The phenotype and genotype of congenital myopathies based on a large pediatric cohort

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Abstract

We report the clinical, histopathological and molecular characterization of 104 patients with congenital myopathy (CM) managed at a single center. The most common histopathological subtype was core myopathy (42%). Patients with severe endomysial fibrosis were more commonly unable to walk than patients with only a mild grade (56% vs 16%). Inability to walk was also more prevalent in patients with severe fatty replacement (44% vs 19%). The genetic etiology was more frequently identified among those patients with "specific" histologic findings (74% vs 62%). A definite molecular diagnosis was reached in 65/104 patients (62%), with RYR1 (24/104) and TTN (8/104) as the most frequent causative genes. Neonatal onset occurred in 56%. Independent ambulation was achieved by 74%. Patients who walked late were more likely to become wheelchair-dependent. Respiratory support was needed in 1/3 patients. Gastrostomy placement was required in 15%. Cardiac involvement was observed in 3%, scoliosis in 43%, and intellectual disability in 6%. This study provides an updated picture of the clinical, histopathological and molecular landscape of CMs. Independently of the causative gene, fibrosis and fatty replacement in muscle biopsy is significantly associated with clinical severity. Mutations in TTN are responsible for a higher proportion of cases than previously thought.

1. Introduction

Congenital myopathies (CMs) are a clinically and genetically heterogeneous group of hereditary muscular disorders typically characterized by hypotonia, early-onset weakness, and distinctive structural abnormalities in muscle biopsy samples (Gonorazky et al., 2018; Jungbluth et al., 2018; Ravenscroft et al., 2018; Claeys, 2019). They have been classified based on distinctive histopathologic features into four broad subtypes: nemaline myopathies, core myopathies, centronuclear myopathies, and congenital fiber type disproportion (North et al., 2014; Phadke, 2019). Advances in molecular genetics have led to a better understanding of the complex relationship between the genotype and the clinicopathologic phenotypes: Mutations in the same gene can result in more than one pathological feature and clinical phenotype. At the same time, mutations in different genes may cause the same clinicopathological features, often due to the similar function of the

defective gene products (Romero and Clarke, 2013; Colombo et al., 2015; Sewry and Wallgren-Pettersson, 2017).

The increasing accessibility of next-generation sequencing methods has resulted in a rising proportion of patients with a genetic diagnosis. Despite this, the genetic cause is still unknown in roughly 30-50% of patients (Maggi et al., 2013; Colombo et al., 2015; Witting et al., 2017). The distribution of genetic and histologic subtypes has been addressed in only a few cohorts (Colombo et al., 2015; Witting et al., 2017; Park et al., 2018). A better understanding of their distribution is key, as new therapies begin to show promising results (Rendu et al., 2013; Childers et al., 2014; Cowling et al., 2014; Sabha et al., 2016; Dowling et al., 2018). Since genetic testing is increasingly the primary diagnostic approach, a more detailed understanding of the relationship between phenotypes and genotypes would be highly helpful for corroborating the genetic findings, which are often difficult to interpret.

We report the clinical, histopathological and molecular characterization of 104 patients with congenital myopathy managed at a single reference center for neuromuscular disorders. We focus in particular on comparing phenotype and genotype.

2. Methods

2.1 Study design and patients

This retrospective cross-sectional data collection study of a clinical series with a diagnosis of congenital myopathy was conducted at Hospital Sant Joan de Déu in Barcelona, Spain. Clinical, histopathologic and genetic data were collected from all patients followed at the Neuromuscular Unit between January 1990 and January 2020 who showed (i) an evocative clinical phenotype (congenital/early childhood onset with hypotonia and/or static/progressive weakness, affecting predominantly proximal/axial muscles, as well as normal/mildly elevated serum creatine kinase), (ii) histopathologic features compatible with CM, and/or (iii) a genetic diagnosis. Phenotype data were collected from patient and family interviews, physical examinations, medical records and patient questionnaires. Muscle biopsies from all patients were specifically reviewed for this study. Data collection was carried out following the guidelines of the Clinical Ethics Committee of Hospital Sant Joan de Déu.

We collected demographic information (age, sex, and ethnic origin) and natural history data (age at symptom onset, age at clinical diagnosis and history of motor developmental milestones gained and/or lost). Other relevant medical and surgical history was collected, with attention to weakness distribution, respiratory function, scoliosis, contractures, as well as cardiac, bulbar (gastrostomy insertion), and cognitive involvement.

2.2 Histopathological studies

We obtained muscle biopsy specimens after informed consent following institutional guidelines. Biopsies were sampled from vastus lateralis or deltoids and were frozen and stained according to standard histological and histochemical techniques. All the muscle biopsies were expressly reviewed, categorized and rated for this study by a pathologist (CJ), two clinical scientists (CJM, AC) and a pediatric neurologist (DNB) who were blind to all phenotypic and genotypic information of the patients. Electron microscopy was performed in selected cases. Cases were classified according to biopsies as 1) nemaline myopathy, 2) core myopathy (including central core disease and multiminicore disease), 3) centronuclear myopathy, 4) congenital fiber type disproportion, and 5) unspecific myopathic changes.

The variables collected after reviewing each muscle biopsy were fiber size variation (yes/no), endomysial fibrosis (rated from "No fibrosis" to "Fibrosis (+++)"), fatty infiltration (rated from "No fatty infiltration" to "Fatty infiltration (+++)"), proportion of fibers with internalized nuclei, proportion of fibers with cores, proportion of fibers with accumulated material, and fiber type predominance. Endomysial fibrosis and fatty infiltration were rated according to visual rating scales specifically designed for this. Reference images were devised (see **Supplementary Figure 1)** . Based on the magnitude, a value between - and +++ was assigned to both endomysial fibrosis and fatty infiltration.

2.3 Genetic and genomic analyses

Genomic DNA was isolated from venous blood samples using a blood DNA extraction kit according to the manufacturer's recommendations. Genetic analyses were performed according to the histologic and clinical phenotype depending on the genetic testing procedures available at the time, including 1) single gene sequencing by PCR amplification and Sanger sequencing of coding exons and 2) next-generation sequencing studies. Different next-generation sequencing methodologies were used to prepare and capture genomic DNA libraries depending on the availability at the time and the histological and clinical phenotype, ranging from customized panels for selected genes to complete exome sequencing (Nextera Rapid Capture and TruSight One, Illumina, San Diego, CA, USA). Informed consent from parents was obtained in every case.

2.4 Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences 24.0 (IBM SPSS Statistics 24.0, Chicago, IL, USA). Descriptive statistics were used to summarize the demographic and medical characteristics of patients. Data are presented as mean ± standard deviation (SD) or median and range where appropriate.

3. Results

3.1 Demographics

Our cohort totaled 104 patients (57 males, 47 females) from 94 unrelated families. Eighty-two out of 104 patients were Spanish of Caucasian origin and 7 of Roma origin. Eight patients were Moroccan, 2 Senegalese, 2 Ecuadorian, 1 Argentinian, 1 Venezuelan, and 1 Filipino. Twelve of the patients were born from consanguineous couples. The mean age at last evaluation was 12.5 years (SD ± 9.2), ranging from the neonatal period to 43 years, because a few selected cases were followed into adulthood and affected parents were included in this work.

3.2 Age at onset, best motor abilities and mobility of the overall series

Antenatal or neonatal onset was common (58/104, 56%), while roughly one in five patients presented beyond the first year of life (21/104, 20%). Six individuals (6/104, 6%) died during their first year of life. Eight of 98 patients (8%) were never able to sit unsupported. Independent ambulation was achieved by 73 of 98 patients (74%). Most of these patients (84%) acquired it after the normal limit of 18 months. Only four patients (5%) who acquired independent ambulation eventually became wheelchair-dependent (mean age: 8.3 years, SD 4. Range: 4-12 years). Three of the four patients who lost the ability to walk had been late walkers (gait acquired at 24, 26 and 48 months, respectively). Patients who achieved independent ambulation after 24 months were more likely to become completely wheelchair-dependent (10.7%) compared with those who acquired ambulation before 24 months (2.2%) (Fisher exact test; p=0.154; OR:5.280). Overall, 48% of patients were able to run.

3.3 Histopathology

A muscle biopsy was performed in 95 of 104 patients (91.3%) at a mean age of 6.5 years (SD:6.4; median:5). The most common diagnosis was core myopathy (40/95, 42%), including central core (9/95), multiminicores (6/95), core-rods (7/95) and dusty or irregular cores (18/95). It was followed by nemaline myopathy (15/95, 16%), centronuclear myopathy (13/95, 14%), and congenital fiber type disproportion (3/95, 3%). Twenty-one patients (22%) had no specific histologic features and were classified as "biopsy with unspecific myopathic changes." Three of the biopsies were classified as "non assessable" (**Figure 1**).

Fibrosis and fatty replacement were significantly more prevalent in the muscle biopsies of patients with severe clinical phenotypes (**Figure 2).** A strong positive correlation between endomysial fibrosis and clinical severity was found. Patients with severe endomysial fibrosis (++ and +++ in the visual rating scale) were more commonly unable to walk independently than patients without endomysial fibrosis or with only a mild grade (56% vs 16%. Chi-square test; p=0.001; OR:0.153). Inability to walk was also more prevalent in patients with high fatty replacement (++ and +++ in the visual rating scale) (44% vs. 19%. p=0.026;

OR:0.286). As the only exception to these two general rules, patients with *MTM1* -CM had severe clinical phenotypes with mild fibrosis and fatty replacement, similar to a previously reported series (Shichiji et al., 2013). A regression model was performed to adjust for age at muscle biopsy, that may be a potential confounding factor, and strong positive correlations were also found between endomysial fibrosis and clinical severity (p=0.001; OR:0.093), and fatty replacement and clinical severity (p=0.011; OR:0.162). Correlations between clinical severity and other muscle biopsy findings, including central displacement of nuclei, cores, and nemaline rods, were not statistically significant. Even so, 5 of the 6 individuals who died during their first year of life were affected by nemaline myopathy and the other one by centronuclear myopathy.

3.4 Gene distribution and genetic-histopathological correlations

A genetic diagnosis was established in 65 of 104 patients (62%), corresponding to 59 of 94 families (63%). It was obtained by single gene sequencing in 14 index patients (24%) and by an NGS gene panel or whole-exome sequencing in 45 index patients (76%). *RYR1* was the most common underlying gene, representing 23.1% of the total (24 of 104), of which 14 (13.5%) had autosomal dominant inheritance and 10 (9.6%) segregated as an autosomal recessive pattern. It was followed by *TTN* (7.7%), *MTM1* (6.7%), *SELENON* (6.7%),*NEB* (3.8%), *DNM2* (2.9%), *ACTA1* (1.9%),*MYH7* (1.9%), *TPM3* (1.9%), *TPM2* (1%), *MYH3*(1%), *PYROXD1* (1%), *DES* (1%), *KLHL40* (1%) and *TRIP4* (1%). **Figure 1** shows the number of patients per individual congenital myopathy subtype. In total, 77 distinct genetic variants were identified. **Table 1** shows the variants and their evidence of pathogenicity and evidence of benign impact to the guidelines of the ACMG (Richards et al., 2015)). NGS gene panels or whole-exome sequencing were performed in 26 of the 35 index patients who still remain unsolved.

