Case Report

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Unravelling the Complexity of Dysferlinopathy: A Case Report Highlighting Digenic Inheritance of DYSF and MYH7 Mutations

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ABSTRACT

Dysferlinopathy encompasses a range of neuromuscular disorders arising from DYSF gene mutations, impacting the essential dysferlin protein's role in muscle membrane repair. Recent research has expanded its functional repertoire to include muscle fiber regeneration and immune modulation. While primarily adhering to autosomal recessive inheritance, rare cases of dominant and digenic inheritance have emerged. This case study features a 38-year-old male with progressive muscle weakness, subject to Multiplex ligation-dependent probe amplification (MLPA) and clinical exome sequencing (CES). CES revealed two heterozygous pathogenic missense variants—DYSF:c.3172C>T(p.Arg1058Trp) and MYH7:c.2400G>T—in the patient's genome. Segregation analysis confirmed maternal and paternal inheritance of these mutations, representing the first documented instance of digenic inheritance involving DYSF and MYH7 in dysferlinopathy. Dysferlinopathy's diverse phenotypic expressions challenge diagnosis, emphasizing clinical manifestations, age of onset, muscle involvement patterns, and diagnostic markers like creatine kinase (CK) levels and muscle biopsy findings. This report highlights the importance of comprehensive genetic assessments in deciphering the determinants of phenotypic variations within dysferlinopathy, inviting further research into digenic inheritance's broader implications in neuromuscular diseases.

Keywords: Dysferlinopathy; Digenic Inheritance; Neuromuscular Disorders; Genetic Diagnosis; Phenotypic Variations

Abbreviations: DYSF: Dysferlin Gene; MLPA: Multiplex Ligation-Dependent Probe Amplification; CES: Clinical Exome Sequencing; CK: Creatine Kinase; MRI: Magnetic Resonance Imaging; EMG: Electrodiagnostic; MD: Muscular Dystrophy; MMD: Miyoshi Muscular Dystrophy; LGMD2B: Limb-Girdle Muscular Dystrophy Type 2B; DMAT: Distal Myopathy with Anterior Tibial Onset; MSM: Myosin Storage Myopathy; SALSA: Sequencing Analysis of Large-Scale Amplifications; CES: Comprehensive Exome Sequencing; MLPA: Multiplex Ligation-Dependent Probe Amplification

Introduction

Inherited myopathies encompass over 200 distinct, individually rare disease subtypes, with a global prevalence of 1 in 6,000 individuals [1]. Dysferlinopathy assumes a prominent position within the neuromuscular disorders, encompassing a spectrum of muscular afflictions. This condition arises due to mutations in the DYSF gene, responsible for encoding the essential dysferlin protein vital for muscle membrane (sarcolemma) repair. Recent research suggests that dysferlin plays an extended role in muscle fiber regeneration and inflammation modulation. Consequently, these genetic alterations initiate a cascade of effects, resulting in various phenotypic variations, notably including Miyoshi muscular dystrophy (MMD) and limb-girdle muscular dystrophy type 2B (LGMD2B), each characterized by

distinct clinical presentations. The inheritance pattern of dysferlinopathy adheres to an autosomal recessive mode, requiring the presence of two mutated DYSF gene copies for the disorder to manifest. While instances of dominant and digenic or multigenic inheritance for this condition are globally rare, this case report offers a comprehensive exploration of dysferlinopathy, shedding light on its intricate genetic dimensions and inheritance patterns.

Case Report

A 38-year-old male patient presented with a history of progressive muscle weakness, which initially manifested at the age of 6 with a gradual onset of fatigue. A tissue biopsy performed at that time revealed features consistent with polymyositis, prompting the initiation of various immunosuppressive therapies, including prednisolone, azathioprine, and methotrexate. The challenges in walking began to surface at the age of 10, intensifying notably by the time the patient reached 16 years of age. A subsequent tissue biopsy indicated lipid deposition, leading to a revised diagnosis of lipid storage disease. Consequently, the immune therapy was gradually tapered, and a regimen of Co-Enzyme Q10 supplementation and B-group vitamins was introduced.

Approximately a year later, mitochondrial myopathy was considered in the differential diagnosis, though the patient continued with a similar therapeutic course. Notably, the patient, who was a daily smoker of 10-15 cigarettes, was concurrently undergoing nicotine replacement therapy as part of smoking cessation efforts.

