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The Final thesis

MIOPATIJA: ATVEJŲ ANALIZĖ IR LITERATŪROS APŽVALGA
MYOPATHY: CASE REPORT AND REVIEW OF LITERATURE

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Contents :

Summary

This study endeavors to scrutinize *Myosin Heavy Chain II*-related disorders across pediatric and adult populations, delineating their clinical manifestations, diagnostic hallmarks, genetic underpinnings, and prognostic implications. Through a comprehensive literature review, a selection of scholarly articles sourced from PubMed has been curated, shedding light on the spectrum of disease severity and progression in genetically confirmed *Myosin Heavy Chain II*-afflicted individuals.

Myosinopathies, a constellation of exceedingly rare inherited muscular afflictions, exhibit diverse phenotypic characteristics attributable to variants occurring within the myosin heavy chain genes located on chromosome 17. Among these, *Myosin Heavy Chain II*, a critical isoform predominantly expressed in fast twitch 2A and 2B muscle fibers, manifests with distinct clinical phenotypes. Autosomal Dominant *Myosin Heavy Chain II* myopathy typically manifests as transient congenital arthrogryposis, succeeded by the insidious onset of progressive proximal limb weakness and external ophthalmoplegia. Notably, characteristic histological findings on muscle biopsy often include diminished type 2A fibers and the presence of rimmed vacuoles.

Conversely, Autosomal Recessive *Myosin Heavy Chain II* myopathy presents with a milder, early-onset, non-progressive proximo-distal weakness of the limbs accompanied by external ophthalmoparesis. Histopathological analyses typically reveal a stark absence of type 2A fibers alongside non-specific myopathic alterations.

The diagnosis and management of myopathy pose formidable challenges for clinicians, notwithstanding recent strides in molecular biology that have facilitated swifter and more precise diagnostic paradigms for genetically or metabolically mediated myopathies. Nonetheless, efficacious therapeutic modalities remain elusive. While gene therapy and stem cell transplantation exhibit promising potential in the realm of myopathy research, concerns regarding the safety profile of adeno-associated virus vectors and the potential for stem cell-associated tumorigenicity have curtailed their widespread clinical implementation.

Presently, rehabilitation therapy stands as the cornerstone of myopathy management, underscoring the critical need for further research endeavors aimed at unraveling the intricate pathophysiological mechanisms underlying *Myosin Heavy Chain II*-related disorders and identifying novel therapeutic avenues to ameliorate disease burden and enhance patient outcomes.

Keywords

MYH2(Myosin Heavy Chain II), Ophthalmoplegia, Ptosis, Muscle weakness, Contractures at birth, Creatine Kinase, Muscle biopsy, Rehabilitation

Introduction

Myopathy refers to a group of disorders characterized by weakness and wasting of muscles. These conditions often involve abnormalities in intracellular or sarcomeric components, resulting in specific morphological changes such as the presence of inclusions within muscle cells.[1] The contractile proteins myosin and actin which are found within individual muscle fibers are arranged into thick and thin filaments, respectively. These filaments are organized into longitudinally repeated banding patterns known as sarcomeres. Sarcomeres in sequence make up myofibrils, with multiple myofibrils present in each fiber. The strength of muscle contraction is influenced by the number of myofibrils organized in parallel within the fiber. Muscle myosin, a molecular motor is composed of a hexamer structure, comprising two heavy chains and two pairs of light chains is the most important protein. The COOH-terminal ends of these heavy chains combine to form a coiled coil structure consisting of two a-helices. These helices aggregate within the cell, serving as the foundation of the thick filaments. [18]

Myosin heavy chain (MyHC) serves as the primary molecular motor in muscle function, constituting the structural framework of sarcomeric thick filaments. The diverse array of Myosin heavy chain isoforms plays a pivotal role in dictating the physiological characteristics of distinct muscle fiber types. Within this context, hereditary myosin myopathies have emerged as a significant cluster of disorders, exhibiting varying clinical and morphological manifestations contingent upon the mutated isoform as well as the type and site of the variant. Variants, whether dominant or recessive, impacting the *Myosin Heavy Chain II(MYH2)*, are linked to early-onset myopathies characterized by diverse degrees of muscle weakness, with a consistent occurrence of ophthalmoplegia. [2]

The goal of this study is to comprehensively analyze the pathogenic variations within the *Myosin heavy chain II* (MYH2) gene, responsible for encoding the fast IIA myosin heavy chain, which contribute to both dominant and recessive skeletal muscle disorders. Variants in the *Myosin heavy chain II (MYH2)* gene result in dominantly and recessively

inherited myopathies. Patients with dominantly inherited *Myosin heavy chain II(MYH2)* missense variants typically present with symptoms such as ophthalmoplegia and progressive weakness in proximal limb muscles. In this case muscle biopsy often reveals the presence of rimmed vacuoles and inclusions, initially classifying this condition as hereditary inclusion body myopathy. Conversely, individuals with recessive *Myosin heavy chain II*(*MYH2)* variants typically manifest an early onset of non-progressive, diffuse weakness accompanied by ophthalmoplegia. For this case muscle biopsy findings in these cases frequently indicate a near or complete absence of type 2A fibers, without evident vacuole or inclusion pathology.[3]

Another objective is to review *Myosin heavy chain* II*(MYH2*) disease in pediatric and adults and at which age symptoms emerge, arise from variants occurring in genes responsible for skeletal muscle myosin heavy chain. [4]

Although myopathy linked to recessive *Myosin Heavy Chain II(MYH2)* variants is uncommon but occurs more frequently compared to dominantly inherited myosin IIa myopathy.[7] Hence, the study also describes the clinical presentation, diagnostic features, genotypes, and outcomes for both the Autosomal dominant and recessive forms of the disease.

Literature selection strategy

The literature search was performed from June 2023 to March 2024, with keywords “MYH2”, “Myopathy” and “Case report” using PubMed. Only original research articles written in English were selected. Both clinical and preclinical studies were included. Full texts of the relevant articles were extracted after being screened for titles and abstracts.

Definitions

For this study there will be a few terms frequently used. In this paragraph, the terms will be given a definiton to avoid potential confusion.

