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MOLECULAR SPECTRUM OF DMD GENE MUTATIONS IN PEDIATRIC DYSTROPHINOPATHY A CASE SERIES FROM A TERTIARY PEDIATRIC NEUROLOGY CENTER IN SOUTH INDIA

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ABSTRACT

Background: Dystrophinopathies, encompassing Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD), are X-linked disorders caused by pathogenic variants in the DMD gene. The molecular spectrum is dominated by intragenic deletions and duplications, although small sequence variants and more complex rearrangements are also recognized. Advances in next-generation sequencing (NGS) and copy-number variant (CNV) analysis have expanded molecular diagnosis, particularly in patients with atypical or nonrepresentative phenotypes.[1–3] **Objective:** To characterize the spectrum of DMD gene mutations identified in children evaluated for suspected dystrophinopathy at a tertiary pediatric neurology center in South India. **Methods:** We retrospectively reviewed eight children referred with clinical suspicion of an inherited neuromuscular disorder/dystrophinopathy. Clinical records and genetic reports were reviewed. Molecular testing was performed using whole-exome sequencing (WES) with CNV analysis or broad neuromuscular NGS-based testing. Variants were categorized according to the classification reported by the respective diagnostic laboratory. **Results:** Among eight children evaluated, five had pathogenic or likely pathogenic hemizygous deletions involving the DMD gene, confirming dystrophinopathy at the molecular level. Four were large multi-exonic deletions involving exons 45–52, while one represented a 176-bp deletion in the DMD region reported as pathogenic and associated with Becker muscular dystrophy. The multi-exonic deletions included exons 46–47, 45–50, 46–52, and 48–52. Thus, all five molecularly confirmed DMD variants were deletions, with clustering within the recognized central deletion-rich region of the DMD gene. Three additional children initially suspected to have dystrophinopathy had variants in SGCB, COL6A2, and FKBP14/DNAJB6, illustrating the diagnostic overlap among pediatric muscular dystrophies. **Conclusion:** In this South Indian pediatric cohort, DMD gene deletions constituted the entire pathogenic DMD molecular spectrum identified, with a striking concentration in the exon 45–52 region. The findings emphasize the value of comprehensive molecular testing and CNV analysis in children with suspected dystrophinopathy and demonstrate the importance of broad genetic evaluation when the phenotype is not molecularly explained by a DMD variant.

KEYWORDS : DMD Gene; Dystrophinopathy; Duchenne Muscular Dystrophy; Becker Muscular Dystrophy; Exon Deletion; Copy-number Variant; Next-generation Sequencing; Pediatric Neurology.

INTRODUCTION

Dystrophinopathies are X-linked muscular dystrophies caused by pathogenic variants in the DMD gene, which encodes dystrophin, a large cytoskeletal protein essential for maintaining muscle fiber integrity. The clinical spectrum ranges from the severe Duchenne muscular dystrophy phenotype to the generally milder Becker muscular dystrophy phenotype.[6,8]

The DMD gene is exceptionally large and susceptible to several classes of pathogenic variation. Large intragenic deletions represent the predominant molecular mechanism, followed by duplications and smaller sequence variants. Gene-targeted deletion/duplication testing and NGS-based approaches have substantially increased the ability to identify these abnormalities.[3,8]

The distribution of DMD deletions is nonrandom. A major deletion-rich region lies in the central portion of the gene, commonly involving exons in the approximate 45–55 region.[3,9] The molecular location and structural consequence of a variant may influence the amount and functionality of dystrophin produced and thereby contribute to the clinical continuum between Duchenne and Becker phenotypes.[6,9] However, genotype–phenotype relationships are not invariably straightforward, and phenotypic variability can occur even among individuals carrying similar variants.

Molecular diagnosis is particularly important in children presenting with atypical or nonrepresentative phenotypes. Broad neuromuscular NGS approaches can identify pathogenic DMD variants in patients whose clinical presentation does not initially conform to classical Duchenne or Becker muscular dystrophy.[3] A recent molecular genetics review further emphasizes the expanding spectrum of DMD variants and the role of integrated genomic and transcriptomic approaches in resolving diagnostically challenging cases.[10]

Dystrophinopathies may also have manifestations beyond skeletal muscle, including neurobehavioral and cognitive involvement.[1,2] Although these features are not the primary focus of the present study, their recognition reinforces the importance of establishing an accurate molecular diagnosis.