At the age of 27, dysphagia related to solid foods became evident, coinciding with the emergence of distal muscular weakness in the patient's clinical presentation. Subsequent to the onset of dysphagia, the patient's condition progressively evolved to encompass bilateral upper and lower extremity proximal and distal weakness, ultimately transforming the myopathic presentation into a more widespread pattern of extremity muscle weakness. Magnetic Resonance Imaging (MRI) investigations disclosed findings of fat atrophy, increased muscle signal, and enchondroma. Electrodiagnostic (EMG) assessments further substantiated a myogenic etiology for the observed abnormalities. Echocardiographic evaluations indicated minimal insufficiency in the aorta, mitral, and tricuspid valves, with a left ventricular ejection fraction measuring at 58%. The patient was subsequently referred to the medical genetics department, where a thorough evaluation prompted Multiplex ligation-dependent probe amplification (MLPA) testing for Duchenne muscular dystrophy and the formulation of a clinical exome sequencing (CES) plan. Clinical examination and patient history at the time revealed distinctive features, including a myopathic gait characterized by a waddling walking pattern, difficulty in rising from a seated position, shortened stride, and general gait instability. The patient also exhibited joint contractures and hand weakness. Notably, no respiratory symptoms were detected, and there were no prominent signs of muscle atrophy or hypertrophy. A comprehensive assessment revealed a generalized reduction in joint range of motion, which could be attributed to the patient's reduced capacity for daily activities. Deep tendon reflexes were assessed as normal, and sensory function evaluation yielded no remarkable findings. The patient's pedigree did not reveal consanguinity, and there were no discernible similarities in phenotypic features. Additionally, the patient's peripartum history was devoid of complications.

Results

MLPA testing using SALSA® MLPA® Probemix DMD-1 P034 and DMD-2 P035 kits, along with analysis using the Coffalyser program, yielded normal results. Clinical exome sequencing (CES) was performed using the DNBSEQ-G50 sequencer (MGI, BGI®, China) and the Kapa hyperchoice Clinical Exome Panel, followed by analysis using the Genomize-SEQ variant analysis platform. Phenotypic filtering in the Genomize-SEQ platform revealed two distinct heterozygous likely pathogenic missense variants associated with the clinical picture, DYSF:c.3172C>T(p.Arg1058Trp) and MYH7:c.2400G>T. Segregation analysis on parental samples confirmed maternal and paternal inheritance of these two mutations, respectively (Figure 1). A list of myopathy-associated genes and genes with digenic or multigenic behaviour in the MD spectrum was extracted from the literature and used to create a custom gene-based filter in the Genomize-SEQ platform (GNE, MYOT, SIL1, GAA,LAMA2, PLEC, POMT1, CAPN3, CHAT, CHRNG, DES, NEB, EMD, MYH2, FKRP, SGCB, SGCD, AMPD1, DOK7, LMNA, ANO5, COL6A3,COL6A1,COL6A2, FLNC, RYR1, GAA, LMNA, LYST,SYNE1, CLCN1, MATR3, MATR3P1, MYH7, MYH7B, TIA1, LDB3, TTN, PABPN1). These filtering processes did not reveal any further significant mutations in the proband. On the other hand, No dosage anomalies were identified through Beadchip MicroArray Technology (Illumina®, Inc., USA) for myopathy-associated gene loci (Figure 2). A list of myopathy-associated genes and genes with digenic or multigenic behaviour in the MD spectrum was extracted from the literature and used to create a custom gene-based filter in the Genomize-SEQ platform (GNE, MYOT, SIL1, GAA,LAMA2, PLEC, POMT1, CAPN3, CHAT, CHRNG, DES, NEB, EMD, MYH2, FKRP, SGCB, SGCD, AMPD1, DOK7, LMNA, ANO5, COL6A3,COL6A1,COL6A2, FLNC, RYR1, GAA, LMNA, LYST,SYNE1, CLCN1, MATR3, MATR3P1, MYH7, MYH7B, TIA1, LDB3, TTN, PABPN1). These filtering processes did not reveal any further significant mutations in the proband. On the other hand, No dosage anomalies were identified through Beadchip MicroArray Technology (Illumina®, Inc., USA) for myopathy-associated gene loci (Figure 2).

