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Identification of two previously unreported Duchenne muscular dystrophy gene variants in a patient diagnosed with a dystrophinopathy: a case report

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Abstract

Introduction Duchenne muscular dystrophy and Becker muscular dystrophy are X-linked recessive disorders affecting muscle function, which are caused by mutations in the dystrophin gene (also known as the Duchenne muscular dystrophy gene). The resulting condition is dictated by the severity of the involved mutation; for instance, Duchenne muscular dystrophy presents in early childhood with rapid progression, whereas Becker muscular dystrophy exhibits a milder, later onset with slower progression. In this report, we present the case of a young patient with clinical symptoms of a dystrophinopathy, whose genetic analysis yielded two previously undescribed mutations within the dystrophin gene.

Case presentation This paper focuses on a 12-year-old Syrian male patient with a 6-year history of progressive gait difficulty, lower limb weakness, and recurrent falls. Physical examination revealed a positive Gowers' sign and pseudohypertrophy, but normal muscle strength. A diagnosis of myopathy was supported by elevated serum creatine kinase and a muscle biopsy showing dystrophic changes in the right quadriceps muscle. While the initial deletion and duplication screening in the Duchenne muscular dystrophy gene using multiplex ligation-dependent probe amplification was negative, further extensive genetic analysis revealed two novel hemizygous variants of uncertain significance in the Duchenne muscular dystrophy gene (c.536A > T p.(Asp179Val) and c.680C > T p.(Ser227Phe), with no other clinically relevant variants in the neuromuscular panel.

Conclusion The identification of novel variants in the Duchenne muscular dystrophy gene, alongside the absence of pathogenic mutations in other genes investigated by the neuromuscular panel, strongly suggests an X-linked dystrophinopathy diagnosis in our patient. This case highlights the need for continued exploration of dystrophinopathies' genetic variants. Further studies are required to elucidate the functional impact of these novel variants and to improve our understanding of the genotypic and phenotypic variability observed in these disorders, which may lead to a revolution in treatment approaches and potentially offer curative options for patients.

Keywords Muscular dystrophy, Neuromuscular diseases, Genetic diseases, Genetic phenomena, Mutation

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Introduction

Becker muscular dystrophy (BMD) and Duchenne muscular dystrophy (DMD) are X-linked recessive disorders caused by mutations in the dystrophin gene (DMD gene), which is located on the Xp21.2 chromosome [1, 2]. This gene encodes dystrophin, a critical protein for maintaining muscle fiber integrity. Mutations of the DMD gene generally induce a premature truncation of the dystrophin, rendering it functionally unstable [1]. A known class of DMD mutations are missense mutations, where a single DNA base pair (nucleotide) is changed and results in the substitution of one amino acid for another within the protein sequence [3]. These genetic alterations exert significant, yet variable, impacts on protein function, hence manifesting in a diverse spectrum of clinical outcomes [4].

Consequently, the severity of these mutations is a key differentiator between DMD and BMD [4, 5]. As such, mutations described in BMD allow some level of dystrophin production, although the protein may be functionally abnormal. Conversely, mutations identified in DMD are often more severe, resulting in significantly reduced or entirely absent functional dystrophin [4–6]. As a consequence, this disparity in dystrophin production induces distinct clinical presentations. Specifically, DMD clinically presents in early childhood (2–3 years old) with frequent falls, difficulty climbing stairs, and delayed motor milestones. Muscle weakness progresses rapidly, with most individuals requiring wheelchairs by adolescence. Subsequently, cardiac and respiratory complications may occur, which impacts life expectancy [7]. In contrast, BMD exhibits a milder and later onset (that is, appears in teens or young adulthood). Muscle weakness progresses slower, allowing ambulation to persist into adulthood [8]. Cardiac involvement is less frequent, occurring later in the disease course [2, 8]. Despite these distinctions, both conditions share characteristic features, such as calf pseudohypertrophy and a waddling gait [9, 10]. DMD and BMD have a combined prevalence of approximately 2 per 10,000 males aged 5–9 years, but DMD holds a threefold greater prevalence than BMD [11]. This discrepancy is likely attributable to the earlier onset of symptoms in DMD.

The number of identified mutations in the DMD gene is extensive and constantly growing, and was reported to exceed 4500 [6]. These mutations are significantly heterogeneous in type and severity, which contributes to the wide spectrum of clinical presentations in DMD and BMD [4, 6]. In this report, we describe the clinical presentation, laboratory workup, and unique genetic findings of a young 12-year-old male patient presenting with clinical symptoms characteristic of a dystrophinopathy, who was found to have two novel distinct DMD gene variants.