Individuals harboring variants in *Myosin Heavy Chain II(MYH2)* exhibit a phenotype characterized by mild weakness in proximal muscles, slight weakness in neck flexors, ophthalmoplegia, and ptosis. Histologically, these patients typically display diminutive or absent type 2 muscle fibers, with a prevalence of type 1 fibers. Consequently, individuals presenting with these distinctive phenotypes are suspected to carry *Myosin Heavy Chain II (MYH2)* variants.[10]

Ophthalmoplegia/Chronic progressive external ophthalmoplegiapresents as a clinical syndrome marked by symmetric bilateral drooping of the eyelids along with limited movement of the eyes. This condition is observed in a range of neuromuscular disorders including mitochondrial disorders, centronuclear myopathies, congenital myasthenic syndromes, and oculopharyngeal muscular dystrophy.[8]

Other term which will be mostly used is congenital ptosis, a seldom-seen condition marked by the downward placement of the upper eyelid from birth, persists if left untreated. It can occur on one side or both sides and may be linked with other eye issues or systemic ailments such as Marcus Gunn, Horner, and Duane syndromes. While congenital ptosis is typically harmless, it can lead to functional, cosmetic, and psychological issues in children. The severity of ptosis, eyelid function, and the risk of amblyopia are factors that influence the timing of surgery and the choice of surgical technique for ophthalmologists. [9]

As we move to the next term which is a serious concern among older individuals often leading to a high mortality rate, aspiration pneumonia refers to the infectious lung condition resulting from the abnormal entry of fluids into the lower respiratory tract. These fluids may include oropharyngeal secretions, particulate matter, or gastric contents. Additionally, the term aspiration pneumonitis describes the acute lung injury caused by inhaling sterile gastric contents. A thorough assessment of swallowing function is essential for an accurate diagnosis. This condition poses a significant threat to lung health, occurring either as acute episodes or chronic conditions due to swallowing problems or gastroesophageal reflux. [10,12]

Finally the last term muscle weakness, which refers to a decrease in the strength or ability of muscles to perform tasks effectively, resulting in reduced force generation or impaired movement. The range of potential causes for true muscle weakness is broad, encompassing neurological, rheumatological, endocrine, genetic, medication-induced, toxin-related, and infectious factors. To pinpoint the underlying cause, a systematic approach is crucial, leveraging patient history, physical examination, and knowledge of potential etiologies.[11]

Disease mechanism and pathology

Myosin is a widely distributed and highly conserved protein present in all eukaryotic cells which serves as a crucial molecular motor facilitating various cellular movements by converting the chemical energy from ATP hydrolysis into mechanical force. These movements include cytokinesis, phagocytosis, and muscle contraction. As it is a vital protein in the body, it plays a fundamental role in both movement and heart function[2,14]. Myosins encompass a diverse superfamily, categorized into different classes, among which are the conventional, or class II, two-headed myosins responsible for filament formation in striated muscle, smooth muscle, and non-muscle cells. The class II conventional muscle myosin is a hexameric protein consisting of two myosin heavy chain subunits and two pairs of non-identical light chain subunits. Myosin heavy chains form dimers via coiled-coil interactions along their elongated tail regions, known as the rod domain. Dimerization of two heavy chains results in a polar structure with distinct regions contributing to motor activity and filament formation. The amino terminus forms a globular head domain that binds to actin and ATP, essential for motor function. Meanwhile, the elongated a-helical coiled-coil C-terminal rod domain possesses filament-forming properties, assembling into thick filaments within sarcomeres.[2]

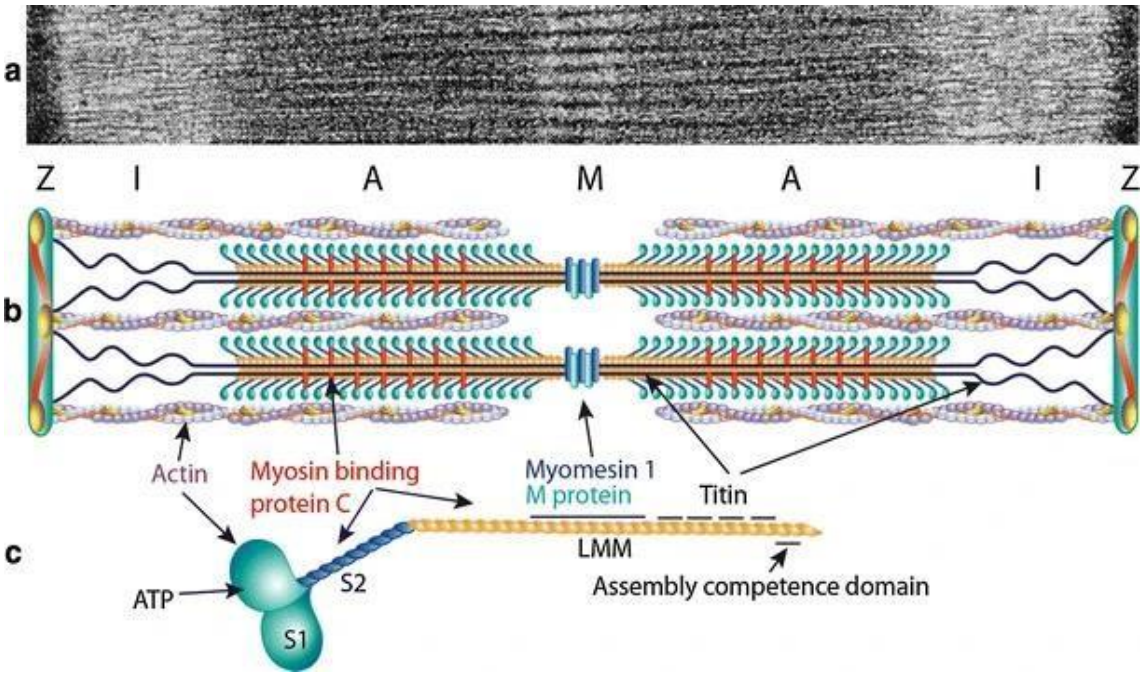

Figure 1. Electron micrograph of a skeletal muscle sarcomere.[2]

Adult human limb skeletal muscle contains three primary myosin heavy chain (MyHC) isoforms: myosin heavy chain (MyHC I) (also known as slow/β-cardiac MyHC), encoded

by the MYH7 gene, is expressed in slow type 1 muscle fibers and in the heart's ventricles; (myosin heavy chain) *MyHC IIa (MYH2)* is found in fast type 2A muscle fibers; and Myocin Heavy Chain IIx (MYH1) is present in fast type 2B muscle fibers. These muscle fiber types possess distinct physiological properties and fulfill unique functions in skeletal muscle operation.[14]

Variants in Myosin Heavy Chain (MyHC) isoforms have been linked to various muscle diseases and in this study we focus on the myosin myopathies which constitute a group of inherited disorders resulting from variants in *Myosin Heavy Chain II*a *(MYH2)* genes. These myopathies can be further subdivided into two categories which include autosomal dominant myopathy with congenital joint contractures, ophthalmoplegia, and rimmed vacuoles, initially identified as inclusion body myopathy (IBM3), stemming from a single point variants in the fast *Myosin Heavy Chain II (MYH2)* gene. On the other hand recessive myopathy with ophthalmoplegia has been associated with truncating variants in *Myosin Heavy Chain II (MYH2).*[13]

Autosomal dominant MyHC IIa myopathy

Autosomal dominant MyHC IIa myopathy, also known as "autosomal dominant myopathy with congenital joint contractures, ophthalmoplegia, and rimmed vacuoles," was first recognized as a muscle disorder in western Sweden. It was linked to chromosome 17p13.1 and later associated with a specific variant in the *Myosin Heavy Chain II(MYH2)* gene, which encodes *MyHC IIa.* This variant replaces a highly conserved glutamate at position 706 with a lysine (E706K). Symptoms typically began before birth, with many patients exhibiting multiple joint contractures at birth that usually resolved early in childhood. Hypotonia was not a prominent feature, and early development was usually unaffected. External ophthalmoplegia, ranging from minor upward gaze impairment in children to widespread ophthalmoparesis in adults, was consistently observed. Muscle weakness and atrophy primarily affected proximal muscles of the shoulder and pelvic girdles, as well as muscles in the back and hands. The severity of muscle weakness varied greatly, with some individuals experiencing progressive weakness that impacted mobility between the ages of 30 and 50. While serum creatine kinase (s-CK) levels were typically normal in mildly affected cases, they were slightly elevated in those with a progressive disease course. [2]

