Mol Cell Biol* **33**, 98-110 (2013).
- 176 Al-Qusairi, L. *et al.* Lack of myotubularin (MTM1) leads to muscle hypotrophy through unbalanced regulation of the autophagy and ubiquitin-proteasome pathways. *FASEB J* **27**, 3384-3394 (2013).
- 177 Durieux, A. C. *et al.* A centronuclear myopathy--dynamin 2 mutation impairs autophagy in mice. *Traffic* **13**, 869-879 (2012).
- 178 Sarparanta, J. *et al.* Interactions with M-band titin and calpain 3 link myospryn (CMYA5) to tibial and limb-girdle muscular dystrophies. *J Biol Chem* **285**, 30304-30315 (2010).
- 179 McClelland, V. *et al.* Vici syndrome associated with sensorineural hearing loss and evidence of neuromuscular involvement on muscle biopsy. *Am J Med Genet A* **152A**, 741-747 (2010).
- 180 Byrne, S. *et al.* EPG5-related Vici syndrome: a paradigm of neurodevelopmental disorders with defective autophagy. *Brain* **139**, 765-781 (2016).

- 181 Rokach, O. *et al.* Epigenetic changes as a common trigger of muscle weakness in congenital myopathies. *Hum Mol Genet* **24**, 4636-4647 (2015).
- 182 North, K. N. *et al.* Approach to the diagnosis of congenital myopathies. *Neuromuscul Disord* **24**, 97-116 (2013).
- 183 Hacoheh, Y. *et al.* Fetal acetylcholine receptor inactivation syndrome: A myopathy due to maternal antibodies. *Neurol Neuroimmunol Neuroinflamm* **2**, e57 (2015).
- 184 Kinali, M. *et al.* Congenital myasthenic syndromes in childhood: diagnostic and management challenges. *J Neuroimmunol* **201-202**, 6-12 (2008).
- 185 Bonnemann, C. G. *et al.* Diagnostic approach to the congenital muscular dystrophies. *Neuromuscul Disord* **24**, 289-311 (2014).
- 186 Selcen, D. Myofibrillar myopathies. *Neuromuscul Disord* **21**, 161-171 (2011).
- 187 Nishino, I. Autophagic vacuolar myopathy. *Semin Pediatr Neurol* **13**, 90-95 (2006).
- 188 Wang, C. H. *et al.* Consensus statement on standard of care for congenital myopathies. *J Child Neurol* **27**, 363-382 (2012).
- 189 Jungbluth, H., Ochala, J., Treves, S. & Gautel, M. Current and future therapeutic approaches to the congenital myopathies. *Semin Cell Dev Biol* **64**, 191-200 (2017).
- 190 Childers, M. K. *et al.* Gene therapy prolongs survival and restores function in murine and canine models of myotubular myopathy. *Sci Transl Med* **6**, 220ra210 (2014).
- 191 Rendu, J. *et al.* Exon skipping as a therapeutic strategy applied to an RYR1 mutation with pseudo-exon inclusion causing a severe core myopathy. *Hum Gene Ther* **24**, 702-713 (2013).
- 192 Monnier, N. *et al.* A homozygous splicing mutation causing a depletion of skeletal muscle RYR1 is associated with multi-minicore disease congenital myopathy with ophthalmoplegia. *Hum Mol Genet* **12**, 1171-1178 (2003).