Case presentation

A 12-year-old Syrian male patient, born at term via elective caesarean section, presented in October 2023 with a 6-year history of progressive gait disturbance, recurrent falls, and mild lower limb and pelvic girdle weakness. He achieved independent ambulation at the age of 1 year. The patient had no medical comorbidities, and his family history was unremarkable for neuromuscular disorders. There was no consanguinity between parents.

Physical examination revealed normal vital signs. Neurological examination was unremarkable, except for a positive Gowers' sign, indicating difficulty rising from the floor without using the arms for support. No muscle atrophy was observed, but his calves showed characteristic pseudohypertrophy. His gait was remarkable for pelvic girdle instability, but he was able to maintain independent ambulation.

His laboratory investigations were suggestive of a myopathy: serum creatine kinase (CK) was elevated at 27,195 U/L (normal range: 24–195 U/L), with elevated lactate dehydrogenase (LDH) levels at 1142 U/L (normal range: 200–450) and aldolase levels at 519 U/L (normal range: < 7.8). A muscle biopsy from the right quadriceps showed dystrophic myopathic changes with decreased dystrophin expression, further supporting the diagnosis of a dystrophinopathy. The patient started physiotherapy, and a cardiorespiratory evaluation was ordered.

Initial genetic testing was focused on the DMD gene, employing multiplex ligation-dependent probe amplification (MLPA) to identify any deletions or duplications. This analysis yielded negative results, ruling out a classical DMD (Duchenne/Becker muscular dystrophy) diagnosis. However, given the clinical and histological findings, further genetic evaluation was pursued. A comprehensive neuromuscular panel was performed, including next-generation sequencing (NGS), copy number variation (CNV) analysis, repeat expansion analysis of the DMPK gene, and MLPA to determine the copy number of the SMN1 and SMN2 genes. This advanced genetic testing revealed two novel hemizygous variants of uncertain significance (VUS) within the DMD gene: c.536A > T, predicted to cause the amino acid substitution p.(Asp179Val), and c.680C > T, predicted to cause p.(Ser227Phe). Particularly, c.536A > T is a specific genetic mutation where a single nucleotide, adenine (A), at position 536 in the DNA sequence of the DMD gene is replaced by thymine (T). Similarly, c.680C > T is a mutation where the cytosine (C) at position 680 in the DNA sequence of the DMD gene is replaced by thymine (T). No other clinically relevant variants were identified within the neuromuscular panel. Repeat expansion analysis of the DMPK gene was negative, and MLPA

confirmed the presence of two SMN1 gene copies with no detectable SMN2 copies.

Discussion

In this article, we presented the case of a young male patient with symptoms suggestive of a muscular dystrophy. The genetic testing revealed two previously unreported variations (c.536A > T and c.680C > T), which are missense mutations within the DMD gene. The DMD variant c.536A > T p.(Asp179Val) causes an amino acid change from aspartate to valine at position 179 in exon 7 of 79, and the DMD variant c.680C > T p.(Ser227Phe) causes an amino acid change from serine to phenylalanine at position 227 in exon 8 of 79.

Generally, mutations in the DMD gene, which encodes for the dystrophin protein, are known to be associated with abnormal dystrophin and the subsequent development of muscular dystrophies, such as DMD and BMD [1]. Dystrophin is an essential protein for muscles as it serves as an integral component of the dystrophin-associated glycoprotein complex (DGC) in the skeletal muscle sarcolemma [1]. The DGC links the intracellular cytoskeleton, responsible for maintaining cellular integrity and function, to the extracellular matrix, which provides essential support and stability to muscle fibers [1].

Neither mutation in our case is a complete stop mutation or frameshift mutation. Instead, they are missense mutations, meaning that they likely alter a single amino acid within the dystrophin protein. This event, in contrast to DMD where frameshift mutations often occur, allows for some production of potentially partially functional dystrophin, as evidenced by the presence of the dystrophin protein seen in our patient's muscle biopsy. The missense nature of these mutations aligns with the milder phenotype observed in our patient compared to the more severe course of DMD, where nonsense mutations leading to truncation/absence of the dystrophin protein usually occur [4–6]. Indeed, the specific clinical presentation plays a paramount role when dealing with VUS. In our case, the presence of dystrophin in the muscle biopsy strengthens the correlation between these missense mutations and the BMD phenotype, rather than DMD.