Similarly to a recent study conducted in Denmark (Witting et al., 2017), the genetic diagnostic yield tend to be higher in patients with specific histologic findings despite it was not statistically significant. A genetic etiology was identified in 74% of patients with specific histologic findings (cores, nemaline myopathy, centronuclear myopathy, or congenital fiber type disproportion), whereas it was identified in 62% of patients with unspecific myopathic changes (Chi-square test; p=0.303; OR:1.731) (**Figure 3**).

Distinct histopathological findings were identified in the most common genetic subtypes (**Figure 4).** Muscle biopsies of *MTM1* patients universally had central nuclei but not fibrosis or fatty infiltration. Among biopsies of *SELENON* patients, multiminicores were common. Within the *TTN* group, internal nuclei, cores and predominance of type 1 fibers were frequent. The majority of *RYR1* patients had central cores.

3.5 Delineation of the phenotype and genotype-phenotype correlation

3.5.1 Age at onset and best motor abilities

Age at onset and best motor abilities achieved by patients varied depending on the causative gene (**Figure 5)** . At opposite ends, individuals with *MTM* -CM invariably presented in the neonatal period (100%) and often never could walk independently (75%), whereas *SELENON* -CM patients frequently presented after the first year of life (58%) and acquired the ability to walk in all the cases. Among patients who walked and eventually became wheelchair-dependent one had *DNM2* -CM, one had *TTN* -CM and one had AR-*RYR1* -CM.

3.5.2 Respiratory involvement, bulbar impairment, scoliosis and cardiac complications

Respiratory support was needed by 34 of 104 patients (33%). Nocturnal noninvasive ventilation (NNIV) support was required by 26.2% of patients (27/103) at a mean age of 7.8 years (SD:4.8) and was more frequent in some subtypes than in others (71% of *SELENON* -CM patients vs. 12% of *TTN* -CM patients). Invasive ventilation was reported in 7 of 103 patients (6.8%), mainly with *MTM1* mutations (3/5, 60%) and from the first year of life (**Figure 6A**). Gastrostomy placement was required in 14.9% (14/101) at a median age of 2 years (mean 5.1, range from birth to 30 years). Three additional patients in whom a nasogastric tube was required died during their first year of life. Three of the 17 patients with gastrostomy improved to the extent that it became unnecessary (removed at 2, 2.5 and 5 years). Scoliosis of variable severity was developed by 42 of 98 patients (42.8%), with 31% of them (13/42) requiring surgery at a mean age of 12 years (median

13 years, SD 4.4, age range: 3-17 years). Kaplan-Meier curves showing ventilation-free, gastrostomy-free, and scoliosis surgery-free patients by age are showed in **Figure 6B.** Cardiac involvement was found only in 3 of 97 patients (3.1%) that were assessed using electrocardiography, echocardiography, and Holter monitoring when it was considered necessary. A mild mitral regurgitation was found in a 10-year-old patient with *TTN* -CM, a mild anterior mitral valve prolapse was observed in a genetically unresolved 29-year-old patient, and an atrial septal defect was detected in a 1-year-old patient with *MTM1* -CM. In 48 of 97 patients (49%) the last cardiac assessment was performed when they were under 10 years old and only 9 of 97 patients (9%) were assessed after the age of 20 years.

3.5.3 Intellectual disability

Interestingly, intellectual disability or psychomotor delay was found in 11 of 99 patients (11%). Five of these 11 patients (64%) had alternative causes to explain their cognitive impairment: four were born prematurely (gestational age at birth: 28, 31, 32 and 36 weeks, respectively) and one required ventilatory support during the neonatal period. Five of the six patients with intellectual disability without alternative explanation (6%) were genetically unresolved. A patient with *DNM2* -CM had refractory epilepsy and mild intellectual disability (IQ: 69).

3.5.4 Clinical clues to the genetic etiology

From our detailed examination, distinct phenotypes could be recognized in the most common genetic subtypes (**Figure 7**). Proximal weakness was almost universal (99/104, 95%), independently of the causative gene. An associated distal involvement was reported in 42 of 104 patients (40%), mainly with *TTN* and *MTM1* mutations (8/8, 100%, and 4/5, 80%, respectively). Overall, facial weakness was observed in 68 of 103 patients (66%). It was almost universally detected in patients with *MTM1* and *RYR1* mutations, whereas it was less common in patients with *TTN* mutations (3/8, 38%). Severe ophthalmoplegia, sometimes associated with ptosis, was exclusively observed in patients with recessive *RYR1* , *MTM1*or *DNM2* (7/10, 70%; 4/4, 100%; and 2/3, 67%), coinciding with previous research (Klein et al., 2012; North et al., 2014). Patients with *SELENON* , and autosomal recessive *RYR1* mutations had a tendency toward scoliosis (5/7, 64% and 8/10, 80%, respectively), compared to the entire cohort (42/99, 42%). A rigid spine was observed in 6 patients with *SELENON* -CM and 1 with *TTN* -CM.

4 Discussion

We provide a comprehensive picture of the natural history of CMs. This includes the updated distribution of genotypes and histologic subtypes in the CM population. Moreover, a holistic assessment of the condition was conducted in order to better define the phenotype–genotype correlation. Clinical characteristics, histopathological patterns and genetic findings were addressed through (1) a long-term clinical follow up, (2) a review of muscle biopsies conducted expressly for this study, and (3) up-to-date genetic results in a large cohort of patients with CM.

From the histopathological point of view, our data demonstrated that the degree of fibrosis and fatty replacement in the muscle biopsy are significantly associated with clinical severity, independently of the causative gene. Core myopathies (central core and multiminicore disease) were the most common histologic subtypes, as reported in UK-based pediatric cohorts (Maggi et al., 2013; Colombo et al., 2015). The genetic diagnosis was more frequently achieved among patients with "specific" histologic findings, and diagnostic yield was particularly high in nemaline myopathies.

Roughly 60% of patients in our CM cohort received a molecular diagnosis, a similar proportion to that found in some series (Witting et al., 2017; Park et al., 2018) but lower than in others in which patients with non-specific histopathological abnormalities were excluded (Maggi et al., 2013; Colombo et al., 2015). As in previous research,*RYR1* mutations were the most common cause of CM. Most notable is the proportion of *TTN* -CM in our cohort, conspicuously higher than in others. A plausible explanation for this difference is that many congenital titinopathies, that were unresolved until recently, are emerging as a consequence of the implementation of NGS into routine clinical practice (Chauveau et al., 2014; Oates et al., 2018). Moreover,

the widespread use of NGS has led to the identification of an increasing number of rare and private titin variants that are still difficult to interpret. Therefore, the number of patients diagnosed with *TTN* -CM is expected to increase further, consolidating *TTN* as the second most common causative gene of congenital myopathy.

Our data verified some clinical data reported in other cohorts of patients with congenital myopathy and explored other aspects, such as cardiac and cognitive involvement, which have been scarcely analyzed. The onset of clinical signs was observed predominantly within the first year of life (slightly more than 50% of patients presented in the neonatal period), independent ambulation was achieved by 3 out of 4 patients, and the course was static or slowly progressive in the majority of cases. However, some specific ambulant patients became wheelchair-dependent before age 12. Interestingly, we found that patients who achieved independent ambulation before age 2 were more likely to keep walking than those who were late walkers. Respiratory support was needed in 1 out of 3 patients and highly dependent on the causative gene: it was needed by all patients with *MTM1* mutations and by roughly 70% of those with *SELENON* mutations. Although it should be noted that cardiac assessment in our cohort were mostly performed at children´s age, a very low prevalence of cardiac involvement was found, in accordance with a recently published cohort of Danish patients with CM (Petri et al., 2019). None of our patients was diagnosed with dilated or hypertrophic cardiomyopathy or had symptoms and/or signs of heart failure. Early-onset scoliosis was common, being observed in more than a third of patients, but severe cases were not frequent: Spine surgery was performed only in 13% of all CMs. Intellectual disability in the absence of prematurity or perinatal events history was observed in 6% of patients. The majority of these patients with intellectual disability had non-specific histopathological abnormalities and remained genetically unresolved. This suggests that there are unrevealed genes involved in the central nervous system pathophysiology that also lead to muscular weakness and induce myopathic changes, as revealed in muscle biopsy.

This study has some limitations. We performed a retrospective review of data collected in the course of patients' clinical care, and therefore, most but not all parameters for every patient were available. Some additional genetically unresolved cases of CM with nonspecific histologic findings may have gone undetected.

In summary, our study of a large cohort of patients with congenital myopathy provides an updated picture of the clinical, histopathological and molecular landscape of the condition. Previous studies had described the main clinical characteristics and some well-established genotype-phenotype correlations in CM. However, a regular updating of information is essential in the current context of gene discovery and continuous identification of new pathogenic variants in already known genes, which leads to substantial variations in the distribution of CM subtypes.

We extend prior studies of CMs by offering a comprehensive analysis of the relationship between the genotype and not only the clinical but also the histopathological phenotype. This information will be helpful to clinicians in three areas. First, it will help clinicians and geneticists to evaluate and interpret the genetic variants of unknown significance. Second, it will allow them to speculate about the most probable underlying causative gene in patients that remain unresolved after NGS studies, prioritize the gene candidates, and hence guide the diagnostic testing strategy. Mutations in noncoding DNA regions, as well as large copy number variations (CNVs) and rearrangements are likely to be the causative mutations in many still-unresolved cases (Pelin and Wallgren-Pettersson, 2019). Third, it will enable clinicians to develop a more accurate prognosis according to genotype and histopathological findings, thus enabling optimized anticipatory clinical care.

Given that gene therapies for CMs are being developed widely, accurate genotype-phenotype correlations and natural history studies are essential to improve clinical trial design and data analysis processes. Multicenter collaborative studies are desirable in order to gain deeper insight into the natural history of the specific CM subgroups and thus better assess the response to the exciting treatment approaches that are in the pipeline.

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Conflicts of interest None of the authors has any conflict of interest to disclose.

Ethics/Consent to participation Data collection was carried out following the guidelines of the Clinical Ethics Committee of Hospital Sant Joan de Déu. All participation was by signed informed consent.