In clinical practice, children with proximal weakness, calf hypertrophy, Gowers' sign, markedly elevated creatine kinase, developmental concerns, or an atypical muscular phenotype may undergo genetic evaluation for dystrophinopathy. However, overlapping phenotypes with limb-girdle and congenital muscular dystrophies can complicate clinical diagnosis.[5,7]

The present study describes the molecular spectrum of DMD gene mutations identified in children evaluated for suspected dystrophinopathy at a tertiary pediatric neurology center in South India, with particular emphasis on the type and exon distribution of pathogenic DMD deletions.

MATERIALS AND METHODS

Study Design and Setting

This was a retrospective descriptive case series of children evaluated at a tertiary pediatric neurology center in Kurnool, Andhra Pradesh, South India.

Study Population

Eight children who underwent molecular investigation for suspected inherited neuromuscular disease/dystrophinopathy were identified from clinical records.

The initial cohort was deliberately retained at eight patients

because three children with clinically overlapping phenotypes were found to have variants outside the DMD gene. These cases were considered diagnostically relevant but were not included in the primary DMD molecular spectrum analysis.

Molecularly Defined Groups

- **Group 1:** DMD-gene dystrophinopathy — 5 children
- **Group 2:** Alternative neuromuscular genetic diagnoses/ uncertain findings — 3 children

Clinical Assessment

Available demographic and clinical information was reviewed, including:

- age and sex;
- age at symptom recognition;
- motor phenotype;
- proximal weakness;
- gait abnormalities;
- Gowers' sign;
- calf hypertrophy;
- contractures;
- developmental or speech abnormalities;
- serum creatine kinase;
- serum transaminases; and
- electrophysiological findings where available.

Genetic Testing

Genetic testing was performed by the diagnostic laboratories using whole-exome sequencing with CNV analysis or broad neuromuscular NGS-based testing, depending on the patient and laboratory.

The following molecular characteristics were extracted:

1. gene;
2. variant type;
3. exon involvement;
4. zygosity;
5. genomic location where available;
6. laboratory classification; and
7. associated disease phenotype.

Variant Interpretation

Variant classification was reported according to the respective laboratory's interpretation. DMD deletions classified as pathogenic or likely pathogenic and clinically concordant were considered molecularly diagnostic.

Importantly, reading-frame status was not independently inferred when it was not explicitly provided in the reports. This was done to avoid assigning a Duchenne or Becker phenotype solely on the basis of exon boundaries without validated transcript-level analysis.

Ethics

The manuscript should state the institutional ethics approval/waiver and consent procedure according to the requirements of the authors' institution before submission. As this is a retrospective case series based on clinical records, the authors should obtain confirmation of the applicable institutional requirement for ethics committee approval and/or waiver.

RESULTS

Overall Molecular Findings

Eight children underwent genetic investigation for suspected inherited neuromuscular disease.

A pathogenic/likely pathogenic DMD-gene variant was identified in five children (62.5%). All five DMD variants were deletions occurring in the hemizygous state.

Four children had large multi-exonic deletions involving the central region of the DMD gene, whereas one child had a smaller deletion reported as 176 bp and classified as pathogenic in association with a Becker muscular dystrophy phenotype.

Three children did not have a pathogenic DMD variant. Instead, their reports demonstrated variants involving SGCB, COL6A2, and FKBP14/DNAJB6, emphasizing the phenotypic overlap between dystrophinopathy and other inherited muscular disorders.

Table 1. Clinical and Molecular Characteristics of the Eight Children Evaluated for Suspected Dystrophinopathy