The identification of these novel variants has substantial therapeutic implications since early molecular diagnosis facilitates personalized management (for example, targeted interventions) [12]. Characterizing these variants also contributes to the expanding genotype–phenotype spectrum of dystrophinopathies [13], improving risk stratification and genetic counseling. For example, early identification of specific mutations can inform the development of precision medicine approaches, including gene-based therapies (for example, emerging exon-skipping therapies designed to restore dystrophin production), with the ultimate goal of improving long-term outcomes for individuals affected by muscular dystrophies [14, 15].

Moreover, the current case highlights the role of comprehensive diagnostic approaches, including advanced genetic testing, in achieving an accurate diagnosis for presentations of muscular dystrophy. Although the initial genetic test failed to detect classical deletions or duplications in the DMD gene, the combined analysis of clinical manifestations, elevated serum enzyme levels, muscle biopsy findings, and the identification of novel variants through advanced genetic testing led to the diagnosis of a probable BMD X-linked dystrophinopathy. These findings also emphasize the importance of genetic counseling for the patient's family to optimize care plan. Female carriers of DMD or BMD, for instance, are at increased risk for cardiomyopathy (with a prevalence ranging from 3% to 33%), even in the absence of overt muscular symptoms, highlighting the importance of cardiac evaluation for female carriers of dystrophin gene mutations [16].

Another noteworthy finding is the presence of two rare variants in the same patient, given the homogeneity of the Arab population's genetics [17]. In fact, the co-occurrence of two distinct and rare genetic mutations within a single individual is a relatively infrequent event. This improbability is further amplified in our current case, considering the low prevalence of the suspected disease [11] and the absence of consanguinity, a known risk factor for such occurrences [18]. However, the possibility of having multiple mutations cannot be entirely dismissed, particularly when the patient's clinical presentation shows significant complexity and the observed signs and symptoms do not correspond to a single known disorder.

Nevertheless, a key limitation of this study pertains to the classification of the identified variants (c.536A > T and c.680C > T) as VUS. As highlighted by Richards *et al.* [19], VUS classification poses a significant challenge in clinical genetics owing to the inherent difficulty in definitively establishing their pathogenicity. These uncertainties complicate the clinical decision-making (that is, accurately assessing disease risk/predicting disease severity) and patient management (that is, guiding appropriate treatment decisions) [20]. The challenge in our case remains in the ambiguity surrounding the effects of these novel identified variants (c.536A > T and c.680C > T) on the dystrophin protein, their contribution to our patient's symptoms, and their impact on the long-term disease severity and patient's prognosis. For instance, the lack of definitive pathogenicity for these variants may hinder the implementation of preventive measures or the initiation of specific therapies, such as cardiac monitoring or interventions, which are fundamental for managing

dystrophinopathies effectively [21]. Therefore, regular clinical monitoring, including physiotherapy and cardiorespiratory evaluation, is crucial for optimizing our patient's long-term management. Functional studies (for example, in vitro studies) are also warranted to elucidate the impact of these novel variants on dystrophin protein function and thus contribute to the growing body of knowledge regarding the phenotypic spectrum of dystrophinopathies. An improved understanding of these muscular diseases' genetic variants is pivotal for the advancement of promising revolutionary gene therapies, such as gene transfer therapy through adeno-associated virus (AAV) vectors utilization for restoring dystrophin [14, 15, 22].

Conclusion

The identification of novel variants in the DMD gene, alongside the absence of pathogenic mutations in other genes investigated by the neuromuscular panel, strongly suggests an X-linked dystrophinopathy diagnosis in our patient. This case highlights the need for continued exploration of dystrophinopathies' genetic variants. Further studies are required to elucidate the functional impact of these novel variants and to improve our understanding of the genotypic and phenotypic variability observed in these disorders, which may lead to a revolution in treatment approaches and potentially offer curative options for patients.

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Author contributions
SG wrote the manuscript; RN and HM were responsible for the data collection and supervision of this work. All authors reviewed the final manuscript and gave their consent.

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Availability of data and materials
In accordance with patient confidentiality requirements, individual data cannot be included.

Declarations

Ethics approval and consent to participate
Following institutional guidelines for case reports with minimal risk and anonymized data, ethics committee approval was not required for this study.

Consent for publication
Written informed consent was obtained from the patient's legal guardian for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors have no conflicts of interest.

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