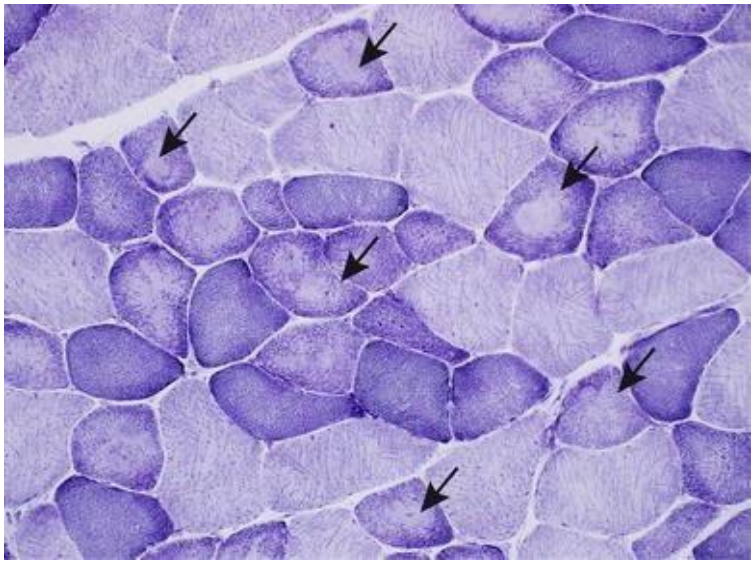

Figure 2. Dominant myosin IIa myopathy. Biopsy of the deltoid muscle of a 38-year-old man showing alterations of the type 2A fibers (*arrows*). NADH-tetrazolium reductase. [2]

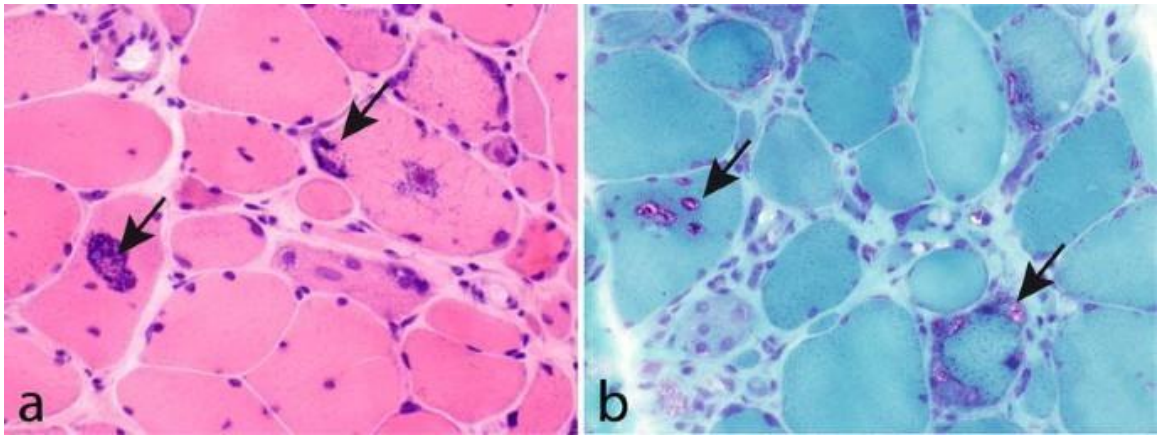

Figure 3. Dominant myosin IIa myopathy. Biopsy of the quadriceps muscle of a 38-year-old man demonstrating variability of fiber size, increased interstitial connective tissue, and frequent fibers with rimmed vacuoles. **a** Hematoxylin and eosin; **b** Gomori trichrome. [2]

Autosomal recessive MyHC IIa myopathy

Recent cases of recessive *MyHC IIa* variants have been reported, characterized by homozygous or compound heterozygous truncating variants in the *Myosin Heavy Chain II*(*MYH2)* gene, resulting in complete loss of MyHC IIa protein and absence of type 2A muscle fibers. Surprisingly, the clinical presentation of these cases is relatively mild, with minor to moderate generalized muscle weakness, including facial weakness. External ophthalmoplegia is a consistent feature, occasionally accompanied by ptosis. MRI findings indicate selective muscle involvement, particularly in the lower limbs' medial gastrocnemius and certain thigh muscles. Muscle biopsies reveal unspecific myopathic

changes, such as fiber size variability, internalized nuclei, and interstitial fatty infiltration, alongside complete loss of MyHC IIa protein. Some samples also exhibit type 1 fiber uniformity. Unlike dominant MyHC IIa myopathy, there are no rimmed vacuoles or protein aggregates identified. [2]