Case	Age/ Sex	Major clinical phenotype	CK	Primary molecular finding	Molecular interpretation	Final molecular category
1	10 y/M	Difficulty running from 3 y; proximal weakness; ankle contractures	Not markedly elevated in report	DMD deletion, exons 46–47	Likely pathogenic	DMD-gene dystrophinopathy
2	8 y/M	Gait difficulty, calf swelling, mild speech delay	636 IU/L	DMD deletion, exons 45–50	Likely pathogenic	DMD-gene dystrophinopathy
3	12 y/M	Progressive proximal weakness, calf hypertrophy	Elevated	DMD deletion, exons 46–52	Likely pathogenic	DMD-gene dystrophinopathy
4	7 y/M	Gait/proximal weakness, positive Gowers' sign	15,560 IU/L	DMD deletion, exons 48–52	Pathogenic	DMD-gene dystrophinopathy
5	10 y/M	Progressive lower-limb weakness, waddling gait, Gowers' sign	16,630 IU/L	DMD deletion, 176 bp; reported at exon 45 region	Pathogenic	Becker muscular dystrophy phenotype
6	10 y/F	Proximal weakness, Gowers' sign; family history of arrhythmia	Elevated	SGCB c.544A>C; p.Thr182Pro, homozygous	Likely pathogenic	SGCB-related LGMD
7	10 mo/M	Hypotonia, predominant motor delay	Not reported	COL6A2 c.2809C>T; p.Arg937Trp, heterozygous	VUS	Not molecularly confirmed as dystrophinopathy
8	6 mo/M	Hypotonia, flaccidity, poor head control, swallowing difficulty	Not reported	FKBP14 c.349G>T; p.Gly117Cys, homozygous; additional DNAJB6 VUS reported	VUS	Not molecularly confirmed as dystrophinopathy

Abbreviations

CK, creatine kinase; DMD, Duchenne muscular dystrophy; LGMD, limb-girdle muscular dystrophy; VUS, variant of uncertain significance.

Table 2. Detailed Molecular Spectrum of DMD Gene Variants

Case	DMD variant	Variant class	Exon involvement	Zygosity	Laboratory classification	Reported phenotype
1	Exonic deletion	CNV	46–47	Hemizygous	Likely pathogenic	DMD/BMD spectrum
2	Exonic deletion	CNV	45–50	Hemizygous	Likely pathogenic	DMD

3	Exonic deletion	CNV	46–52	Hemizygous	Likely pathogenic	DMD/BMD spectrum
4	Exonic deletion	CNV	48–52	Hemizygous	Pathogenic	DMD
5	176-bp deletion	Small deletion	Exon 45 region*	Hemizygous	Pathogenic	BMD

*The report identifies a 176-bp deletion at chrX:31,986,455–31,986,631 and associates it with Becker muscular dystrophy. The precise exon annotation should be verified against the laboratory's reference transcript before final submission.

Table 3. Distribution of Pathogenic DMD Variants in the Vohort

Molecular characteristic	n	% of DMD-confirmed cases (n=5)
DMD deletions	5	100
Hemizygous variants	5	100
Multi-exonic deletions	4	80
Small deletion	1	20
Deletions involving exon 45	3*	60
Deletions involving exons 46–52	3	60
Variants confined to the central deletion-rich region	5	100

*Includes cases 2, 3 and 5 based on the exon annotation in the supplied reports.

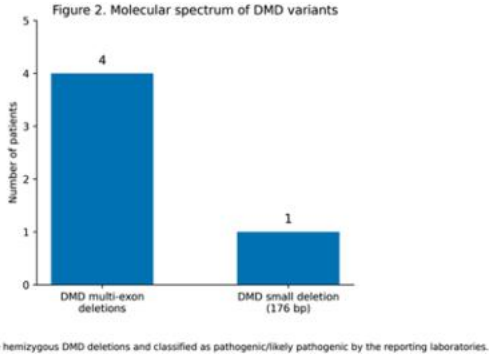


Figure 1. DMD Gene Deletion Spectrum

Recommended publication figure: schematic representation of the DMD gene showing exons 44–52 on the horizontal axis, with individual deletion intervals for Cases 1–5.

Figure Legend

Figure 1. Distribution of DMD gene deletions identified in five molecularly confirmed pediatric dystrophinopathies. The majority of variants were large multi-exonic deletions involving the central portion of the DMD gene. Cases 1–4 demonstrated deletions spanning exons 46–52, while Case 5 had a smaller 176-bp deletion reported in the exon 45 region. The figure illustrates clustering of pathogenic variants within the deletion-rich central region of the DMD gene..