Data availability Any data not published within the article will be shared from the corresponding author, upon reasonable request.

Web resources :

CADD,*https://cadd.gs.washington.edu/snv*

ClinVar,*https://www.ncbi.nlm.nih.gov/clinvar/*

Franklin,*https://franklin.genoox.com/clinical-db/home*

GnomAD,*https://gnomad.broadinstitute.org*

Human Gene Mutation Database,*http://www.hgmd.cf.ac.uk/ac/index.php*

HGVS nomenclature recommendations,*http://www.hgvs.org/content/guidelines*

LOVD, *http://www.lovd.nl/*

Mutalyzer,*https://mutalyzer.nl/index*

Mutation taster,*http://www.mutationtaster.org*

OMIM, *https://www.omim.org/*

PolyPhen-2,*http://genetics.bwh.harvard.edu/pph2/index.shtml*

Provean,*http://provean.jcvi.org/genome_submit_2.php?species=human*

UCSC Genome Browser,*https://genome-euro.ucsc.edu/index.html*

Varsome, *https://varsome.com*

References

Chauveau C, Rowell J, Ferreiro A. 2014. A rising titan: TTN review and mutation update. Hum Mutat 35:1046–1059.

Childers MK, Joubert R, Poulard K, Moal C, Grange RW, Doering JA, Lawlor MW, Rider BE, Jamet T, Danièle N, Martin S, Rivière C, et al. 2014. Gene therapy prolongs survival and restores function in murine and canine models of myotubular myopathy. Sci Transl Med 6:220ra10.

Claeys KG. 2019. Congenital myopathies: an update. Dev Med Child Neurol 62:297–302.

Colombo I, Scoto M, Manzur AY, Robb SA, Maggi L, Gowda V, Cullup T, Yau M, Phadke R, Sewry C, Jungbluth H, Muntoni F. 2015. Congenital myopathies : Natural history of a large pediatric cohort. Neurology 84:28–35.

Cowling BS, Chevremont T, Prokic I, Kretz C, Ferry A, Coirault C, Koutsopoulos O, Laugel V, Romero NB, Laporte J. 2014. Reducing dynamin 2 expression rescues X-linked centronuclear myopathy. J Clin Invest 124:1350–1363.

Dowling JJ, D. Gonorazky H, Cohn RD, Campbell C. 2018. Treating pediatric neuromuscular disorders: The future is now. Am J Med Genet Part A 176:804–841.

Gonorazky HD, Bonnemann CG, Dowling JJ. 2018. The genetics of congenital myopathies. Handb Clin Neurol 148:549–564.

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. Nat Rev Neurol 14:151–167.

Klein A, Lillis S, Munteanu I, Scoto M, Zhou H, Quinlivan R, Straub V, Manzur AY, Roper H, Jeannet PY, Rakowicz W, Jones DH, et al. 2012. Clinical and genetic findings in a large cohort of patients with ryanodine receptor 1 gene-associated myopathies. Hum Mutat 33:981–988.

Maggi L, Scoto M, Cirak S, Robb SA, Klein A, Lillis S, Cullup T, Feng L, Manzur AY, Sewry CA, Abbs S, Jungbluth H, et al. 2013. Congenital myopathies–clinical features and frequency of individual subtypes diagnosed over a 5-year period in the United Kingdom. Neuromuscul Disord 23:195–205.

North KN, Wang CH, Clarke N, Jungbluth H, Vainzof M, Dowling JJ, Amburgey K, Quijano-Roy S, Beggs AH, Sewry C, Laing NG, Bonnemann CG, et al. 2014. Approach to the diagnosis of congenital myopathies. Neuromuscul Disord 24:97–116.

Oates EC, Jones KJ, Donkervoort S, Charlton A, Brammah S, Smith JE, Ware JS, Yau KS, Swanson LC, Whiffin N, Peduto AJ, Bournazos A, et al. 2018. Congenital Titinopathy: Comprehensive characterization and pathogenic insights. Ann Neurol 83:1105–1124.

Park YE, Shin JH, Kim HS, Lee CH, Kim DS. 2018. Characterization of congenital myopathies at a Korean neuromuscular center. Muscle and Nerve 58:235–244.

Pelin K, Wallgren-Pettersson C. 2019. Update on the Genetics of Congenital Myopathies. Semin Pediatr Neurol 29:12–22.

Petri H, Wahbi K, Witting N, Kober L, Bundgaard H, Kamoun E, Vellieux G, Stojkovic T, Behin A, Laforet P, Vissing J. 2019. Congenital myopathies are mainly associated with a mild cardiac phenotype. J Neurol 266:1367–1375.

Phadke R. 2019. Myopathology of Congenital Myopathies: Bridging the Old and the New. Semin Pediatr Neurol 29:55–70.

Ravenscroft G, Bryson-Richardson RJ, Nowak KJ, Laing NG. 2018. Recent advances in understanding congenital myopathies. F1000Research 7:1921.

Rendu J, Brocard J, Denarier E, Monnier N, Pietri-Rouxel F, Beley C, Roux-Buisson N, Gilbert-Dussardier B, Perez MJ, Romero N, Garcia L, Lunardi J, et al. 2013. 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.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL. 2015. Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 17:405–424.

Romero NB, Clarke NF. 2013. Congenital myopathies. Handb Clin Neurol 113:1321–1336.

Sabha N, Volpatti JR, Gonorazky H, Reifler A, Davidson AE, Li X, Eltayeb NM, Dall'Armi C, Paolo G Di, Brooks S V., Buj-Bello A, Feldman EL, et al. 2016. PIK3C2B inhibition improves function and prolongs survival in myotubular myopathy animal models. J Clin Invest 126:3613–3625.

Sewry CA, Wallgren-Pettersson C. 2017. Myopathology in congenital myopathies. Neuropathol Appl Neurobiol 43:5–23.

Shichiji M, Biancalana V, Fardeau M, Hogrel JY, Osawa M, Laporte J, Romero NB. 2013. Extensive morphological and immunohistochemical characterization in myotubular myopathy. Brain Behav 3:476–486.

Witting N, Werlauff U, Duno M, Vissing J. 2017. Phenotypes, genotypes, and prevalence of congenital myopathies older than 5 years in Denmark. Neurol Genet 3:e140.

Table 1 . Clinical, histopathological and genetic information of all patients of our cohort. Note: Nucleotide numbering is according to the reference transcripts *RYR1* NM_000540.2; *TTN* NM_001267550.1: *SELENON* NM_020451.2; *MTM1* NM_000252.2;*NEB* NM_001164507.1; *DNM2* NM_001005360.2; *MYH7* NM_000257.2; *TPM3* NM_152263.2;*TPM2* NM_003289.3; *MYH3* NM_002470.3; *PYROXD1* NM_024854.3; *DES* NM_001927.3; *ACTA1* NM_001100.3;*KLHL40* NM_152393.3; *TRIP4* NM_016213.4. Evidence of pathogenicity and evidence of benign impact of variants according to the guidelines of the ACMG are indicated (Richards et al., 2015). Abbreviations: ACMG=American College of Medical Genetics and Genomics; LP=Likely pathogenic; NGT= nasogastric tube; NIV= non-invasive ventilation; NNIV= nocturnal non-invasive ventilation; Pat=Pathogenic; TRAC= permanent tracheostomy; OTI= orotracheal intubation; VUS=Variant of uncertain significance.

Pt	Fam	Sex	Age last seen/ death (y)	Gene (pattern of inheritance)	Mutation(s) ACMG evidence of pathogenicity	Histopathological pattern	Age at onset (symptoms)	Maximal motor ability (age; y)	Ptosis/ Ophthalmoplegia Facial weakness/ Neck flexors weakness/ Proximal weakness/ Distal weakness	Gastrostomy (age; y)	Respiratory Support (age; y)	Respiratory Support (age; y)	Scoli (Sur Yes/ age a surg (y))
1	1	F	6	*RYR1* (AD)	**c.7111G>A; p.Glu2371Lys** LP (PM1, PM2, PM6, PP3, PP5)	Cores	2m (hypotonia)	Walking (2.5)	n/n/y/y/y/n				Yes (no surg
2	2	F	21	*RYR1* (AD)	**c.14581C>T; p.Arg4861Cys** Pat (PM1, PM2, PM5, PM6, PP3, PP5)	Cores	Newborn (hypotonia)	Sitting (1)	n/n/y/y/y/n	NNIV (13y)	NNIV (13y)		Yes (surg at 13

Pt	Fam	Sex	Age last seen/ death (y)	Gene (pattern of inheritance)	Mutation(s) ACMG evidence of pathogenicity	Histopathological pattern	Age at onset (y) (symptoms)	Maximal motor ability (age; y)	Ptosis/ Ophthalmoplegia Facial weakness/ Neck flexors weakness/ Proximal weakness/ Distal weakness	Gastrostomy (age; y)	Respiratory Support (age; y)	Respiratory Support (age; y)	Scoli (Sur Yes/ age a surg (y))
3	3	F	6	*RYR1* (AD)	**c.14693T>C; p.Ile4898Thr** Pat (PM1, PM2, PM6, PP3, PP5)		Newborn (hypotonia)	Sitting (0.5)	n/n/n/n/y/n				
4	4	M	9	*RYR1* (AD)	**c.14819C>T; p.Ala4940Val** LP (PM1, PM2, PM5, PM6, PP3)		Newborn (severe weakness, arthrogryposis)	Sitting (4)	n/n/y/y/y/n		NNIV (8m)	NNIV (8m)	Yes (surg at 3)
5	5	F	7	*RYR1* (AD)	**c.14582G>A; p.Arg4861His** LP (PM1, PM2, PM6, PP3)		Newborn (hypotonia)	Walking (3)	n/n/y/y/y/n				Yes (no surg
6	6	F	43	*RYR1* (AD)	**c.14498A>G; p.His4833Pro** LP (PM1, PM2, PP1, PP3)		1y (weakness)	Walking (2.5) (Running)	n/n/y/y/y/n				