- 193 Barton-Davis, E. R., Cordier, L., Shoturma, D. I., Leland, S. E. & Sweeney, H. L. Aminoglycoside antibiotics restore dystrophin function to skeletal muscles of mdx mice. *J Clin Invest* **104**, 375-381 (1999).
- 194 MacArthur, D. G. & Lek, M. The uncertain road towards genomic medicine. *Trends Genet* **28**, 303-305 (2012).
- 195 Cowling, B. S. *et al.* Reducing dynamin 2 expression rescues X-linked centronuclear myopathy. *J Clin Invest* **124**, 1350-1363 (2014).
- 196 Sabha, N. *et al.* PIK3C2B inhibition improves function and prolongs survival in myotubular myopathy animal models. *J Clin Invest* **126**, 3613-3625 (2016).
- 197 Ravenscroft, G. *et al.* Cardiac alpha-actin over-expression therapy in dominant ACTA1 disease. *Hum Mol Genet* **22**, 3987-3997 (2013).
- 198 Nowak, K. J. *et al.* Nemaline myopathy caused by absence of alpha-skeletal muscle actin. *Ann Neurol* **61**, 175-184 (2007).
- 199 Lawlor, M. W. *et al.* Enzyme replacement therapy rescues weakness and improves muscle pathology in mice with X-linked myotubular myopathy. *Hum Mol Genet* **22**, 1525-1538 (2013).
- 200 Fruen, B. R., Mickelson, J. R. & Louis, C. F. Dantrolene inhibition of sarcoplasmic reticulum Ca²⁺ release by direct and specific action at skeletal muscle ryanodine receptors. *J Biol Chem* **272**, 26965-26971 (1997).
- 201 Timmins, M. A. *et al.* Malignant hyperthermia testing in probands without adverse anesthetic reaction. *Anesthesiology* **123**, 548-556 (2015).
- 202 Michalek-Sauberer, A. & Gilly, H. Prophylactic use of dantrolene in a patient with central core disease. *Anesth Analg* **86**, 915-916 (1998).

- 203 Jungbluth, H., Dowling, J. J., Ferreiro, A. & Muntoni, F. 217th ENMC International Workshop: RYR1-related myopathies, Naarden, The Netherlands, 29-31 January 2016. *Neuromuscul Disord* **26**, 624-633 (2016).
- 204 Andersson, D. C. & Marks, A. R. Fixing ryanodine receptor Ca leak - a novel therapeutic strategy for contractile failure in heart and skeletal muscle. *Drug Discov Today Dis Mech* **7**, e151-e157 (2010).
- 205 Marks, A. R. Calcium cycling proteins and heart failure: mechanisms and therapeutics. *J Clin Invest* **123**, 46-52 (2013).
- 206 Pold, R. *et al.* Long-term AICAR administration and exercise prevents diabetes in ZDF rats. *Diabetes* **54**, 928-934 (2005).
- 207 Lanner, J. T. *et al.* AICAR prevents heat-induced sudden death in RyR1 mutant mice independent of AMPK activation. *Nat Med* **18**, 244-251 (2012).
- 208 de Winter, J. M. *et al.* Troponin activator augments muscle force in nemaline myopathy patients with nebulin mutations. *J Med Genet* **50**, 383-392 (2013).
- 209 de Winter, J. M. *et al.* Effect of levosimendan on the contractility of muscle fibers from nemaline myopathy patients with mutations in the nebulin gene. *Skelet Muscle* **5**, 12 (2015).
- 210 Amthor, H. & Hoogaars, W. M. Interference with myostatin/ActRIIB signaling as a therapeutic strategy for Duchenne muscular dystrophy. *Curr Gene Ther* **12**, 245-259 (2012).
- 211 Durham, W. J. *et al.* RyR1 S-nitrosylation underlies environmental heat stroke and sudden death in Y522S RyR1 knockin mice. *Cell* **133**, 53-65 (2008).
- 212 Dowling, J. J. *et al.* Oxidative stress and successful antioxidant treatment in models of RYR1-related myopathy. *Brain* **135**, 1115-1127 (2012).

