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Case Report

In-frame versus out-of-frame Duchenne muscular dystrophy deletions: a comparative case report highlighting genotype–phenotype correlation in the therapeutic era

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ABSTRACT

Dystrophinopathies, including Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD), are X-linked neuromuscular disorders caused by mutations in the DMD gene. We describe two male patients with dystrophinopathies due to large deletions in the DMD gene. Case 1 is a 23-year-old male with adult-onset proximal muscle weakness and preserved ambulation. Genetic analysis revealed an in-frame deletion of exons 45–48, consistent with Becker muscular dystrophy. Case 2 is a 7-year-old child presenting with early-onset progressive muscle weakness, a positive Gower's sign, loss of ambulation, and markedly elevated creatine kinase levels. Multiplex ligation-dependent probe amplification (MLPA) identified an out-of-frame deletion spanning exons 46–57, confirming a diagnosis of Duchenne muscular dystrophy. Reading-frame status produced notably distinct clinical manifestations, despite the same gene and comparable mutational processes. The dystrophin reading-frame rule remains valid in this comparative case report, which also emphasises the importance of accurate molecular diagnosis for prognosis, genetic counselling, and treatment stratification in the era of precision medicine. To our knowledge, comparative genotype–phenotype case documentation from South Asian populations remains limited. This comparative case report adds valuable data from an underrepresented population.

Keywords: Duchenne muscular dystrophy, Becker muscular dystrophy, DMD gene, Reading-frame rule, Genotype–phenotype correlation, Exon deletion

INTRODUCTION

Dystrophinopathies are a group of X-linked neuromuscular disorders caused by pathogenic variants in the Duchenne muscular dystrophy (DMD) gene. DMD is the most common inherited neuromuscular disorder, characterised by early-onset progressive muscle weakness and loss of ambulation in childhood. The incidence of DMD, the most prevalent type of muscular dystrophy, is roughly 1 in 5000 live males. In contrast, Becker muscular dystrophy (BMD) presents with a milder and more variable phenotype.[1]

The dystrophin reading-frame rule is simple yet powerful. It explains much of the phenotypic variability observed in dystrophinopathies. Mutations that preserve the translational reading frame generally allow the production of a partially functional dystrophin protein, resulting in BMD, and are less severe. In contrast, frame-disrupting mutations lead to the absence of dystrophin and cause DMD. Most studies indicate that this rule accounts for approximately 90–95% of genotype–phenotype correlations.[2]

In the era of mutation-specific therapy, molecular profiling is now not only clinically useful but also therapeutically

significant. Over several years, molecular diagnosis and its clinical significance have extended beyond disease verification. These include mutation-specific treatments such as novel gene-replacement therapies and exon skipping, and accurate molecular diagnosis has therefore become crucial for both prognostication and therapeutic decision-making. We herein discuss a comparative case report of two male patients with DMD deletions that demonstrates the clinical importance of reading frame in the modern era.

CASE REPORT

Case 1: Becker muscular dystrophy

A 23-year-old male presented with gradually progressive proximal muscle weakness beginning in late adolescence. He remained independently ambulant at the time of evaluation, but he reported difficulty rising from a squat and mounting stairs. No notable family history of neuromuscular illness was found.

Clinical examination revealed mild proximal muscle weakness involving the pelvic girdle muscles. No contractures were noted. Cardiac and respiratory evaluations were within normal limits at presentation. Serum creatine kinase levels were elevated.

Whole-exome sequencing (WES) with copy number variant (CNV) analysis identified an in-frame deletion of exons 45–48 in the DMD gene. Based on clinical features and molecular findings, a diagnosis of Becker muscular dystrophy was established.

Treatment and follow-up

The patient was advised to undergo regular physiotherapy and periodic neurological follow-up. Baseline cardiac and respiratory evaluations were normal, and annual surveillance was recommended due to the risk of cardiomyopathy associated with Becker muscular dystrophy. Genetic counselling was provided on the hereditary nature of the disorder and the recurrence risk within the family. At the latest follow-up, the patient remained ambulant, with stable functional status and no evidence of cardiac or respiratory complications.

Case 2: Duchenne muscular dystrophy

A 7-year-old male child presented with early-onset, progressive muscle weakness, frequent falls, difficulty rising from the floor, and delayed motor milestones. Clinical examination revealed proximal muscle weakness, calf pseudohypertrophy, and a positive Gower's sign. The patient was no longer able to walk independently.

Serum creatine kinase levels were markedly elevated. Multiplex ligation-dependent probe amplification (MLPA) analysis of the DMD gene revealed an out-of-frame deletion involving exons 46–57. These findings confirmed the diagnosis of Duchenne muscular dystrophy.

Treatment and follow-up

Following diagnosis, the patient was enrolled in a structured physiotherapy and rehabilitation programme at our institution. Aquatic physiotherapy was delivered in a therapeutic pool maintained at 32–34°C, with 45-minute sessions held three times weekly. The programme focused on maintaining functional mobility, preserving joint range of motion, improving postural control and balance, enhancing low-intensity cardiorespiratory endurance, and reducing the risk of contractures. Therapy included warm-up exercises, active-assisted range-of-motion exercises, low-intensity concentric strengthening, balance training, breathing exercises, and relaxation techniques. Activities that caused excessive muscle strain, such as running, jumping, and competitive exercise, were avoided. During therapy sessions, the patient was monitored for fatigue, breathlessness, gait deterioration, and post-exercise muscle pain. At follow-up, the patient continued to participate in the rehabilitation programme and remained under regular neurological assessment. Functional status, joint range of motion, respiratory effort, and overall motor function were periodically evaluated to monitor disease progression and therapeutic response.