Pt	Fam	Sex	Age last seen/ death (y)	Gene (pattern of inheritance)	Mutation(s) ACMG evidence of pathogenicity	Histopathological pattern	Age at onset (y) (symptoms)	Maximal motor ability (age; y)	Ptosis/ Ophthalmoplegia Facial weakness/ Neck flexors weakness/ Proximal weakness/ Distal weakness	Gastrostomy (age; y)	Respiratory Support (age; y)	Respiratory Support (age; y)	Scoli (Sur Yes/ age a surg (y))
7	6	M	12	*RYR1* (AD)	**c.14498A>C; p.His4833Pro** LP (PM1, PM2, PP1, PP3)	Not performed	2y (weakness)	Walking (1.2) (Running)	n/n/y/y/y/n				
8	7	M	5	*RYR1* (AD)	**c.13913G>T; p.Gly4638Val** LP (PM1, PM2, PM5, PM6, PP3)		1.5y (motor delay)	Walking (1.6)	n/n/y/y/y/n				
9	8	F	36	*RYR1* (AD)	**c.13910C>A; p.Thr4637Lys** LP (PM2, PM5, PM6, PP3)		Newborn (hypotonia)	Sitting (1.5)	n/n/y/y/y/n				Yes (surg at 15
10	9	M	8	*RYR1* (AD)	**c.14804G>A; p.Gly4935Asp** LP (PM1, PM5, PM6, PP3)		Newborn (hypotonia)	Walking (2)	n/n/y/y/y/n				Yes (no surg

Pt	Fam	Sex	Age last seen/ death (y)	Gene (pattern of inheritance)	Mutation(s) ACMG evidence of pathogenicity	Histopathological pattern	Age at onset (y) (symptoms)	Maximal motor ability (age; y)	Ptosis/ Ophthalmoplegia Facial weakness/ Neck flexors weakness/ Proximal weakness/ Distal weakness	Gastrostomy (age; y)	Respiratory Support (age; y)	Respiratory Support (age; y)	Scoli (Sur Yes/ age a surg (y))
11	10	M	23	*RYR1* (AD)	**c.13732T>G; p.Leu4578Val** VUS (PM2, PM6, PP3)	Unspecific	Prenatal (arthrogryposis)	Sitting	n/y/y/y/y/n				Yes (surg at 16
12	11	F	10	*RYR1* (AD)	**c.11696A>G; p.Gln 3899Arg** LP (PM2, PM6, PP1, PP3)	Unspecific	1y (weakness)	Walking (1) (Running)	n/n/y/y/y/n				
13	11	F	38	*RYR1* (AD)	**c.11696A>G; p.Gln 3899Arg** LP (PM2, PM6, PP1, PP3)	Not performed	10m (weakness)	Walking (1.2) (Running)	n/n/y/y/y/n				Yes (no surg
14	12	M	8	*RYR1* (AD)	**c.12083C>T; p.Ser4028Leu** LP (PM2, PM6, PP5)	Unspecific	1y (weakness)	Walking (0.9) (Running)	n/n/y/y/y/y				

Pt	Fam	Sex	Age last seen/ death (y)	Gene (pattern of inheritance)	Mutation(s) ACMG evidence of pathogenicity	Histopathological pattern	Age at onset (y) (symptoms)	Maximal motor ability (age; y)	Ptosis/ Ophthalmoplegia Facial weakness/ Neck flexors weakness/ Proximal weakness/ Distal weakness	Gastrostomy (age; y)	Respiratory Support (age; y)	Respiratory Support (age; y)	Scoli (Sur Yes/ age a surg (y))
15	13	M	14	*RYR1* (AR)	**c.9157C>T; p.Arg3053*** Pat (PVS1, PM2, PM3, PP5) **c.7027G>A; p.Gly2343Ser** Pat (PM1, PM2, PM3, PP3, PP5)	CNM	3y (weakness)	Walking (1.2) (Running)	y/y/y/y/y/n				Yes (no surg
16	14	M	12	*RYR1* (AR)	**c.3362A>G; p.Tyr1121Cys** LP (PM2, PM3, PP5) **c.6891G>C; p.Lys2297Asn** VUS (PM2, PM3, PP3)	CNM	Newborn (severe weakness)	Sitting (4)	y/y/y/y/y/n	Yes (first year)	TRAC (1m)	TRAC (1m)	Yes (surg at 7)

Pt	Fam	Sex	Age last seen/ death (y)	Gene (pattern of inheritance)	Mutation(s) ACMG evidence of pathogenicity	Histopathological pattern	Age at onset (y) (symptoms)	Maximal motor ability (age; y)	Ptosis/ Ophthalmoplegia Facial weakness/ Neck flexors weakness/ Proximal weakness/ Distal weakness	Gastrostomy (age; y)	Respiratory Support (age; y)	Respiratory Support (age; y)	Scoli (Sur Yes/ age a surg (y))
17	15	M	16	*RYR1* (AR)	**c.641C>T; p.Thr214Met** VUS (PM1, PM2, PM3) **c.3523G>A; p.Glu1175Lys** VUS (PM2, PM3)	Cores	1y (weakness)	Walking (1.4)	n/n/y/y/y/n				Yes (no surg
18	16	M	7	*RYR1* (AR)	**c.11198C>A; p.Cys3733Tyr** VUS (PM2, PM3, PP3) **c.14630G>A; p.Cys4877Tyr** LP (PM1, PM2, PM3, PP3)	Unspecific	Newborn (hypotonia)	Sitting (3)	n/y/y/y/y/n	Yes (first year; removed at 2y)			Yes (no surg

Pt	Fam	Sex	Age last seen/ death (y)	Gene (pattern of inheritance)	Mutation(s) ACMG evidence of pathogenicity	Histopathological pattern	Age at onset (symptoms)	Maximal motor ability (age; y)	Ptosis/ Ophthalmoplegia Facial weakness/ Neck flexors weakness/ Proximal weakness/ Distal weakness	Gastrostomy (age; y)	Respiratory Support (age; y)	Respiratory Support (age; y)	Scoli (Sur Yes/ age a surg (y))
19	17	F	23	*RYR1* (AR)	**c.13691G>A; p.Arg4564Gln** VUS (PM2, PM3, PP3) **c.13892A>G; p.Tyr4631Cys** LP (PM1, PM2, PM3, PM5, PP3, PP5)	Cores	Prenatal (arthrogryposis)	Sitting (1.5 y)	n/n/y/y/y/n				Yes (surg at 12
20	17	F	21	*RYR1* (AR)	**c.13691G>A; p.Arg4564Gln** VUS (PM2, PM3, PP3) **c.13892A>G; p.Tyr4631Cys** LP (PM1, PM2, PM3, PM5, PP3, PP5)	Cores	Newborn (hypotonia)	Sitting (1 y)	n/n/y/y/y/n				Yes (no surg

Pt	Fam	Sex	Age last seen/ death (y)	Gene (pattern of inheritance)	Mutation(s) ACMG evidence of pathogenicity	Histopathological pattern	Age at onset (y) (symptoms)	Maximal motor ability (age; y)	Ptosis/ Ophthalmoplegia Facial weakness/ Neck flexors weakness/ Proximal weakness/ Distal weakness	Gastrostomy (age; y)	Respiratory Support (age; y)	Respiratory Support (age; y)	Scoli (Sur Yes/ age a surg (y))
21	18	F	14	*RYR1* (AR)	**c.325C>T; p.Arg109Trp** Pat (PM2, PM3, PP3, PP5) **c.8953C>T; p.Arg2985*** Pat (PVS1, PM2, PM3)	CCD	Newborn (hypotonia)	Walking (4)	n/y/y/y/y/n		NNIV (4y)	NNIV (4y)	Yes (surg at 11
22	19	F	13	*RYR1* (AR)	**c.325C>T; p.Arg109Trp** Pat (PM2, PM3, PP3, PP5) **c.6721C>T; p.Arg2241*** Pat (PVS1, PM2, PM3, PP5)	Variable	12m (weakness)	Walking (1) (Running)	n/y/y/n/y/n				

Pt	Fam	Sex	Age last seen/ death (y)	Gene (pattern of inheritance)	Mutation(s) ACMG evidence of pathogenicity	Histopathological pattern	Age at onset (y) (symptoms)	Maximal motor ability (age; y)	Ptosis/ Ophthalmoplegia Facial weakness/ Neck flexors weakness/ Proximal weakness/ Distal weakness	Gastrostomy (age; y)	Respiratory Support (age; y)	Respiratory Support (age; y)	Scoli (Sur Yes/ age a surg (y))
23	20	M	4	*RYR1* (AR)	**c.4837C>T; p.Gln1613*** Pat (PM2, PM3, PP3, PP5) **c.7027G>A; p.Gly2343Ser** Pat (PM1, PM2, PM3, PP3, PP5)	NM	5w (hypotonia)	Walking (1;8) (Running)	y/y/y/y/y/n				
24	21	F	15 d (death)	*RYR1* (AR)	**c.9415delG; p.Val3139fs** Pat (PVS1, PM2, PM3) **c.122T>C; p.Phe41Ser** LP (PM2, PM3, PP3, PP5)	Cores	Newborn (hypotonia)	Death (15d)	?/?/?/?/y/n				

Pt	Fam	Sex	Age last seen/ death (y)	Gene (pattern of inheritance)	Mutation(s) ACMG evidence of pathogenicity	Histopathological pattern	Age at onset (y) (symptoms)	Maximal motor ability (age; y)	Ptosis/ Ophthalmoplegia Facial weakness/ Neck flexors weakness/ Proximal weakness/ Distal weakness	Gastrostomy (age; y)	Respiratory Support (age; y)	Respiratory Support (age; y)	Scoli (Yes/ age a surg (y))
25	22	M	8	*TTN*	**c.19714+1G>A** LP (PVS1, PM2, PM3) **c.20056C>T; p.Arg6686*** Pat (PVS1, PM2, PM3)	Cores	Newborn (hypotonia)	Walking (1.5) (Running)	n/n/y/y/y/y				
26	23	F	12	*TTN*	**c.38661_38665del-GAAAA** Pat (PVS1, PM2, PM3) **c.17741-1G>A** LP (PVSP1, PM2, PM3, PP3, PP5)	Cores	Newborn (hypotonia)	Sitting (1.7)	n/n/n/y/y/y				Yes (no surg

Pt	Fam	Sex	Age last seen/ death (y)	Gene (pattern of inheritance)	Mutation(s) ACMG evidence of pathogenicity	Histopathological pattern	Age at onset (y) (symptoms)	Maximal motor ability (age; y)	Ptosis/ Ophthalmoplegia Facial weakness/ Neck flexors weakness/ Proximal weakness/ Distal weakness	Gastrostomy (age; y)	Respiratory Support (age; y)	Respiratory Support (age; y)	Scoli (Sur Yes/ age a surg (y))
27	24	M	8	*TTN*	**c.38655_-38659del; p.Lys12887Asnfs*6** Pat (PVS1, PM2, PM3, PP3) **c.38655_-38659del; p.Lys12887Asnfs*6** Pat (PVS1, PM2, PM3, PP3)	Cores	Newborn (hypotonia)	Sitting (1.3)	n/n/n/y/y/y				Yes (no surg
28	25	M	4	*TTN*	**c.59626G>A; p.Asp19876Asn** VUS (PM2, PM3) **c.38661_-38665del; p.Lys12887Asnfs*6** Pat (PVS1, PM2, PM3, PP3)	Dystrophic, non-specific	Newborn (hypotonia)	Sitting (1.5)	n/n/n/y/y/y				