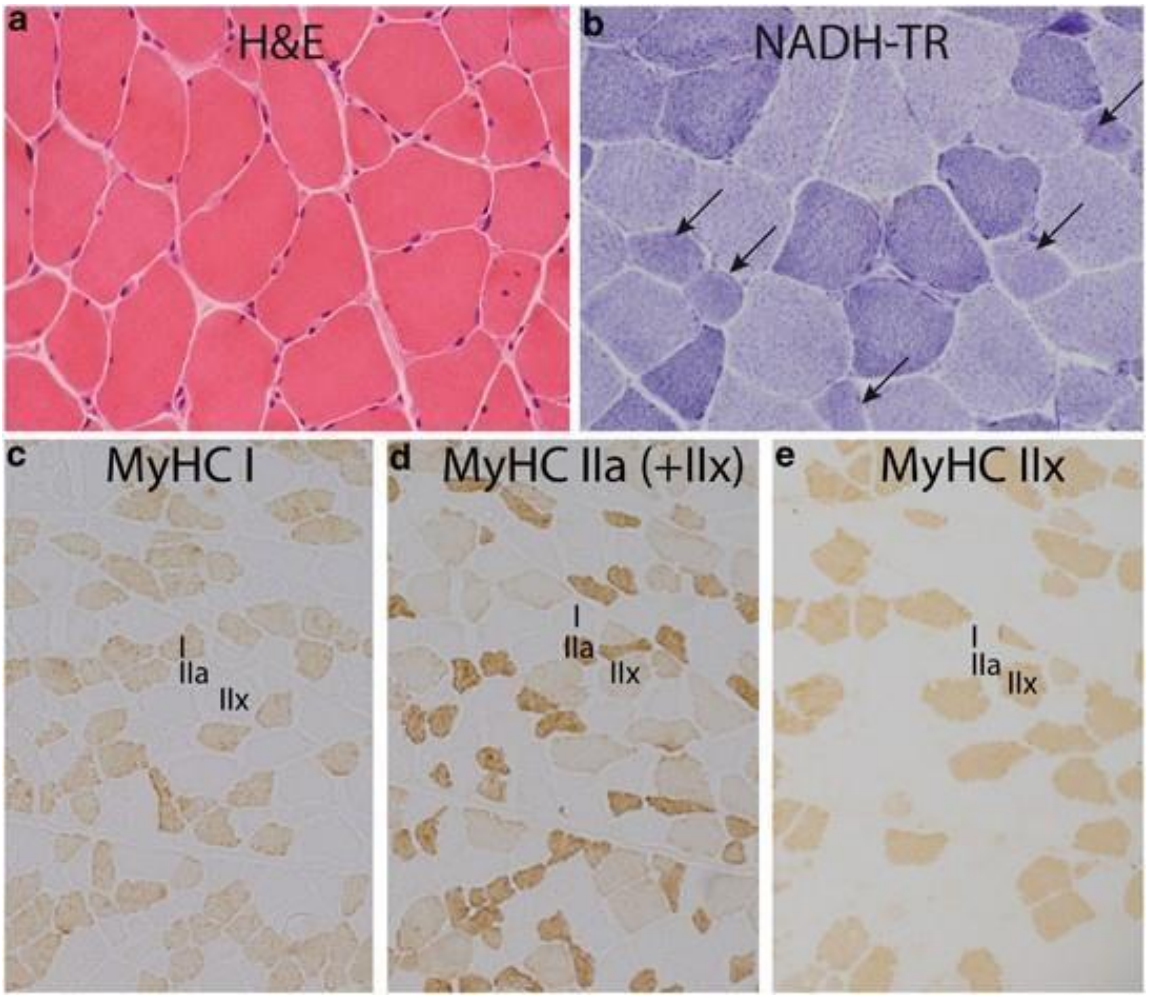

Figure 4. Deltoid muscle of patient showing increased variability of fiber size with small type 2A fibers (arrows). (**a**) Hematoxylin and eosin. (**b**) NADH-tetrazolium reductase. (**c**–**e**) Immunohistochemical staining of MyHC isoforms on serial muscle sections. The MyHC IIa antibody recognizes to some extent also MyHC IIx. [13]

Clinical description of the cases

Case 1.

A 47-year-old man, born to non-consanguineous parents in India and assessed in 2021, presented with a 20-year history of postprandial esophageal reflux followed by 12 years of gradually worsening difficulty in rising from the floor and climbing stairs. He reported no myalgia, fatigue, or oculo-bulbar symptoms, and there was no family history of similar

issues. On examination, he exhibited proptosis of 18 mm with restricted eye movement and facial weakness. Upper limb power was normal, but hip weakness was observed. All tendon reflexes were hyperactive. Given gastrointestinal symptoms alongside pelvic girdle weakness and ophthalmoparesis, mitochondrial myopathy was considered. Investigations revealed elevated serum creatine kinase levels 808 U/L and muscle biopsy indicated secondary myopathic changes. Magnetic resonance imaging showed significant fatty infiltration in several muscles. Clinical exome sequencing was conducted using a custom capture kit in the patient, uncovering rare homozygous *Myosin Heavy Chain II*(*MYH2)* variants. Specifically, a novel single nucleotide duplication, c.348 + 2dup (hg38; chr17: g.10547473dupA), was identified at the 5' splice site in intron 4. This duplication was predicted to alter splicing, as indicated by a score of 0.5 by the splice AI tool. Furthermore, mitochondrial genome sequencing returned negative results. Mitochondrial genome sequencing was negative.[8]

Case 2.

In 2022, a 48-year-old Indian man presented with 12-year bilateral eyelid drooping, progressing gradually without double vision. He experienced fatigable limb weakness but no dysarthria or dysphagia. Examination showed asymmetric ptosis, restricted eye movements, and mild facial weakness. Muscle strength was normal, with hyperactive tendon reflexes. Considerations included mitochondrial chronic progressive external ophthalmoparesis (CPEO) and congenital myasthenic syndromes. Serum creatine kinase levels were elevated at 356 U/L, and muscle biopsy revealed fiber size variations with nuclear internalization. Clinical exome sequencing was conducted using a custom capture kit in the patient, identified rare homozygous *Myosin Heavy Chain II*(*MYH2).* Specifically, a single nucleotide deletion, c.4438del (hg38; chr17: g.10525550del), leading to a frameshift (p. Ala1480ProfsTer11), was detected. This variant has been previously reported as pathogenic in clinvar. Mitochondrial genome sequencing was negative.[8]

Case 3.

A 43-year-old Italian man, born to healthy, unrelated parents, had a typical childhood without joint contractures. Although he enjoyed sports during adolescence, he experienced mild exercise intolerance and significant lower limb weakness at 17,

affecting his ability to participate in physical activities. Despite normal serum creatine kinase levels, electromyography revealed neuromuscular abnormalities. By age 20, he developed mild ptosis and muscle atrophy, progressing to ophthalmoparesis and mild diplopia by 25. Swallowing difficulties were absent. In his 30s, he faced challenges climbing stairs due to progressive muscle weakness, with elevated Creatine Kinase upto 1,500 U/L, and electromyography revealed a widespread myopathic pattern. Myasthenia gravis was ruled out based on negative electromyography repetitive nerve stimulation and the lack of specific serological antibodies. Chronic inflammatory demyelinating polyneuropathy was excluded following international criteria. Complete ophthalmoplegia, scapular winging, and a waddling gait ensued. Muscle biopsies at ages 17 and 39 revealed characteristic abnormalities, including rimmed vacuoles and fiber size variability. Genetic analyses for various muscle disorders were unremarkable, but targeted gene panel analysis identified two novel *Myosin Heavy Chain II(MYH2)* variants in compound heterozygosity.

The possessed two new heterozygous truncating variants in the *Myosin Heavy Chain II(MYH2)* gene: one in the myosin motor domain (p.Arg793Ter) and the other in the coiled coil rod domain (p.Glu1461Ter). Despite having these two truncating variants, the patient still produced small amounts of *Myosin Heavy Chain II(MYH2)* mRNA, resulting in the production of limited myosin IIa in type 2B fibers. Subsequent sequencing confirmed these variants in the patient and his parents, who showed no muscle involvement. Transcript analysis revealed abnormal MyHCI predominance in the patient, suggesting potential mRNA decay due to the identified variants.[15]

Case 4.