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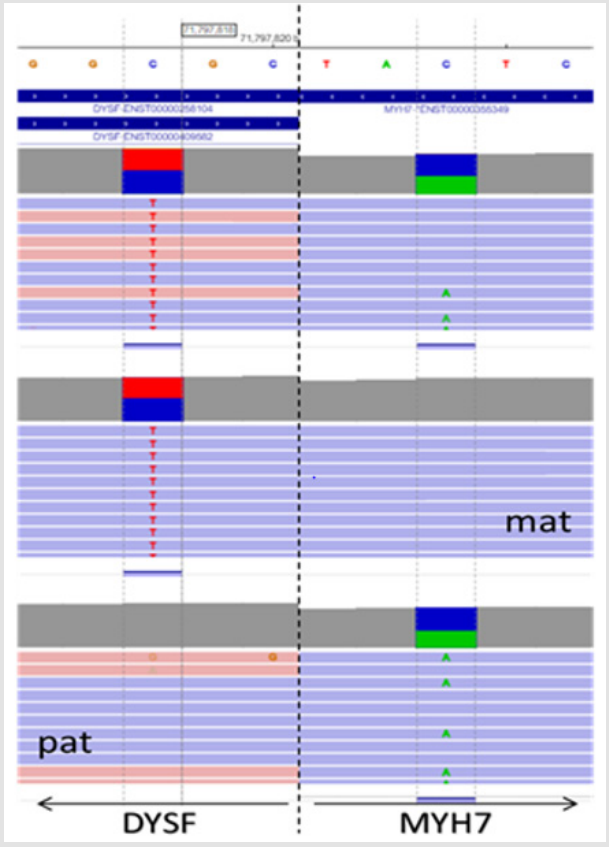

Figure 1: Detected mutation in proband and related segregation analysis; mat: Maternal. pat: Paternal. Genomize-SEQ platform- Integrative Genomics Viewer (IGV) view.

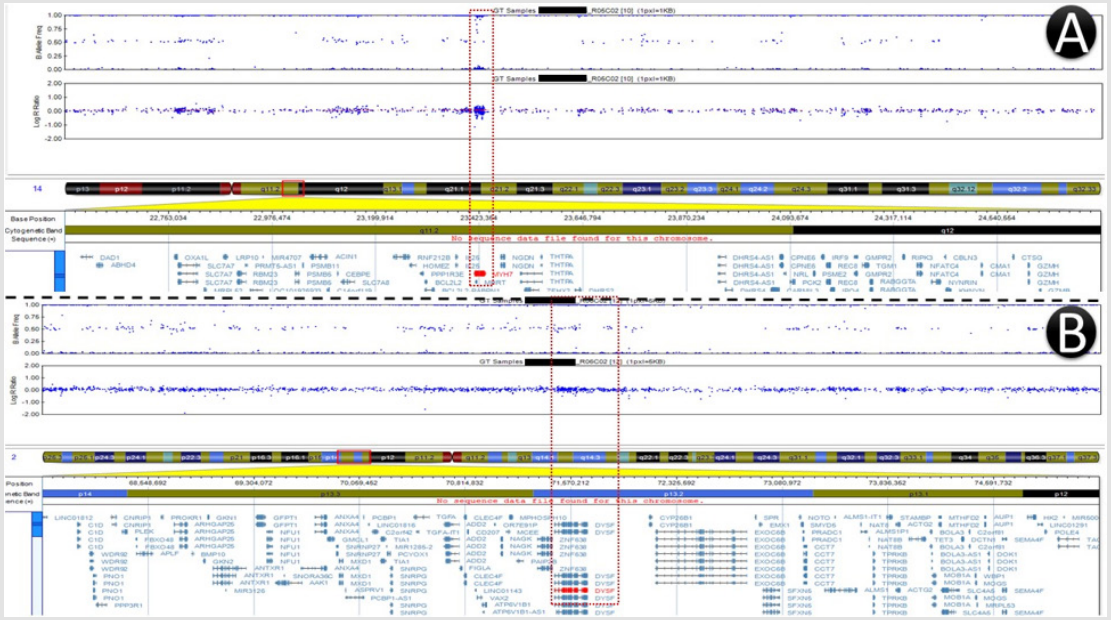

Figure 2: MYH7(A) and DYSF(B) genes natural dosages. İllumina Genome Studio Software v2.0.5, Using cnvPartition 3.2.0 plugin. Chromosome Browser tab.