Pt	Fam	Sex	Age last seen/ death (y)	Gene (pattern of inheritance)	Mutation(s) ACMG evidence of pathogenicity	Histopathological pattern	Age at onset (y) (symptoms)	Maximal motor ability (age; y)	Ptosis/ Ophthalmoplegia Facial weakness/ Neck flexors weakness/ Proximal weakness/ Distal weakness	Gastrostomy (age; y)	Respiratory Support (age; y)	Respiratory Support (age; y)	Scoli (Sur Yes/ age a surg (y))
29	26	M	9	*TTN*	**c.5884C>T; p.Gln1962*** Pat (PVS1, PM2, PM3) **c.19426+2T>A** LP (PVSP1, PM2, PM3)	Yes	1y (weakness)	Walking (1) (Running)	n/n/n/y/y/y				
30	27	F	3	*TTN*	**c.54615_54616delAA; p.Glu18207fs** Pat (PVS1, PM2, PM3) **c.61815A>G;p.Ile20605Met** VUS (PM2, PM3)	Unspecific	Newborn (hypotonia)	Sitting	n/n/n/y/y/y				

Pt	Fam	Sex	Age last seen/ death (y)	Gene (pattern of inheritance)	Mutation(s) ACMG evidence of pathogenicity	Histopathological pattern	Age at onset (y) (symptoms)	Maximal motor ability (age; y)	Ptosis/ Ophthalmoplegia Facial weakness/ Neck flexors weakness/ Proximal weakness/ Distal weakness	Gastrostomy (age; y)	Respiratory Support (age; y)	Respiratory Support (age; y)	Scoli (Sur Yes/ age a surg (y))
31	28	M	10	*TTN*	**c.8200_8217del; p.Asn2734_Gln2739del** LP (PM2, PM3, PM4) **c.8200_8217del; p.Asn2734_Gln2739del** LP (PM2, PM3, PM4)	Unspecific	Newborn (hypotonia)	Walking (2)	n/n/y/y/y/y		NNIV (7y)	NNIV (7y)	Yes (no surg Rigi spine
32	29	M	22	*TTN*	**c.13228G>A; p.Glu4410Lys** LP (PM2, PM3) **c.50248+1G>C** Pat (PVS1, PM2, PM3)	Unspecific	Newborn (hypotonia)	Walking (4)	n/n/y/n/y/y				

Pt	Fam	Sex	Age last seen/ death (y)	Gene (pattern of inheritance)	Mutation(s) ACMG evidence of pathogenicity	Histopathological pattern	Age at onset (y) (symptoms)	Maximal motor ability (age; y)	Ptosis/ Ophthalmoplegia Facial weakness/ Neck flexors weakness/ Proximal weakness/ Distal weakness	Gastrostomy (age; y)	Respiratory Support (age; y)	Respiratory Support (age; y)	Scoli (Sur Yes/ age a surg (y))
33	30	F	5	*SELENON*, AR	**c.301+1G>T** Pat (PVS1, PM2, PM3, PM5) **c.1269C>A; p.Tyr423*** Pat (PVS1, PM2, PM3)	Non-specific	6m (weakness)	Walking (1.5) (Running)	n/n/n/y/y/n				Yes (no surg Rigi spine
34	31	M	15	*SELENON*, AR	**c.951delC; p.Ile318Serfs*22** Pat (PVS1, PM2, PM3) **c.951delC; p.Ile318Serfs*22** Pat (PVS1, PM2, PM3)	Cat	1.5y (weakness)	Walking (1.9)	n/n/n/y/y/n		NNIV (13y)	NNIV (13y)	Yes (surg at 15)/ Rigi spine

Pt	Fam	Sex	Age last seen/ death (y)	Gene (pattern of inheritance)	Mutation(s) ACMG evidence of pathogenicity	Histopathological pattern	Age at onset (y) (symptoms)	Maximal motor ability (age; y)	Ptosis/ Ophthalmoplegia Facial weakness/ Neck flexors weakness/ Proximal weakness/ Distal weakness	Gastrostomy (age; y)	Respiratory Support (age; y)	Respiratory Support (age; y)	Scoli (Sur Yes/ age a surg (y))
35	31	M	15	*SELENON*	**c.951delC;** **p.Ile318Serfs*22** Pat (PVS1, PM2, PM3) **c.951delC; p.Ile318Serfs*22** Pat (PVS1, PM2, PM3)	Cores	Newborn (hypotonia)	Walking (1.9)	n/n/n/y/y/n		NNIV (14y)	NNIV (14y)	Yes (surg at 13)/ Rigid spine
36	32	M	13	*SELENON*	**c.943G>C;** **p.Gly315Arg** LP (PM2, PM3, PM5, PP3) **c.943G>C; p.Gly315Arg** LP (PM2, PM3, PM5, PP3)	Cores	1.5y (weakness)	Walking (1.3) (Running)	n/n/n/y/y/n		NNIV (7y)	NNIV (7y)	

Pt	Fam	Sex	Age last seen/ death (y)	Gene (pattern of inheritance)	Mutation(s) ACMG evidence of pathogenicity	Histopathological pattern	Age at onset (y) (symptoms)	Maximal motor ability (age; y)	Ptosis/ Ophthalmoplegia Facial weakness/ Neck flexors weakness/ Proximal weakness/ Distal weakness	Gastrostomy (age; y)	Respiratory Support (age; y)	Respiratory Support (age; y)	Scoli (Sur Yes/ age a surg (y))
37	33	M	18	*SELENON*	**c.1404-1G>A** Pat (PVS1, PM2, PM3) **c.1189C>T; p.Gln397Ter** Pat (PVS1, PM2, PM3)	Cores	9m (weakness)	Walking (1.5) (Running)	n/n/n/y/y/n				Rigi spine
38	34	F	12 y (death)	*SELENON*	**c.877C>T; p.His293Tyr** LP (PM2, PM3, PM5, PP3) **c.877C>T; p.His293Tyr** LP (PM2, PM3, PM5, PP3)	Cores	Newborn (hypotonia)	Walking (3)	n/n/n/y/y/n	NNIV (4y)	NNIV (4y)	Yes (no surg Rigi spine

Pt	Fam	Sex	Age last seen/ death (y)	Gene (pattern of inheritance)	Mutation(s) ACMG evidence of pathogenicity	Histopathological pattern	Age at onset (y) (symptoms)	Maximal motor ability (age; y)	Ptosis/ Ophthalmoplegia Facial weakness/ Neck flexors weakness/ Proximal weakness/ Distal weakness	Gastrostomy (age; y)	Respiratory Support (age; y)	Respiratory Support (age; y)	Scoli (Sur Yes/ age a surg (y))
39	34	F	8	*SELENON*	**c.877C>T; p.His293Tyr** LP (PM2, PM3, PM5, PP3) **c.877C>T; p.His293Tyr** LP (PM2, PM3, PM5, PP3)	CNM, Performed	Newborn (hypotonia)	Walking (2)	n/n/n/y/y/n		NNIV (7y)	NNIV (7y)	Yes (no surg Rigi spine
40	35	F	16	*MTM1*	**c.960del; p.Asp310Glufs*12** Pat (PVS1, PM2, PM6)	CNM	2y (weakness)	Walking (1.7) (Running)	n/n/y(asymmetric)/n/y(asymmetric)/n				
41	36	M	3	*MTM1*	**Deletion exons 7-15 NC_-000023.10:g.149807405-149840078del** LP (2B, 2D)	CNM	Newborn (hypotonia)	No sitting	n/y/y/y/y/n	Yes (first year)	TRAC (first year)	TRAC (first year)	

Pt	Fam	Sex	Age last seen/ death (y)	Gene (pattern of inheritance)	Mutation(s) ACMG evidence of pathogenicity	Histopathological pattern	Age at onset (y) (symptoms)	Maximal motor ability (age; y)	Ptosis/ Ophthalmoplegia Facial weakness/ Neck flexors weakness/ Proximal weakness/ Distal weakness	Gastrostomy (age; y)	Respiratory Support (age; y)	Respiratory Support (age; y)	Scoli (Sur Yes/ age a surg (y))
42	37	M	2 m (death)	*MTM1*	**Deletion exons 1-15 c.(?_-76)_-(*1548_-?)del** Pat (2A, 4L)	CNM	Newborn (hypotonia)	Death (2m)	n/y/y/y/y/y	NGT until death	NIV until death	NIV until death	Deat at 2 mon
43	38	M	11	*MTM1*	**c.605T>C; p.Leu202Ser** LP (PM1, PM2, PM6, PP2, PP3, PP5)	CNM	Newborn (hypotonia)	Walking (13)	n/y/y/y/y/y		NNIV (2y)	NNIV (2y)	
44	39	M	1	*MTM1*	**Deletion exons 3-14 NC_-000023.10:g.149761973_-149837797del** Pat (2B, 2E, 4L)	CNM	Newborn (hypotonia)	No sitting	n/?/y/y/y/y	Yes (first year)	TRAC (first year)	TRAC (first year)	

Pt	Fam	Sex	Age last seen/ death (y)	Gene (pattern of inheritance)	Mutation(s) ACMG evidence of pathogenicity	Histopathological pattern	Age at onset (y) (symptoms)	Maximal motor ability (age; y)	Ptosis/ Ophthalmoplegia Facial weakness/ Neck flexors weakness/ Proximal weakness/ Distal weakness	Gastrostomy (age; y)	Respiratory Support (age; y)	Respiratory Support (age; y)	Scoli (Sur Yes/ age a surg (y))
45	39	F	35	*MTM1*	**Deletion exons 3-14 NC_000023.10:g.149761973_149837797del** Pat (2B, 2E, 4L)	CNM	34 (asymmetric weakness)	Walking (1) (Running)	n/n/n/n/y (asymmetric)/n				
46	40	M	1	*MTM1*	**c.1420C>T; p.Arg474*** Pat (PVS1, PM2, PM6, PP5)	CNM	Newborn (hypotonia)	No sitting	n/y/y/y/y/y	Yes (first year)	TRAC (first year)	TRAC (first year)	
47	41	F	9	*NEB*	**c.1493A>G; p.Asp498Gly** VUS (PM2, PM3, BP4) **c.21076C>T; p.Arg7026*** Pat (PVS1, PM2, PM3, PP5)	NM	Newborn (hypotonia)	Walking (4)	n/n/y/y/y/y				