The patient, a 32-year-old male of Northern Indian descent, was born to consanguineous first cousin parents. His early motor development was generally normal, although he achieved running and jumping milestones later than his peers. Weakness progressively worsened in his 20s, accompanied by proximal weakness, dysphagia with solid food, and a weak cough. At age 32, the patient presented with near-complete ophthalmoplegia, mild eye and lip closure weakness, non-fatigable ptosis, nasal speech, and mildly increased joint laxity without contractures. Muscle atrophy was diffuse, most notable in the quadriceps. Strength assessment revealed symmetric weakness, notably in the deltoids, biceps, triceps, iliopsoas, quadriceps, and hamstrings. His gait reflected pelvic girdle

weakness, and he required a modified Gower maneuver to rise from the floor. Reflexes were generally normal, and sensation was intact. Serum creatine kinase levels were elevated, ranging from 595 to 893 IU/L. Acetylcholine receptor antibodies were absent, and nerve conduction studies were normal. Electromyography indicated an active myopathy, with fibrillations, positive sharp waves, and small units in the deltoids and biceps. Ultrasound revealed increased signal in proximal arms and legs, with selective involvement of the medial gastrocnemius. A biceps muscle biopsy displayed marked fiber size variation, hypertrophied fibers, rimmed vacuoles, increased endomysial connective tissue, pyknotic nuclear clumps, and altered internal architecture. ATPase staining revealed poorly differentiated fiber types, with predominance of type 1 fibers. Immunofluorescent myosin stains demonstrated MyHCIIa expression primarily in small fibers or larger fibers with abnormal internal architecture, often co-existing with MyHCI in type 2 fibers. Mitochondrial enzyme assays were normal. Genetic analysis via exome sequencing identified a homozygous variant in *Myosin Heavy Chain II(MYH2)* (c.737 G>A, p.R246H) with damaging predictions by in silico analysis tools and conservation across species. This variant, also conserved between myosin isoforms, has been associated with dominant cardiomyopathies in MYH7 (p.R243H).[6]

Case 5.

At seven weeks old, the infant exhibited noisy breathing and a wet cough persisting since birth, worsened during feeding, resulting in episodes of choking and cyanosis. He is the third child of healthy, non-consanguineous Muslim Arab parents, weighing 3.2 kg at birth after a 41-week gestation period marked by polyhydramnios. The clinical presentation of *MYH2* congenital myopathy includes complete ophthalmoplegia, mild muscle weakness, and dysphagia. Laboratory tests, including a complete blood count, electrolytes, glucose, liver and kidney function tests, and serum]creatine kinase levels, returned normal results. A chest X-ray revealed bilateral opacities, particularly in the right upper lobe. Flexible bronchoscopy depicted a normal upper and lower airway anatomy, with saliva accumulation observed in the larynx and lower airways. Esophageal pH monitoring over a 24-hour period and brain MRI results were within normal range. Due to severe aspiration and reflux, the patient underwent gastrostomy and Nissen fundoplication. Given the comparable clinical presentation of the siblings, we suspected a genetic condition and proceeded with exome sequence analysis as part of the ongoing

investigation. Peripheral blood DNA underwent exonic sequence enrichment using an Agilent Technologies kit, followed by sequencing using HiSeq2000 (Illumina), producing 100 paired-end bases. DNAnexus software aligned reads and identified variants using hg19 (GRCh37) as reference. Whole-exome sequencing resulted in 53.87 million mapped reads, yielding twelve variants. Homozygosity for a novel *Myosin Heavy Chain II(MYH2)*variant (Chr17: NM_001100112:exon21:c.2398delG:p.G800fs) was observed in the patient, with heterozygous carriers identified in asymptomatic parents and sister.[10]

Case 6.

A 12-year-old Arab boy, previously managed at a different hospital, experienced dysphagia since birth. At one month old, he underwent gastrostomy, followed by Nissen fundoplication at 18 months. By age 4, he was diagnosed with swallowing dysfunction attributed to upper esophageal sphincter dysfunction, leading to cricopharyngeal myotomy and subsequent botulinum toxin injections. At 10 years old, he underwent pneumonectomy due to recurrent pneumonia and chronic lung insults. Despite normal motor, language, and cognitive development, he later developed ophthalmoplegia, nystagmus, and mild weakness of neck flexors and proximal muscles. Laboratory tests, including complete blood count, electrolytes, glucose, liver and kidney function tests, and serum creatine kinase, were normal. Chest X-ray revealed bilateral opacities, particularly in the right upper lobe. Flexible bronchoscopy demonstrated normal upper and lower airway anatomy, with saliva accumulation in the larynx and lower airways. Videofluoroscopy indicated aspirations during swallowing. Genetic analysis revealed homozygosity for a novel single base deletion in the myosin heavy chain 2 gene, *Myosin Heavy Chain II(MYH2)* (Chr17: NM_001100112:exon21:c.2398delG:p.G800fs).[10]

Case 7.

The patient, a 12-year-old Italian girl, is the second child of healthy non-consanguineous parents. Born at 36 weeks of gestation, she experienced severe respiratory distress shortly after birth, requiring assisted ventilation. Initial hypotonia with preserved anti-gravity limb movements, myopathic facial features, and swallowing difficulties were noted. While respiratory function improved over time, severe dysphagia persisted, necessitating gastrostomy. Normal CPK levels and electromyography findings ruled out myotonic disorders and autoimmune neuromuscular diseases. A muscle biopsy at 9 months showed

features consistent with congenital myopathy, further supported by clinical improvement over time. Despite the achievement of independent ambulation at 2 years and gastrostomy removal at 4 years, characteristic myopathic facial features, ptosis, ophthalmoplegia, and mild scoliosis persisted. Muscle MRI revealed diffuse thigh involvement, particularly in the vastus lateralis, rectus femoris, and semitendinosus muscles, as well as marked changes in the lateral head of the gastrocnemius at the calf level. Genetic analysis identified a heterozygous variant (c.5737T>C) in exon 39 of the *Myosin Heavy Chain II(MYH2)* gene, predicted to be damaging. This variant, leading to a change from leucine to proline at position 1870 (L1870P) within the myosin tail, disrupts the normal helical coiled coil structure critical for myosin filament assembly, suggesting its pathogenic role in the observed phenotype. Muscle biopsy confirmed fiber size variability and connective tissue proliferation without inflammation or necrosis, consistent with congenital myopathy. Immunochemistry demonstrated predominance of type I fibers and rare, hypotrophic type II fibers. Muscle MRI highlighted the extent of muscle involvement, particularly in the pelvic girdle, thighs, and calves.[4]

Case 8.

A 48-year-old man from Spain, born to non-consanguineous parents, was referred to our hospital due to persistent mild elevation of creatine kinase (CK) levels (300–550 U/L). He achieved normal motor milestones initially but experienced mild muscle weakness since adolescence. Neurological examination revealed severe external ophthalmoplegia without ptosis and weakness of the orbicularis oculi muscles. Motor examination showed mild symmetric proximal weakness (4/5, Medical Research Council scale) in various muscles. He had a positive Gowers sign. The patient had early-onset cataracts, and some of his siblings also exhibited ophthalmoparesis and proximal weakness.

Muscle biopsy showed mild variability in fiber size and an increase in internal nuclei, with a predominance of type I fibers. Molecular diagnosis revealed a homozygous nonsense variant (c.1498G>T) in the *Myosin Heavy Chain II(MYH2)* gene, resulting in a premature stop codon (p.Glu500Ter). This variant, not previously reported in public databases, is likely to impair the function of the MyHC IIa protein. The patient's phenotype suggests a recessive *Myosin Heavy Chain II(MYH2)* variant, characterized by early-onset nonfluctuating mild proximal weakness with severe ophthalmoplegia.