Discussion

Within the intricate tapestry of myopathic disorders, dysferlinopathy occupies a distinctive niche, offering a glimpse into the complexities of diagnosing and understanding neuromuscular conditions through the lens of medical genetics. This subgroup of myopathies is primarily characterized by its autosomal recessive inheritance pattern, a genetic framework long held as a cornerstone in our comprehension of the disease. This classical model dictates the necessity of two mutated copies of the DYSF gene for the clinical manifestation of dysferlinopathy. Yet, within the realm of dysferlinopathy, a multifaceted spectrum of muscular ailments unfolds, each presenting a unique clinical portrait. The principal players in this clinical ensemble are Miyoshi muscular dystrophy (MMD) and limb-girdle muscular dystrophy type 2B (LGMD2B). Additionally, two less frequented phenotypes emerge: asymptomatic hyperCKemia and distal myopathy with an anterior tibial region onset (DMAT). This diversity in clinical presentations necessitates careful consideration of factors such as age of onset and the distinctive pattern of muscle weakness and atrophy. MMD, a luminary in this constellation, typically makes its debut around the age of 19, casting its spotlight on leg muscles before gradually extending its reach to the thighs and gluteal muscles. LGMD2B, on the other hand, commands an early entrance with weakness and atrophy in pelvic and shoulder muscles, its progress deliberate and measured. Asymptomatic hyperCKemia is an enigma, revealing elevated serum CK levels alone, while DMAT carves its identity through early and pronounced distal muscle weakness, most notably in the anterior leg muscles [1,2]. The diagnostic journey in dysferlinopathy has been significantly enriched by molecular genetics. Sequencing analysis, a formidable ally in the quest for genetic truths, successfully identifies mutations in approximately 98.6% of dysferlinopathy cases. However, the remaining 1.4%, characterized by elusive dosage changes in genes necessitating deletion or amplification assessments, poses an intriguing challenge. Our protagonist, the DYSF gene, encodes the essential dysferlin protein, known for its pivotal role in sarcolemma membrane repair. Recent revelations have expanded dysferlin's repertoire, now encompassing functions that aid in muscle fiber regeneration and immune modulation. Across the stage stands MYH7, the gene behind the beta-myosin heavy chain, a linchpin in the muscle contraction process.

In our case report, the plot thickens. Contrary to the traditional script of autosomal recessive inheritance, our patient unveils a heterozygous pathogenic DYSF mutation (DYSF:c.3172C>T(p.Arg1058Trp)), a mutation that in isolation typically falls short of heralding the arrival of dysferlinopathy. Yet, this narrative takes an unexpected turn as it intertwines with a concomitant heterozygous pathogenic MYH7 mutation (MYH7:c.2400G>T). The synergy of these two distinct mutations sparks intrigue. DYSF, with its role in sarcolemma membrane repair and more, harmonizes with MYH7's mastery in muscle contraction. The duo, although not known to have a direct or indirect pathway relationship, dances in tandem, orchestrating a complex and unique presentation of dysferlinopathy in our patient. This revelation of digenic behavior reframes our understanding of dysferlinopathy. Rather than adhering strictly to the recessive inheritance model, our patient's case introduces a novel paradigm. It emphasizes the intricate genetic choreography that may underlie neuromuscular disorders and raises tantalizing questions about the precise mechanisms through which these mutations orchestrate the clinical symphony. Digenic inheritance, a captivating phenomenon witnessed here, transcends the boundaries of a single gene's impact. It involves the cooperative interaction of two distinct genes, each contributing to the overall clinical picture. This intricate interplay adds layers of complexity to our understanding of disease etiology. Dysferlinopathy is not the lone example of digenic behavior within the realm of myopathies. Instances of digenic inheritance have also been reported in Emery-Dreifuss muscular dystrophy, limb-girdle muscular dystrophy, Ullrich congenital muscular dystrophy, and facioscapulohumeral muscular dystrophy, underscoring the multifaceted nature of these disorders [3]. On a similar occasion, in the broader context of muscular disorders, there are intriguing reports of digenic behavior involving the MYH2 gene. This gene encodes another myosin heavy chain, specifically the type 2A isoform, which is typically associated with fast-twitch muscle fibers. In a distinctive manifestation, MYH2 mutations have been linked to congenital myopathy with fiber-type disproportion (CFTD), a condition characterized by an abnormal size disproportion between type 1 (slow-twitch) and type 2 (fast-twitch) muscle fibers. The interplay of MYH2 mutations with other genetic factors showcases the intricate landscape of myopathic disorders, where different genes converge to shape clinical outcomes. On the other hand, there have been a few isolated reports of dominantly behaving DYSF gene mutations globally, but our case presents a unique and intriguing contrast. Segregation analysis conducted on the parental samples indicated maternal inheritance of the DYSF mutation without any clinical manifestation in the mother. This finding is particularly noteworthy as it diverges from the typical patterns observed in dominant DYSF mutations and underscores the complexity of our patient's genetic profile [4]. In conclusion, our case report challenges the traditional recessive inheritance model in dysferlinopathy by unveiling the intricate phenomenon of digenic inheritance. The coexistence of heterozygous mutations in both the DYSF and MYH7 genes led to the phenotypic expression of dysferlinopathy, defying the conventional boundaries. This unique scenario underscores the captivating complexity inherent in diagnosing myopathic disorders within the purview of medical genetics, emphasizing the necessity for holistic genetic assessments that consider the potential interplay of multiple genetic factors. The exploration of digenic inheritance offers a captivating avenue for unraveling the underlying mechanisms of neuromuscular disorders, promising to guide precise diagnoses and personalized therapeutic interventions.

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Conflict of Interest

All the authors confirm that they have no conflict of interest.

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Ali Torabi. Biomed J Sci & Tech Res