- 213 Natera-de Benito, D. *et al.* KLHL40-related nemaline myopathy with a sustained, positive response to treatment with acetylcholinesterase inhibitors. *J Neurol* **263**, 517-523 (2016).
- 214 Robb, S. A. *et al.* Impaired neuromuscular transmission and response to acetylcholinesterase inhibitors in centronuclear myopathies. *Neuromuscul Disord* **21**, 379-386(2011).
- 215 Gibbs, E. M. *et al.* Neuromuscular junction abnormalities in DNMT2-related centronuclear myopathy. *J Mol Med* **91**, 727-737 (2013).
- 216 Dowling, J. J. *et al.* Myotubular myopathy and the neuromuscular junction: a novel therapeutic approach from mouse models. *Dis Model Mech* **5**, 852-859 (2012).
- 217 Messina, S. *et al.* Pilot trial of salbutamol in central core and multi-minicore diseases. *Neuropediatrics* **35**, 262-266 (2004).
- 218 Schreuder, L. T. *et al.* Successful use of albuterol in a patient with central core disease and mitochondrial dysfunction. *J Inherit Metab Dis* **33**, S205-209 (2010).
- 219 Jungbluth, H., Dowling, J. J., Ferreira, A. & Muntoni, F. 182nd ENMC International Workshop: RYR1-related myopathies, 15-17th April 2011, Naarden, The Netherlands. *Neuromuscul Disord* **22**, 453-462 (2012).
- 220 Nguyen, M. A. *et al.* Hypertrophy and dietary tyrosine ameliorate the phenotypes of a mouse model of severe nemaline myopathy. *Brain* **134**, 3516-3529 (2011).
- 221 Ryan, M. M. *et al.* Dietary L-tyrosine supplementation in nemaline myopathy. *J Child Neurol* **23**, 609-613 (2008).
- 222 Winter, L. *et al.* Chemical chaperone ameliorates pathological protein aggregation in plectin-deficient muscle. *J Clin Invest* **124**, 1144-1157 (2014).
- 223 Kusaczuk, M., Bartoszewicz, M. & Cechowska-Pasko, M. Phenylbutyric Acid: simple structure - multiple effects. *Curr Pharm Des* **21**, 2147-2166 (2015).

- 224 Cuadrado-Tejedor, M., Ricobaraza, A. L., Torrijo, R., Franco, R. & Garcia-Osta, A. Phenylbutyrate is a multifaceted drug that exerts neuroprotective effects and reverses the Alzheimer s disease-like phenotype of a commonly used mouse model. *Curr Pharm Des* **19**, 5076-5084 (2013).
- 225 Lee, C. S. *et al.* A chemical chaperone improves muscle function in mice with a RyR1 mutation. *Nat Commun* **8**, 14659 (2017).
- 226 Vega, H., Agellon, L. B. & Michalak, M. The rise of proteostasis promoters. *IUBMB Life* **68**, 943-954 (2016).
- 227 Yuste-Checa, P. *et al.* Pharmacological Chaperoning: A Potential Treatment for PMM2-CDG. *Hum Mutat* **38**, 160-168 (2017).

Table 1

Gene symbol	Chromosome location	Protein	Condition	Inheritance
Proteins involved in SR calcium release, ECC and/or triadic assembly				
RYR1	19q13.1	Ryanodine receptor 1 (skeletal)	CCD MmD CNM CFTD KDS	AD, AR AD, AR AR AR AR, AD
<i>STAC3</i>	12q13.3	SH3 and Cystein-rich domain 3	NAM	AR
<i>ORAI1</i>	12q24.31	Calcium release-activated calcium modulator 1	TAM	AD
<i>STIM1</i>	11p15.4	Stromal interactin molecular 1	TAM Stormorken syndrome	AD AD
MTM1	Xq28	Myotubularin	<u>XLMTM</u>	X-linked
BIN1	2q14	Amphiphysin	CNM	AR, AD
DNM2	19p13.2	Dynamamin 2	<i>CNM</i>	AD
<i>SPEG</i>	2q35	SPEG complex locus	CM with CN and cardiomyopathy	AR
<i>CCDC78</i>	16p13.3	Coiled-coil domain containing protein 78	CM with cores and CN	AD
<i>CACNA1S</i>	1q32	Calcium channel, voltage-dependent, L type, alpha 1S subunit	CM with EOM	AD, AR
SEPN1	1p36.13	Selenoprotein N1	MmD CFTD	AR AR
Proteins involved in thick-thin filament assembly and interaction, myofibrillar force generation and protein turnover				
NEB	2q22	Nebulin	NM	AR
ACTA1	1q42.1	Alpha actin, skeletal muscle	NM CFTD Cap myopathy	AD, AR AD, AR AD, AR AD, AR
<i>TNNT1</i>	19q13.4	Slow troponin T	NM	AR
TPM2	9p13	Tropomyosin 2 (beta)	NM Cap myopathy DA1A DA2B Escobar syndrome	AD AD AD AD AR
TPM3	1q21.2	Tropomyosin 3	NM CFTD Cap myopathy	AD AD AD
<i>MYH2</i>	17p13.1	Myosin, heavy polypeptide 2, skeletal muscle	CM with EOM	AD, AR
<i>MYH3</i>	17p13.1	Myosin, heavy polypeptide 3, skeletal muscle, embryonic	DA 2A, 2B and 8	AD
<i>MYH7</i>	14q12	Myosin, heavy polypeptide 7, cardiac muscle, beta	CFTD MmD MSM	AD AR AR
<i>MYH8</i>	17p13.1	Myosin, heavy polypeptide 8, skeletal muscle, neonatal	Trismus, pseudocamptodactyly syndrome Carney complex	AD AD
<i>KBTBD13</i>	15q22.31	Kelch repeat and BTB (POZ) domain containing 13	NM with cores	AD