Pt	Fam	Sex	Age last seen/ death (y)	Gene (pattern of inheritance)	Mutation(s) ACMG evidence of pathogenicity	Histopathological pattern	Age at onset (y) (symptoms)	Maximal motor ability (age; y)	Ptosis/ Ophthalmoplegia Facial weakness/ Neck flexors weakness/ Proximal weakness/ Distal weakness	Gastrostomy (age; y)	Respiratory Support (age; y)	Respiratory Support (age; y)	Scoli (Sur Yes/ age a surg (y))
48	42	M	4	*NEB*	**c.24407_24410dup; p.Leu8137Phefs*18** Pat (PVS1, PM2, PM3, PP3) **c.8425C>T; p.Arg2809*** Pat (PVS1, PM2, PM3)	not performed	4m (motor delay)	Sitting (0.9)	n/n/y/y/y/y	Yes (2y)	TRAC (3y)	TRAC (3y)	Yes (no surg
49	43	F	16	*NEB*	**c.2106+3A>C; p.Ala667_Asp702del** VUS (PM2, PM3, PP3) **c.21076C>T; p.Arg7026*** Pat (PVS1, PM2, PM3, PP5)	NA	1y (motor delay)	Walking (1.5) (Running)	n/n/y/y/y/y	Yes (14y)	NNIV (14y)	NNIV (14y)	Yes (no surg

Pt	Fam	Sex	Age last seen/ death (y)	Gene (pattern of inheritance)	Mutation(s) ACMG evidence of pathogenicity	Histopathological pattern	Age at onset (y) (symptoms)	Maximal motor ability (age; y)	Ptosis/ Ophthalmoplegia Facial weakness/ Neck flexors weakness/ Proximal weakness/ Distal weakness	Gastrostomy (age; y)	Respiratory Support (age; y)	Respiratory Support (age; y)	Scoli (Sur Yes/ age a surg (y))
50	44	F	15	*NEB*	**c.1161C>G; p.Tyr387*** Pat (PVS1, PM2, PM3, PP5) **c.612+1G>A** LP (PVS1, PM2, PM3)	CNM	1.5y (weakness)	Walking (1.5) (Running)	n/n/y/y/y/n				
51	45	M	22	*DNM2*	**c.1102G>A; p.Glu368Lys** Pat (PM1, PM2, PM3, PM5, PM6, PP3, PP5)	CNM	First year (hypotonia, cervical weakness)	Walking (1.2) (Running)	y/y/y/y/y/y				Yes (no surg
52	46	M	18	*DNM2*	**c.869G>A; p.Arg290Gln** LP (PS3, PM2)	Cores	3y (ptosis)	Walking (1.2) (Running)	y/n/y/n/y/y				

Pt	Fam	Sex	Age last seen/ death (y)	Gene (pattern of inheritance)	Mutation(s) ACMG evidence of pathogenicity	Histopathological pattern	Age at onset (y) (symptoms)	Maximal motor ability (age; y)	Ptosis/ Ophthalmoplegia Facial weakness/ Neck flexors weakness/ Proximal weakness/ Distal weakness	Gastrostomy (age; y)	Respiratory Support (age; y)	Respiratory Support (age; y)	Scoli (Sur Yes/ age a surg (y))
53	47	M	15	*DNM2*	**c.1102G>A; p.Glu368Lys** Pat (PM1, PM2, PM5, PM6, PP3, PP5)	CNM	First year (hypotonia, weakness)	Walking (2)	y/y/y/y/y/y		NNIV (8y)	NNIV (8y)	Yes (no surg
54	48	M	6	*MYH7*	**c.5655G>A; p.1854_-1885del** LP (PM2, PM6, PP3, PP5)	Unspecific	3m (motor delay)	Walking (1.8)	n/n/y/y/y/n				Yes (no surg
55	49	M	29	*MYH7*	**c.5117T>C; p.Leu1706Pro** LP (PM1, PM2, PM6, PP2, PP3, PP5)	Cores	2y (gait disorder)	Walking (1.4) (Running)	n/n/n/n/n/y				

Pt	Fam	Sex	Age last seen/ death (y)	Gene (pattern of inheritance)	Mutation(s) ACMG evidence of pathogenicity	Histopathological pattern	Age at onset (y) (symptoms)	Maximal motor ability (age; y)	Ptosis/ Ophthalmoplegia Facial weakness/ Neck flexors weakness/ Proximal weakness/ Distal weakness	Gastrostomy (age; y)	Respiratory Support (age; y)	Respiratory Support (age; y)	Scoli (Sur Yes/ age a surg (y))
56	50	F	17	*TPM3*	**c.503G>A; p.Arg168His** Pat (PM1, PM2, PM5, PM6, PP2, PP3)	Unspecific	1y (motor dely)	Walking (1.5) (Running)	n/n/y/n/y/n				
57	51	F	5	*TPM3*	**c.502C>T; p.Arg168Cys** Pat (PM1, PM2, PM5, PM6, PP2, PP3)	Unspecific	Newborn (hypotonia)	Walking (2) (Running)	n/n/y/y/y/y		NNIV (4y)	NNIV (4y)	
58	52	F	20	*TPM2*	**c.613A>G; p.Lys205Glu** Pat (PVS1, PM2, PM3)	NM	1y (motor delay)	Walking (2) (Running)	n/n/y/y/n/n		NNIV (17y)	NNIV (17y)	Yes (surg at 17
59	53	F	8	*MYH3*	**c.737G>C; p.Gly246Ala** VUS (PM2, PM6, PP3)	Unspecific	Newborn (congenital talipes equinovarus)	Walking (1.3) (Running)	n/n/y/n/n/y				

Pt	Fam	Sex	Age last seen/ death (y)	Gene (pattern of inheritance)	Mutation(s) ACMG evidence of pathogenicity	Histopathological pattern	Age at onset (y) (symptoms)	Maximal motor ability (age; y)	Ptosis/ Ophthalmoplegia Facial weakness/ Neck flexors weakness/ Proximal weakness/ Distal weakness	Gastrostomy (age; y)	Respiratory Support (age; y)	Respiratory Support (age; y)	Scoli (Sur Yes/ age a surg (y))
60	54	F	20	*PYROXD1*	**c.1285+1G>A** LP (PVS1, PM2, PM3, PP5) **c.788T>G; p.Val263Gly** VUS (PM2, PM3)	Non-specific	18m (weakness)	Walking (1.5)	n/n/y/y/y/y				Yes (no surg
61	55	F	4	*DES*	**c.322G>T; p.Glu108*** Pat (PVS1, PM2, PM3, PP5) **c.322G>T; p.Glu108*** Pat (PVS1, PM2, PM3, PP5)	Non-specific	Newborn (hypotonia)	Walking (1.8)	y/n/y/y/y/y	Yes (1.5y)	NNIV (4y)	NNIV (4y)	
62	56	M	10	*ACTA1*	**c.925C>T; p.Pro309Ser** LP (PM1, PM2, PM6, PP2, PP3)	CFTD	Newborn (hypotonia)	Walking (3.5)	n/n/y/y/y/y		NNIV (3y)	NNIV (3y)	Yes (no surg

Pt	Fam	Sex	Age last seen/ death (y)	Gene (pattern of inheritance)	Mutation(s) ACMG evidence of pathogenicity	Histopathological pattern	Age at onset (y) (symptoms)	Maximal motor ability (age; y)	Ptosis/ Ophthalmoplegia Facial weakness/ Neck flexors weakness/ Proximal weakness/ Distal weakness	Gastrostomy (age; y)	Respiratory Support (age; y)	Respiratory Support (age; y)	Scoli (Sur Yes/ age a surg (y))
63	57	M	9	*ACTA1*	**c.772C>G; p.Arg258Gly** LP (PM1, PM2, PM5, PM6, PP2, PP3)	NM	Newborn (hypotonia)	Walking (3.5)	n/n/y/y/y/y	Yes (2m)			Yes (surg at 4)
64	58	F	14	*KLHL40*	**c.604delG; p.Ala202Argfs*56** Pat (PVS1, PM2, PM3) **c.1513G>C; p.Ala505Pro** VUS (PM2, PM3, PP3)	NM	Newborn (hypotonia)	Walking (2.5) (Running)	n/n/y/y/y/y	Yes (first year)			

Pt	Fam	Sex	Age last seen/ death (y)	Gene (pattern of inheritance)	Mutation(s) ACMG evidence of pathogenicity	Histopathological pattern	Age at onset (y) (symptoms)	Maximal motor ability (age; y)	Ptosis/ Ophthalmoplegia Facial weakness/ Neck flexors weakness/ Proximal weakness/ Distal weakness	Gastrostomy (age; y)	Respiratory Support (age; y)	Respiratory Support (age; y)	Scoli (Sur Yes/ age a surg (y))
65	59	M	26	*TRIP4*	**c.55_-56insCT; p.Gln19fs*47** Pat (PVS1, PM2, PM3) **c.1197delA; p.Ser399fs*12** Pat (PVS1, PM2, PM3)	Not assessable	Newborn (hypotonia)	Walking (2.5)	n/n/y/y/y/n		NNIV (14y)	NNIV (14y)	Yes (surg at 16
66	60	M	21	Unsolved		Cores	Newborn (hypotonia)	Walking (2)	y/y/y/y/y/n		NNIV (11y)	NNIV (11y)	Yes (no surg
67	61	F	12	Unsolved		CNM	12m (motor delay)	Walking (1.5) (Running)	n/n/n/y/y/n				
68	62	F	4	Unsolved		Cores	Newborn (hypotonia)	No sitting	n/n/n/y/y/y				Yes (no surg
69	63	M	9	Unsolved		Cores	First months (hypotonia)	Walking (2.5) (Running)	n/n/y/y/y/y		NNIV (8y)	NNIV (8y)	
70	64	M	10	Unsolved		Unspecific	Prenatal (Arthrogryposis)	Walking (1.2) (Running)	n/n/n/n/y/y				
71	65	F	10	Unsolved		Unspecific	2y (weakness)	Walking (1) (Running)	n/n/n/n/y/n				