Comparative analysis

In both cases, the DMD gene showed large exon deletions. However, the primary difference lay in how the deletion affected the translational reading frame. The in-frame deletion in case 1 resulted in a milder Becker phenotype with preserved ambulation throughout adulthood, whereas the out-of-frame deletion in case 2 produced a severe Duchenne phenotype with early loss of ambulation.

The direct comparison highlights the critical role of reading-frame status in determining disease severity, progression, and clinical outcomes (Table 1).

Table 1: Comparison of DMD and BMD.

Variables	Case 1	Case 2
Age of presentation	23 years	7 years
Clinical severity	Mild to moderate	Severe
Ambulation	Preserved	Severely impaired
Gower sign	Absent	Present
Genetic testing	WES and CNV	MLPA
DMD gene variant	Deletion of exons 45 – 48	Deletion of exons 46-57
Reading frame	In-frame	Out of frame
Phenotype	Becker's muscular dystrophy	Duchenne muscular dystrophy

Reading-frame state not only accounts for clinical severity but also has direct therapeutic implications. For exon-skipping strategies aimed at restoring the reading frame, deletions in the exon 45–55 hotspot region are of particular interest. For the Duchenne mutation discussed here, theoretical techniques for multi-exon skipping may provide a means to restore an in-frame transcript and modify the phenotype from severe to BMD. On the other hand, attention in the Becker case is based on observation (at least with respect to respiratory and cardiomyopathy) and on the fact that the reading frame appears to have already been restored.

DISCUSSION

This case report clearly demonstrates the dystrophin reading-frame rule in clinical practice. Although the rule is well established, its relevance has grown significantly in the context of precision medicine. Accurate molecular classification now informs prognosis, surveillance strategies, genetic counselling, and eligibility for mutation-specific therapies.

The molecular basis of the genotype–phenotype correlation in Duchenne and Becker muscular dystrophy has been elucidated by studies showing that BMD results from preservation of the reading frame. In contrast, a severe Duchenne phenotype is caused by disruption of the translational reading frame.[3] In patients with DMD, the translational open reading frame (ORF) is shifted, and each deletion results in a shortened, aberrant protein product. A BMD deletion predicts a shorter, lower-molecular-weight protein while preserving the translational ORF. It is assumed that the smaller protein product has a milder clinical phenotype and is semi-functional.[4] Both patients in our series retained large deletions within the recognised exon 45–55 hotspot region of the DMD gene, which accounts for a substantial proportion of pathogenic variants reported worldwide.

A milder Becker muscular dystrophy phenotype, with maintained ambulation into adulthood, resulted from the in-frame deletion involving exons 45–48 in case 1, which preserved the dystrophin reading frame. In contrast to DMD, partial dystrophin expression in these settings is typically associated with a slower disease progression and better long-term outcomes. However, long-term consequences, including dilated cardiomyopathy and respiratory insufficiency, continue to be major contributors to morbidity, demonstrating that BMD is not a benign illness. The establishment of routine cardiac monitoring is enabled by early molecular diagnosis.[4]

In contrast, the out-of-frame deletion in case 2, affecting exons 46–57, disrupted dystrophin synthesis, resulting in the characteristic Duchenne phenotype characterised by early-onset progressive muscular weakness and infantile loss of ambulation. Membrane instability, increased myofiber degradation, and adipose and fibrotic tissue replacement result from the absence of functional dystrophin. The clinical severity of this case aligns with known genotype-phenotype associations reported in prior research.[5]

The reading-frame rule explains the majority of cases. However, exceptions have been noted due to alternative splicing, spontaneous exon skipping, and the effects of modifier genes such as SPP1 and LTBP4, which can alter disease course.[6,7] The concordance observed in our cases underscores the robustness of reading-frame prediction when genotype and phenotype are clearly aligned.

From a diagnostic perspective, multiplex ligation-dependent probe amplification (MLPA) remains the gold standard for detecting large deletions and duplications in the DMD gene.[8] However, next-generation sequencing platforms that incorporate copy number variant analysis provide a complementary approach, particularly for atypical or late-onset presentations. The use of these molecular techniques in our cases highlights the evolving landscape of genetic diagnostics in neuromuscular disorders.

Dystrophin immunohistochemistry was not performed. However, current standards recognise molecular diagnosis as definitive in most dystrophinopathies, particularly when there is strong genotype–phenotype concordance, as observed in our cases.

Importantly, data from South Asian populations remain underrepresented in global dystrophinopathy databases. Reporting such cases contributes to the growing body of population-specific genomic data while reinforcing universally applicable biological principles.

Limitations

The absence of dystrophin expression studies, such as muscle biopsy or immunohistochemistry, is a limitation. Invasive diagnostic tests are primarily performed in cases that are inconclusive or atypical.

CONCLUSION

This comparative case report reinforces the dystrophin reading-frame rule as a key determinant of clinical severity in dystrophinopathies. In the current therapeutic era, precise molecular diagnosis is essential not only for confirming the diagnosis but also for guiding prognosis, genetic counselling, and personalised treatment strategies.

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