Abnormalities in muscle fiber differentiation and the presence of hybrid fibers expressing both fast and slow myosin further support the diagnosis.[3]

Case 9.

An Australian man of Italian descent, born to unrelated parents, first experienced difficulty climbing stairs and foot inversion at age 20. His condition progressively worsened, leading to muscle weakness, facial weakness, foot drop, and respiratory problems by age 50. Despite normal CPK levels and electromyography results, muscle MRI at age 58 revealed extensive fat replacement, especially in the lower limbs. Initial genetic testing ruled out various neuromuscular disorders, but targeted sequencing identified a harmful variant in *Myosin Heavy Chain II*(*MYH2)* (c.5630T>C p.L1877P). Further analysis showed reduced expression of MYH isoform transcripts in the patient's muscles, consistent with the observed muscle phenotype. The variant was not found in his parents or unaffected siblings, suggesting it arose as a new variant or one of the parents had a genetic change in their reproductive cells. This case underscores the importance of genetic analysis in diagnosing neuromuscular disorders and highlights the role of Myosin Heavy Chain II variant in such conditions.[15]

Case 10.

The patient, a 32-year-old man of northern Indian descent, born to first cousin parents, experienced delayed motor milestones but an otherwise unremarkable birth and early development. In his 20s, he began experiencing progressive weakness, dysphagia, and a weak cough. Remarkably, his 21-year-old brother displayed similar albeit milder symptoms, primarily difficulty climbing stairs. At age 32, the patient presented with near complete ophthalmoplegia, mild weakness in eye and lip closure, non-fatigable ptosis, nasal speech, and mildly increased joint laxity without contractures. Notably, he exhibited diffuse muscle atrophy, most prominent in the quadriceps, and specific muscle strength assessments revealed weakness consistent with pelvic girdle weakness. Diagnostic tests indicated elevated serum creatine kinase levels, abnormal electromyography findings, and muscle biopsy revealed marked fiber size variation and altered internal architecture, along with abnormal myosin expression patterns. Exome sequencing identified a homozygous variant in the *Myosin Heavy Chain II(MYH2)* gene (c.737 G>A, p.R246H), predicted to be damaging and confirmed in both parents. This variant, highly conserved

among lower species, is associated with myosin isoforms, with similar variant in MYH7 linked to dominant cardiomyopathies. The findings suggest a genetic basis for the patient's myopathic condition, explaining observed clinical symptoms and muscle pathology. Additionally, in silico analysis tools predict the variant's deleterious effect, supporting its significance in the context of the patient's condition.[6]

Case 11.

An 8-year-old boy of Sri Lankan heritage, first exhibited external ophthalmoplegia at the age of 5. While he complained of nocturnal leg pains, relieved by pressure from his parents, there was no history of generalized weakness, fatigue, or muscle abnormalities. Mild weakness was noted in shoulder abduction and neck flexion, along with partial external ophthalmoplegia, mild upper facial muscle weakness, mild ptosis, and slight lumbar lordosis. Neurological examination was otherwise unremarkable. Both asymptomatic parents, non-consanguineous, showed no signs of muscle weakness upon examination, and his younger sister was clinically normal. Serum creatine kinase and lactate/pyruvate levels were within normal range. Mitochondrial DNA analysis revealed no common variants, and muscle biopsies showed type 1 fiber uniformity with no significant abnormalities except for MYH7 expression. Genetic testing identified a novel homozygous variant (c.533C>T) affecting the last conserved nucleotide of exon 4 in *Myosin Heavy Chain II(MYH2)*, resulting in a threonine-to-isoleucine substitution at position 178 (p.Thr178Ile). This variant was confirmed in the patient's unaffected heterozygous parents. The identified *Myosin Heavy Chain II(MYH2)* variant has been previously associated with Freeman–Sheldon and Sheldon–Hall syndromes, indicating its deleterious impact on myosin function, despite its occurrence in the embryonic MyHC paralog with a dominant inheritance pattern.[13]

Case 12.

The family under study was of Jewish descent from Iran and exhibited a high degree of consanguinity. The proband, a 51-year-old woman (patient A), showed slow progression of external ophthalmoplegia along with mild facial and proximal limb muscle weakness, likely starting in late childhood. One brother (patient B) and one sister (patient C) displayed similar clinical manifestations. Medical records indicated external ophthalmoplegia in the father at age 36, suggesting an autosomal recessive disease with

homozygosity or pseudodominant inheritance. The family's testing revealed normal creatine kinase levels, electrocardiography, and echocardiography. Electromyography showed borderline mixed results, while biceps muscle biopsy of the proband showed poor fiber type differentiation without specific alterations. Genetic analysis identified a missense variant (c.706G>A) in exon 6, which was homozygous in all three siblings (A, B, and C), indicating inheritance from both parents. This variant resulted in the substitution of the conserved nonpolar amino acid alanine at position 236 with the polar uncharged threonine.[13]

Case 13.

The patient, of English ancestry, had no family history of neuromuscular disease and experienced no neonatal issues. Ophthalmoplegia, without ptosis, was observed at age 12, followed by the onset of severe epilepsy at 43, accompanied by mild proximal muscle weakness. Examination revealed thin musculature, severe ophthalmoplegia without ptosis, and mild weakness in the face, neck flexion, and proximal limbs, with some grip weakness and mild finger contractures. Despite difficulty rising from a low squat, he could walk unaided, with normal distal leg muscles. Unexpectedly, he died at 45 during sleep, with postmortem indicating advanced coronary artery disease, likely due to cardiac arrhythmia. Muscle tissue RNA analysis revealed reduced MyHC IIa expression and increased variability of fiber size, consistent with immunohistochemistry results showing small type 2A muscle fibers expressing MyHC IIa. Genetic testing identified a novel homozygous missense variant (c.1591T>C) in exon 14, resulting in the substitution of the nonpolar amino acid methionine at position 531 with the polar uncharged threonine. Unfortunately, parental genetic information was unavailable for analysis.[13]

Case 14.

The patient, a Swedish man with a Finnish mother, developed near-complete ophthalmoplegia at 57. He experienced mild slowness in running as a child but was active in various sports. Examination revealed slight weakness in neck, elbow, and hip flexion, moderate weakness in abdominal muscles and handgrip, with normal cardiac function and forced vital capacity. Serum CK levels were slightly elevated. Deltoid muscle biopsy showed fatty infiltration and extreme predominance of type 1 fibers, with structural abnormalities in some fibers. Genetic analysis identified two variants: a novel

heterozygous missense variant (c.1331C>T) in exon 12, changing arginine to cysteine at position 445, and a heterozygous nonsense variant (c.2405T>A) in exon 19, introducing a premature stop codon at position 802. The missense variant was inherited from the father, while the nonsense variant came from the Finnish mother. Analysis of cDNA revealed mRNA decay of the mutated allele with the stop codon. The mutated residue (p.Arg445) is analogous to a residue associated with cardiomyopathy in another myosin isoform. The second variant (p.Leu802Ter) has been previously identified in Finnish patients. The patient's unaffected brother carried only the missense variant, suggesting its non-dominant nature. This study highlights the pathogenic potential of these variants, shedding light on the significance of specific amino acid residues in myosin function and their implications for cardiac health.[13]

Case 15.