KLHL40	2p22.1	Kelch-like family member 40	NM	AR
KLHL41	2q31.1	Kelch-like family member 41	NM	AR
LMOD3	3p14.1	Leiomodin 3 (fetal)	NM	AR
MYBP3	11p11.2	Cardiac myosin binding protein-C	CM with cardiomyopathy	AR
MYPN	10q21.3	Myopalladin	NM with cardiomyopathy	AR
TTN	2q31	Titin	CNM MmD	AR AR
Proteins involved in other cellular processes or with unknown functions				
CFL2	14q12	Cofilin 2 (muscle)	NM with cores	AR
CNTN1	12q11-q12	Contactin-1	CM lethal	AR
ECEL1	2q37.1	Endothelin converting enzyme-like protein 1	DA5	AR
PIEZO2	18p11.2 1-22	Piezo-Type mechanosensitive ion channel component 2	Marden-Walker syndrome DA3 DA5 DA with impaired proprioception	AD AD AD AR
MEGF10	5q23.2	Multiple EGF-like-domains 10	CM with minicores CM with areflexia, respiratory distress and dysphagia	AR AR
HACD1	10p12.3 3	Protein tyrosine phosphatase-like (3-Hydroxyacyl-CoA dehydratase	CM	AR
SCN4A	17q23.3	Sodium channel, voltage gated type IV, alpha subunit	CM	AR
TRIM32	9q33.2	Tripartite motif-containing 32	Sarcotubular myopathy	AR
PYROXD1	12p12.1	Pyridine nucleotide-disulfide oxidoreductase domain-containing protein	CM	AR

Table 2

Gene	RYR1	RYR1	SEPN1		MTM1	DNM2	NEB	ACTA1	
Frequency	+++	+++	++	++	++	+	++	++	+

Onset									
- Infancy	++	+++	+		+++	+	+++	++	+++
- Childhood	+++	++	+++	+	+	+	+	++	+
- Adulthood	++	+	-	-	-	+++	-	-	-
Clinical									
- EOM	+	+++	-	-	+++	+++	-	-	++
- Bulbar	+	+++	++	++	+++	++	++	++	+++
- Distal	-	+	-	++	+	+++	++	+	+
- Respiratory	+	++	+++	++	+++	+	++	++	+++
- Cardiac	-	+	+ ^a		-	-	-	+	
- Contractures	+	+	+		+++	++	++	++	+++
Histopathology									
- Cores	+++	+++	+++	++	-	+	+	+	
- Central nuclei	++	++	-		+++	+++	-	-	
- Nemaline rods	+	+	-	+	-	-	+++	+++	+++
- FTD	+	+++	+	+	+	-	-	+	
- Connective	++	++	++		-	+	-	-	