Pt	Fam	Sex	Age last seen/ death (y)	Gene (pattern of inheritance)	Mutation(s) ACMG evidence of pathogenicity	Histopathological pattern	Age at onset (y) (symptoms)	Maximal motor ability (age; y)	Ptosis/ Ophthalmoplegia Facial weakness/ Neck flexors weakness/ Proximal weakness/ Distal weakness	Gastrostomy (age; y)	Respiratory Support (age; y)	Respiratory Support (age; y)	Scoli (Sur Yes/ age a surg (y))
72	66	M	4	Unsolved		Cores	1y (weakness)	Walking (2.5) (Running)	n/n/n/y/y/n				
73	67	M	4	Unsolved		Not assessable	Prenatal (Arthrogryposis)	Sitting (1.5)	n/n/n/y/y/y				
74	68	M	21	Unsolved		Cores	1y (weakness)	Walking (1.5) (Running)	n/n/n/n/y/n				
75	69	F	2 y (death)	Unsolved		Cores	Newborn (hypotonia)	No sitting	n/n/y/y/y/y		NIV until death	NIV until death	
76	70	F	4	Unsolved		Unspecific	3m (weakness)	Sitting (2)	n/n/n/y/y/y		NNIV (2y)	NNIV (2y)	
77	71	F	14	Unsolved		Not assessable	Prenatal (Arthrogryposis)	Walking (2)	n/n/n/y/y/y				Yes (no surg
78	72	M	14	Unsolved		Cores	12m (motor delay)	Walking (2) (Running)	n/n/n/y/y/n				
79	73	F	19	Unsolved		FTD	Newborn (congenital talipes equinovarus)	Walking (2) (Running)	n/n/y/y/y/y				
80	74	F	4	Unsolved		Unspecific	Newborn (hypotonia)	Walking (1.5) (Running)	n/n/y/y/y/y	NGT until 12m	NIV until 18m	NIV until 18m	

Pt	Fam	Sex	Age last seen/ death (y)	Gene (pattern of inheritance)	Mutation(s) ACMG evidence of pathogenicity	Histopathological pattern	Age at onset (y) (symptoms)	Maximal motor ability (age; y)	Ptosis/ Ophthalmoplegia Facial weakness/ Neck flexors weakness/ Proximal weakness/ Distal weakness	Gastrostomy (age; y)	Respiratory Support (age; y)	Respiratory Support (age; y)	Scoli (Sur Yes/ age a surg (y))
81	75	M	13	Unsolved		NM	Newborn (hypotonia)	No sitting	n/n/y/y/y/y	Yes (first year)	TRAC (first year)	TRAC (first year)	Yes (no surg
82	76	F	6	Unsolved		Unspecific	18m (weakness)	Walking (1.4) (Running)	n/n/n/n/y/n				
83	77	M	4	Unsolved		Unspecific	Newborn (hypotonia)	Walking (3)	n/n/n/y/y/n	Yes (first year; removed at 2y)	NIV (first year)	NIV (first year)	Yes (no surg
84	78	M	30	Unsolved		Cores	Newborn (hypotonia)	Sitting (0.5)	n/n/y/y/y/y				Yes (surg at 14)
85	79	M	17	Unsolved		Cores	Newborn (hypotonia)	Walking (1.5) (Running)	n/n/n/y/y/n				Yes (no surg
86	80	M	2 m (death)	Unsolved		Unspecific	Newborn (hypotonia)	Death (2m)	?/?/y/y/y/y	NGT until death	NIV until death	NIV until death	Deat at 2m
87	81	F	20	Unsolved		not performed	12m (motor delay)	Walking (2) (Running)	n/n/n/y/y/n				

Pt	Fam	Sex	Age last seen/ death (y)	Gene (pattern of inheritance)	Mutation(s) ACMG evidence of pathogenicity	Histopathological pattern	Age at onset (y) (symptoms)	Maximal motor ability (age; y)	Ptosis/ Ophthalmoplegia Facial weakness/ Neck flexors weakness/ Proximal weakness/ Distal weakness	Gastrostomy (age; y)	Respiratory Support (age; y)	Respiratory Support (age; y)	Scoli (Sur Yes/ age a surg (y))
88	81	F	12	Unsolved		Cores	12m (motor delay)	Walking (1.5) (Running)	n/n/n/y/y/n				
89	81	F	5	Unsolved		not performed	12m (motor delay)	Walking (1.8) (Running)	n/n/n/y/y/n				
90	81	M	12	Unsolved		Cores	12m (motor delay)	Walking (1.5) (Running)	n/n/n/y/y/n				
91	82	F	4	Unsolved		Unspecific	Newborn (hypotonia)	Sitting (2)	n/n/y/y/y/n				Yes (no surg
92	83	M	29	Unsolved		Unspecific	Newborn (hypotonia)	Walking (4)	n/n/y/y/y/y				
93	84	M	2	Unsolved		CNM	Newborn (hypotonia)	No sitting	n/y/y/y/y/n				

Pt	Fam	Sex	Age last seen/ death (y)	Gene (pattern of inheritance)	Mutation(s) ACMG evidence of pathogenicity	Histopathological pattern	Age at onset (y) (symptoms)	Maximal motor ability (age; y)	Ptosis/ Ophthalmoplegia Facial weakness/ Neck flexors weakness/ Proximal weakness/ Distal weakness	Gastrostomy (age; y)	Respiratory Support (age; y)	Respiratory Support (age; y)	Scoli (Sur Yes/ age a surg (y))
94	85	M	12	Unsolved		CNM	2y (weakness)	Walking (1.5) (Running)	n/n/y/n/n/y				
95	86	F	8	Unsolved		Cores	Newborn (hypotonia)	Walking (2)	n/n/y/y/y/y	Yes (2y)			
96	87	F	18	Unsolved		Cores	Newborn (hypotonia)	Walking (1.8) (Running)	?/n/y/y/y/y				
97	88	M	12	Unsolved		NM	Newborn (hypotonia)	Walking (3)	n/n/y/y/y/y	Yes (2y; removed at 5y)	NNIV (8y)	NNIV (8y)	
98	89	M	2 m (death)	Unsolved		NM	Newborn (hypotonia)	Death (2m)	n/n/y/y/y/y	NGT until death	NIV until death	NIV until death	Deat at 2m
99	90	M	17	Unsolved		NM	Newborn (hypotonia)	Walking (1.3) (Running)	n/n/y/y/y/n				Yes (no surg
100	91	F	1 d (death)	Unsolved		NM	Newborn (hypotonia)	Death (1d)	?/?/y/y/y/y	Death at 1d	OTI until death	OTI until death	Deat at 1d
101	91	M	1 d (death)	Unsolved		NM	Newborn (hypotonia)	Death (1d)	?/?/y/y/y/y	Death at 1d	OTI until death	OTI until death	Deat at 1d

Pt	Fam	Sex	Age last seen/ death (y)	Gene (pattern of inheritance)	Mutation(s) ACMG evidence of pathogenicity	Histopathological pattern	Age at onset (y) (symptoms)	Maximal motor ability (age; y)	Ptosis/ Ophthalmoplegia Facial weakness/ Neck flexors weakness/ Proximal weakness/ Distal weakness	Gastrostomy (age; y)	Respiratory Support (age; y)	Respiratory Support (age; y)	Scoli (Sur Yes/ age a surg (y))
102	92	F	5	Unsolved		Cores	12m (motor delay)	Walking (1.8) (Running)	n/y/n/y/y/n				
103	93	M	32	Unsolved		NM	1-2y (frequent falls and weakness)	Walking (1.4) (Running)	n/n/n/y/y/n				
104	94	F	31	Unsolved		NM	1-2y (frequent falls and weakness)	Walking (1.2) (Running)	n/n/n/n/y/y				

Figure legends

Figure 1 . Pie charts show prevalence of histopathologic subtypes (A) and causative genes (B). NM = nemaline myopathy; CNM = centronuclear myopathy; CFTD = congenital fiber type disproportion; NA = non-assessable; AD = autosomal dominant; AR = autosomal recessive.

Figure 2 . Bar charts show that the proportion of patients who never achieved the ability to walk is higher among those who had higher fibrosis (A) or fatty infiltration (B) in their muscle biopsies.

Figure 3 . The genetic diagnostic yield is highly dependent on histologic findings. Bar charts illustrate the causative genes found in our patients and how the prevalences vary depending on the main histologic findings in the muscle biopsy.

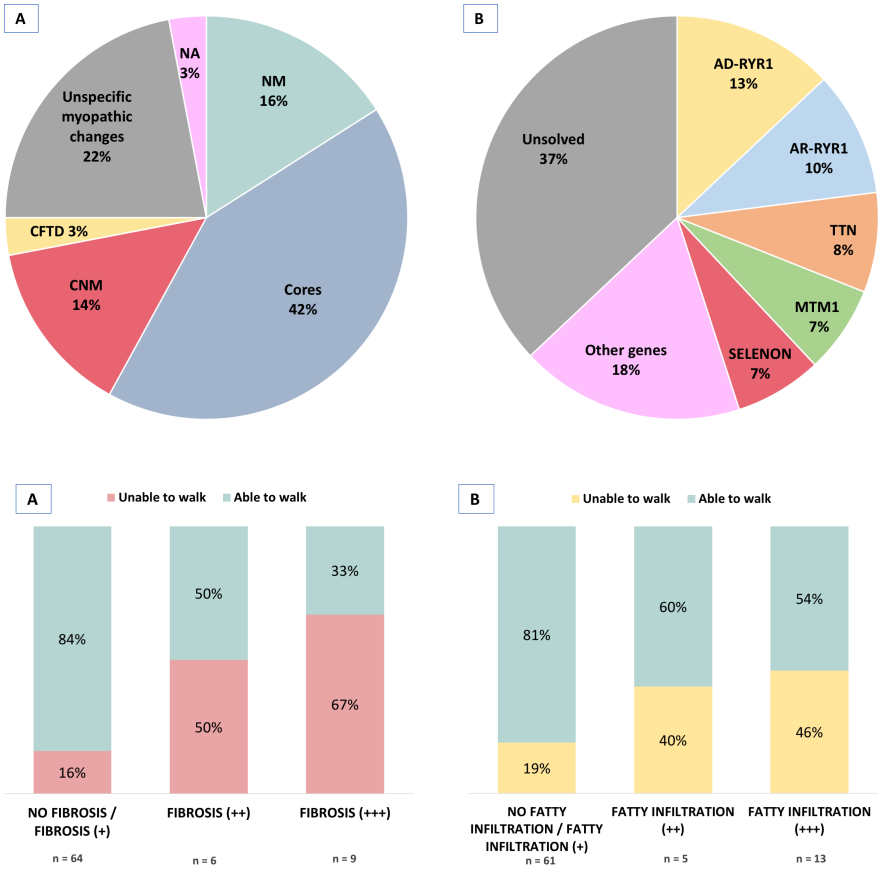
Figure 4 . Bar charts show the percentage of patients with each genetic mutation that have each kind of muscle abnormality, as observed in muscle biopsies.