The patient, of Indian descent but from the United Kingdom, had no family history of neuromuscular disease. Early in life, he struggled with a weak suck and required special feeding methods. Despite this, he excelled in sports during childhood. However, in his twenties, he began experiencing ptosis, and by his forties, proximal weakness emerged. At age 60, examination revealed ptosis, near complete ophthalmoplegia, and marked periocular weakness. While he exhibited neck flexion and proximal weakness, distal muscles remained unaffected, enabling him to walk unaided. MRI of his thighs revealed significant fatty infiltration in certain muscles while sparing others. Quadriceps muscle biopsy displayed fatty infiltration, fiber size variability, and internalized nuclei. Genetic analysis identified a novel frameshift variant (p.(Lys1451SerfsTer40)) in exon 29, suggesting a recessive inheritance pattern. Interestingly, while four novel missense variants appeared recessive, they affected paralogs dominant in embryonic MyHC (MYH3), implying vulnerability to heterozygous variants during early development. Similarly, a missense variant at residue p.Arg442 in slow/β cardiac, paralogous to *Myosin Heavy Chain II(MYH2)* p.Arg445, was dominant, suggesting possible haploinsufficiency or dominant negative effects in these cases. The pathogenicity of dominant MYH7 and MYH3 variants may involve dysfunctional protein incorporation into sarcomeres or other mechanisms.[13]

Case 16.

Three members of the same family underwent assessment for mild to moderate generalized muscle weakness since early childhood, with minor progression. Patient A, a UK female, exhibited symptoms from childhood, including facial muscle weakness, pronounced ophthalmoplegia, and neck flexion weakness. Muscle imaging was not conducted, but electromyography (EMG) showed myopathic changes. Muscle biopsies from quadriceps and deltoid muscles revealed type 1 fiber uniformity. A dominant missense variant in *Myosin Heavy Chain II(MYH2)* (p.E706K) was identified, associated with ophthalmoplegia and abnormal type 2A muscle fibers, along with a splice site variant and a nonsense variant.

Patient B, also a UK female, had an asymptomatic onset except for a "lazy eye" in childhood. Similar symptoms of facial muscle weakness and pronounced ophthalmoplegia were observed, with muscle biopsies showing similar fiber characteristics. The same *Myosin Heavy Chain II(MYH2)* variant was found, along with splice site and nonsense variants. Patient C, a UK male, remained asymptomatic until examination at age 44, displaying similar symptoms to the other family members. Muscle biopsies revealed comparable findings, and the same *Myosin Heavy Chain II(MYH2)* variant was identified. Overall, all three patients exhibited facial muscle weakness, pronounced ophthalmoplegia, and neck flexion weakness, along with similar muscle biopsy results. The *Myosin Heavy Chain II(MYH2)* variant (p.E706K) was consistent across all cases, associated with ophthalmoplegia and abnormal type 2A muscle fibers. Additionally, splice site and nonsense variants were detected, suggesting a genetic basis for the observed skeletal myopathy.[14]

Case 17.

The patient is a 58-year-old Finnish male who has experienced general muscle weakness since childhood. He exhibits pronounced ophthalmoplegia without ptosis and facial muscle weakness. Upper limb strength is graded between 4 and 5 on the Medical Research Council (MRC) scale, while abdominal muscle weakness is graded at 3. Mild proximal weakness is noted in the lower limbs. Although congenital pectus carinatum was surgically corrected, strength training did not yield improvement. Muscle imaging revealed moderate diffuse fatty degenerative changes in the thigh and medial gastrocnemius. Creatine kinase levels were normal, and electromyography (EMG) showed mild myopathic changes. A biopsy from the vastus lateralis of the quadriceps

femoris muscle displayed myopathic features, including increased variability in fiber size and internalized nuclei. There was absence of type 2A muscle fibers, and immunohistochemical staining indicated expression of myosin heavy chain I and IIx, but not IIa. Genetic analysis revealed a heterozygous variant affecting the splice site of intron 15, leading to exon skipping and a frame shift variant. Another heterozygous nonsense variant was identified in exon 19. SDS-PAGE analysis confirmed the absence of MyHC IIa protein in quadriceps muscle specimens, indicating a *Myosin Heavy Chain II(MYH2)* defect characterized by the total absence of fast IIa fibers.[14]

Case 18.

The patient is a 59-year-old Finnish male who experienced muscle weakness since early childhood. He presented with ptosis, ophthalmoplegia, and mild overall weakness from an early age, with notable weakness in facial muscles, upper limbs, and abdominal muscles. Muscle imaging revealed moderate diffuse fatty degenerative changes in the thigh and medial gastrocnemius. Despite normal Creatine Kinase levels, EMG results indicated myopathic changes. Muscle biopsy of the quadriceps muscle showed absence of type IIa MyHC fibers, along with marked variability in fiber size, internalized muscle fiber nuclei, increased interstitial fat and connective tissue, and type 1 fiber uniformity. Subsequent biopsies at ages 55 and 58 revealed type 1 fiber predominance and slight disorganization of the intermyofibrillar network. MRI at age 58 displayed fatty infiltration in various leg muscles. A defect in *Myosin Heavy Chain II(MYH2)* was indicated by the total absence of fast IIa fibers in proximal muscle biopsy specimens. Genetic analysis revealed a heterozygous variant affecting the splice site of intron 15, leading to exon 16 skipping and a reading frame shift, as well as a heterozygous nonsense variant in exon 19. These variants likely contribute to the observed skeletal myopathy, characterized by early onset muscle weakness and progressive ophthalmoplegia.[14]

Table 1. Summary of characterstics of MYH2 Autosomal Dominant and Autosomal Recessive phenotypes.[15]

Characteristics	Dominant phenotype	Recessive phenotype
Onset	Adulthood	Childhood
Congenital contractures	Present	Absent
Scoliosis	Infrequent	Frequent
Weakness	Distal and proximal	Proximal > distal
	Legs > Arms	Legs > Arms
		Distal and proximal
		Legs > arms
Facial weakness	Infrequent	Present
Ophthalmoplegia	Present	Present
CK level (U/L)	2–10x	Normal to 4x
Disease progression	Progressive	Non-progressive
Biopsy	Dystrophic changes, severe fibro-fatty substitution, rimmed vacuoles. Absence of 2A fibers with residual MyHCIIa. Nuclear inclusion filaments.	Dystrophic changes, severe fibro-fatty substitution, rimmed vacuoles. Reduced number and size of type 2A fibers. Nuclear inclusion of 15–21 filaments.

Treatment methods

The diagnosis and treatment of myopathy present challenges for clinicians, but recent advancements in molecular biology have facilitated early and precise diagnosis of myopathy caused by inherited genetic or metabolic factors. Despite these advances, effective treatment remains elusive. Gene therapy and stem cell transplantation have shown promise in myopathy research, but concerns about the safety of the adeno-associated virus vector and the potential for stem cell tumorigenicity have hindered their widespread clinical application. Currently, rehabilitation therapy stands as the primary option for managing myopathy.