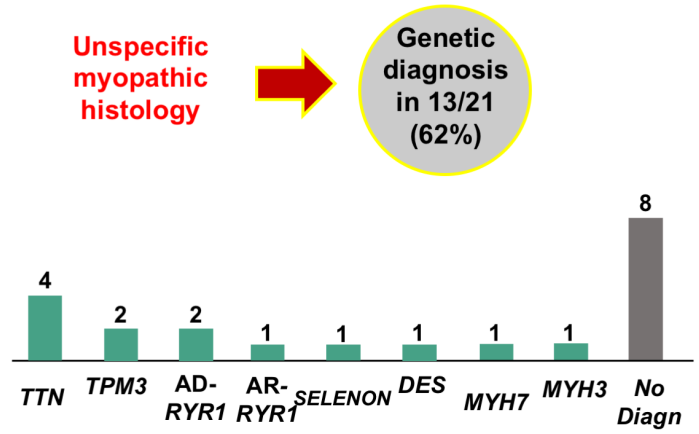
Figure 5 . (A) Age of onset according to genotype. (B) Maximal motor ability according to genotype. All patients with *SELENON* mutations walked independently, whereas only 25% of *MTM1* patients did.

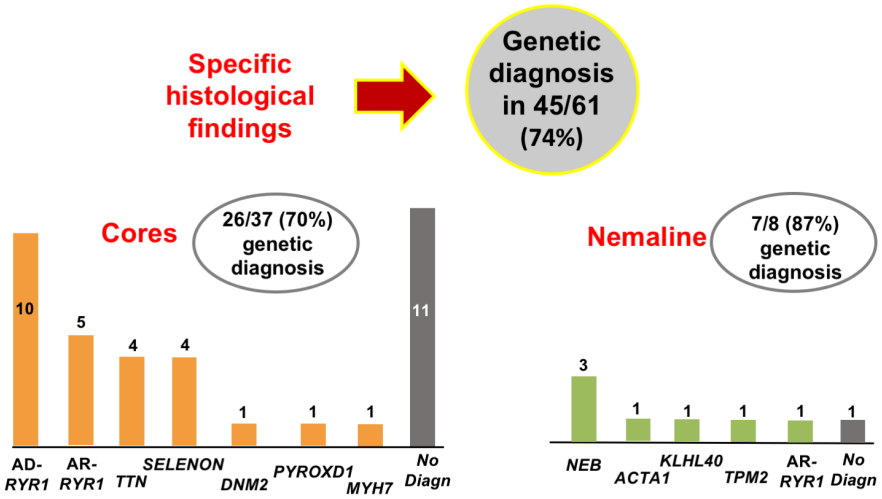
Figure 6 . (A) Prevalence of nocturnal non-invasive ventilation (NNIV) and invasive ventilation according to causative genes. (B) Kaplan-Meier curves show ventilation-free, gastrostomy-free, and scoliosis surgery-free patients by age.

Figure 7 . Radar charts illustrate the clinical phenotypes observed in our patients according to their genotype.

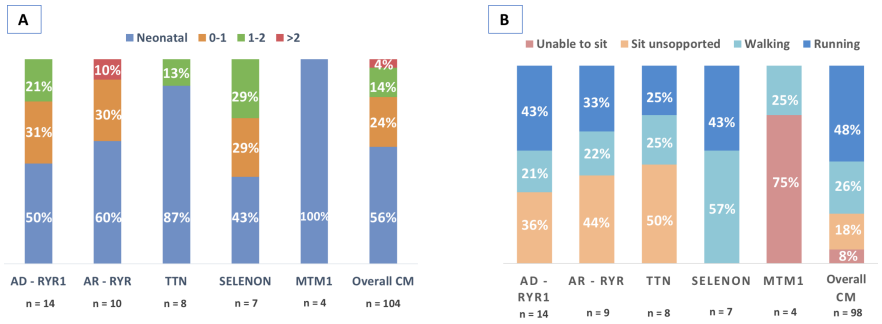
Supplementary figure 1. Visual rating scales categorizing the endomysial fibrosis and fatty infiltration detected in our patients according to their magnitude. Reference images of some of the patients included in this work are shown. **Endomysial fibrosis** : - Not present (Patient 70 at 6 years old); + Mild (Patient 2 at 16 years old); ++ Moderate (Patient 26 at 2 months old); +++ Severe (Patient 8 at 9 years old). **Fatty infiltration** : - Not present (Patient 45 at 6 months old); + Mild (Patient 18 at 1 week old); ++ Moderate (Patient 39 at 11 years old); +++ Severe (Patient 50 at 15 years old).

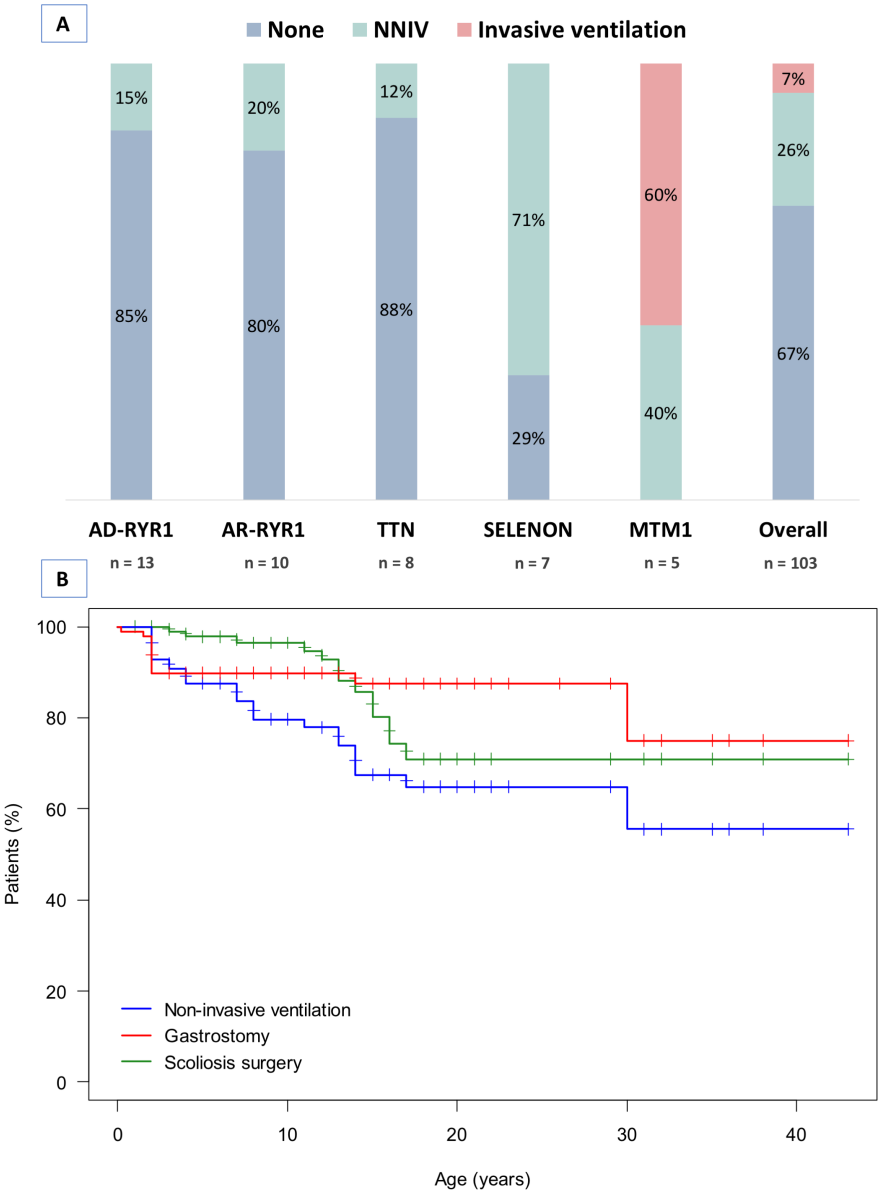


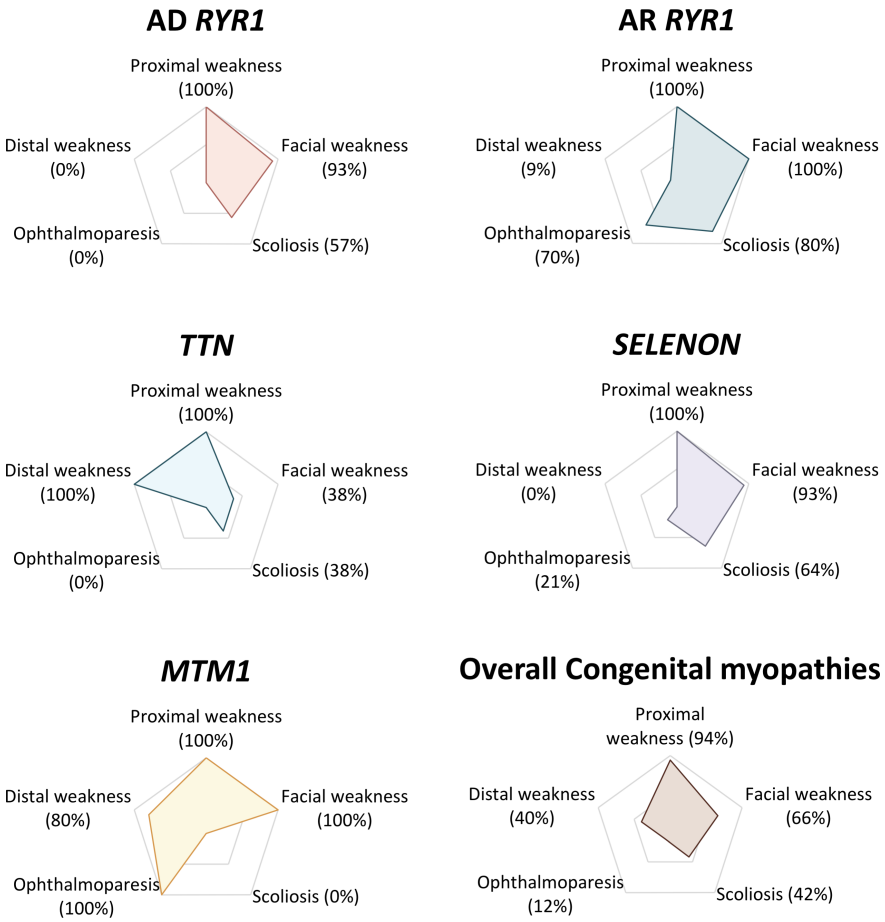




	AD – *RYR1*	AR – *RYR1*	*TTN*	*SELENON*	*MTM1*	Overall CM
Fibrosis	33%	44%	29%	0%	0%	21%
Fatty infiltration	17%	44%	14%	0%	0%	21%
Internal nuclei	25%	44%	86%	40%	100%	42%
Cores	83%	67%	71%	80%	20%	61%
Accumulated material	50%	67%	71%	40%	0%	46%
Type 1 fiber predominance	100%	71%	100%	50%	80%	76%







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