Precision medicine has emerged as a novel approach to treating myopathy, taking into account individual genetic and environmental factors. This approach tailors treatment plans to each patient's unique characteristics. For instance, patients with similar symptoms but different underlying genetic causes, such as mitochondrial myopathy and muscular dystrophy, may require distinct treatment strategies.

Despite the importance of *Myosin Heavy Chain II(MYH2)* variants in myopathy, few studies have focused on treatment strategies for patients with these variants, and clinical guidelines for addressing different *Myosin Heavy Chain II(MYH2)* variants are lacking. This thesis spread light on the successful application of precision rehabilitation medicine in a patient with two *Myosin Heavy Chain II(MYH2)* missense variants. Individualized comprehensive rehabilitation training approaches which have been shown to significantly alleviate symptoms, enhance independent living capacity, and improve quality of life for patients with *Myosin Heavy Chain II(MYH2)* -related myopathy.[16]

Table 2. Types of exercises approach based on genetic etiology of the patient.[16]

Type of Training	**Approaches**
Endurance Exercise	Exercise on a stationary bicycle for 15 minutes at moderate intensity, twice per day, 3 days/week. The training time can be gradually increased to 30 minutes per session.
Eye Movement Exercise	Move eyes in different directions to track a moving ball in the therapist's hand.
Ambulation Exercise	Sit-to-stand training; stand-to-sit training; squat-to-stand training; walking activities, such as walking forward and backward and turning around an obstacle; and stair activity training, such as climbing stairs with various step heights.
Balance Exercise	Weight shifting; single-leg supporting training; and balance plate training, such as playing ball with a therapist with both legs standing on a balance plate or during single-leg standing.
Motor Skill Training	Jumping forward and upward; kicking large and light balls; and throwing a ball at different targets.
Strength Training (Original)	Strengthening the masseter muscle, the hip, knee and ankle extensors and flexors, and muscles of the shoulder girdle via resistance training against the patient's own gravity and neuromuscular electrical stimulation once daily.

Discussion

MYH2-related myopathy represents the initial instance of a human muscle disorder linked to a mutation within one of the skeletal muscle-specific MyHC isoforms.[4] The comprehensive clinical descriptions provided in this study explain the diverse phenotypic manifestations and genetic foundations associated with *Myosin Heavy Chain II(MYH2)* related myopathies across a broad spectrum of age groups and ethnic backgrounds. Through the thorough examination of individual cases, a refined understanding of the clinical presentation, diagnostic journey, and treatment challenges inherent to *Myosin Heavy Chain II(MYH2)* -related disorders is gathered, shedding light on the complicated interaction between genetic variations and phenotypic expressions.

The cases presented, emphasise the heterogeneity inherent to *Myosin Heavy Chain II(MYH2)* -related myopathies, ranging from early-onset congenital presentations with joint contractures to adult-onset progressive weakness and ophthalmoplegia. The delineation of distinct clinical phenotypes, such as autosomal dominant versus recessive manifestations, further enriches our understanding of the varied disease trajectories observed within this spectrum. Notably, the identification of novel variants alongside previously reported pathogenic mutations in *Myosin Heavy Chain II(MYH2)* underscores the ongoing need for vigilant genetic characterization to elucidate the full spectrum of disease-associated variants and their implications for clinical management.

The diagnostics portrayed in these cases highlights the complexity inherent to *Myosin Heavy Chain II(MYH2)* -related myopathies, often requiring a multidisciplinary approach about clinical evaluation, muscle biopsy, genetic testing, and advanced imaging modalities. Moreover, the challenges posed by the rarity and phenotypic variability of *Myosin Heavy Chain II(MYH2)* -related disorders underline the objective for increased clinical suspicion and tailored diagnostic algorithms to accelerate accurate diagnoses and inform personalized treatment strategies.

Despite the advances made in molecular diagnostics, therapeutic interventions for *Myosin Heavy Chain II(MYH2)* -related myopathies remain limited, emphasizing the urgent need for innovative therapeutic modalities. According to this study gene therapy and stem cell transplantation can be promisable, concerns regarding safety and efficacy necessitate further research to portray their role in the clinical management of *Myosin Heavy Chain II(MYH2)* -related disorders. In this context, the standard shift towards precision medicine emerges as a beacon of hope, offering individualized treatment strategies designed to the

unique genetic and clinical profiles of patients with *Myosin Heavy Chain II(MYH2)* -related myopathies.

The successful application of precision rehabilitation therapy medicine in a patient with *Myosin Heavy Chain II(MYH2)* missense variants highlightes the transformative potential of tailored rehabilitation interventions in bettering symptoms, enhancing functional capacity, and improving quality of life for individuals afflicted with *Myosin Heavy Chain II(MYH2)* -related myopathies, hence is only indicative, but not generalizable. By leveraging comprehensive rehabilitation training approaches, clinicians can optimize outcomes and empower patients to navigate the challenges posed by *Myosin Heavy Chain II(MYH2)* -related disorders with strength and accuracy.

Conclusion

In conclusion, the explanation of the clinical, genetic, and therapeutic landscape of *Myosin Heavy Chain II(MYH2)* -related myopathies through detailed case descriptions and thoughtful discussion highlightes the necessity for continued research endeavors aimed at unraveling the intricacies of this complex disease entity. By harnessing the collaborative efforts of clinicians, researchers, and patients, we can pave the way towards enhanced diagnostic precision, therapeutic innovation, and ultimately, improved outcomes for individuals affected by *Myosin Heavy Chain II(MYH2)* -related myopathies. With the limited number of cases currently available, it is essential to conduct more comprehensive screening in both adults and children. This expanded screening will help capture a wider range of presentations and manifestations of this myopathy, providing a more thorough understanding of its spectrum. Further research and studies are needed to advance precision therapy, and treatment strategies should be standardized to benefit a broader population.

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Attachments:

1. Figure 1.Electron micrograph of a skeletal muscle sarcomere.[2]
2. Figure 2. Dominant myosin IIa myopathy. Biopsy of the deltoid muscle of a 38-year-old man showing alterations of the type 2A fibers (arrows). NADH-tetrazolium reductase. [2]
3. Figure 3. Dominant myosin IIa myopathy. Biopsy of the quadriceps muscle of a 38-year-old man demonstrating variability of fiber size, increased interstitial connective tissue, and frequent fibers with rimmed vacuoles. a Hematoxylin and eosin; b Gomori trichrome. [2]
4. Figure 4. Deltoid muscle of patient showing increased variability of fiber size with small type 2A fibers (arrows). (**a**) Hematoxylin and eosin. (**b**) NADH-tetrazolium reductase. (**c**–**e**) Immunohistochemical staining of MyHC isoforms on serial muscle sections. The MyHC IIa antibody recognizes to some extent also MyHC IIx. [13]

5. Figure 5. Table summarizing characterstics of MYH2 Autosomal Dominant and Autosomal Recessive phenotypes.[15]
6. Figure 6. Types of exercises approach based on genetic etiology of the patient.[16]

Warranty

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