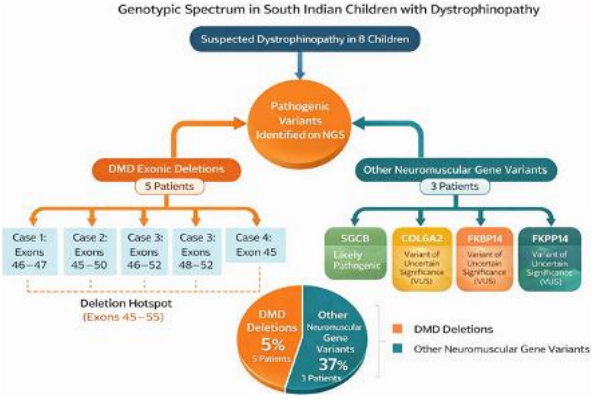


Figure 2. Molecular Spectrum of DMD Variants

Figure Legend

Figure 2. Molecular spectrum of pathogenic DMD variants in the study cohort. All five molecularly confirmed dystrophinopathy cases carried hemizygous DMD deletions. Four were multi-exonic deletions and one was a 176-bp deletion. No pathogenic DMD duplication, nonsense, missense, canonical splice-site, or insertion variant was identified in this series.

DISCUSSION

The present case series demonstrates a deletion-predominant molecular spectrum of dystrophinopathy in children evaluated at a tertiary pediatric neurology center in South India. Among eight children investigated for suspected inherited muscular disease, five had pathogenic or likely pathogenic DMD variants, and all five were deletions.

The most striking finding was the clustering of variants within the central exon region of the DMD gene, with the four large deletions involving exons 45–52. This observation is consistent with the recognized deletion-rich region of the DMD gene and with previous molecular studies demonstrating that deletions constitute a major proportion of pathogenic DMD variants.[3,9]

Na et al. evaluated 24 males with dystrophinopathy and identified exon deletions in 13 patients (54.2%) using multiplex PCR. Their study also demonstrated a relationship between the molecular defect, dystrophin protein expression, and the clinical DMD/BMD phenotype.[9] These observations reinforce the importance of combining molecular characterization with clinical and, where appropriate, protein-level assessment.

The molecular architecture observed in our cohort also illustrates the limitations of describing DMD variants solely by exon number. The clinical consequences of a deletion depend not only on its location but also on whether the resulting transcript preserves the translational reading frame, whether alternative splicing occurs, and whether residual functional dystrophin is produced. Consequently, a deletion involving several exons cannot automatically be labeled as Duchenne or Becker without appropriate transcript-level or clinical correlation.

This is particularly relevant to the distinction between DMD and BMD. Becker muscular dystrophy generally reflects preservation of some functional dystrophin, whereas Duchenne muscular dystrophy is usually associated with severe disruption or absence of functional dystrophin.[6,8] The reports in our series appropriately classified some deletions within the broader DMD/BMD spectrum rather than assigning a molecular phenotype solely from exon boundaries.

An important observation was the identification of a 176-bp DMD deletion in Case 5, reported as pathogenic and associated with a Becker phenotype. This finding demonstrates that the molecular spectrum extends beyond the commonly recognized large exon-level CNVs. Contemporary reviews emphasize that DMD diagnostics now encompass large deletions and duplications as well as small sequence-level variants and more complex molecular mechanisms.[10]

The present findings also support the use of comprehensive molecular testing in children with clinically suspected dystrophinopathy. Traditional approaches such as multiplex PCR can detect common deletion patterns but have limited sensitivity and may fail to characterize atypical variants. Modern NGS-based approaches allow simultaneous evaluation of sequence variants and, depending on the assay and laboratory pipeline, CNVs.[3]

The report by Wang et al. is particularly relevant to the present study because it emphasizes the utility of broad

neuromuscular NGS testing in patients with nonrepresentative dystrophinopathy phenotypes.[3] This is important in pediatric neurology, where early manifestations may overlap with limb-girdle muscular dystrophies, congenital myopathies, metabolic myopathies, and other neuromuscular conditions.

Our three DMD-negative cases illustrate this diagnostic overlap. One child had a homozygous SGCB variant associated with limb-girdle muscular dystrophy, while two infants had variants of uncertain significance involving COL6A2 and FKBP14/DNAJB6. These cases were not included in the primary DMD molecular spectrum analysis because their reports did not establish a pathogenic DMD variant. Their presence, however, demonstrates the practical importance of broad testing rather than restricting molecular analysis to DMD when the phenotype is suggestive but atypical.

The clinical importance of molecular diagnosis extends beyond establishing an etiological label. Accurate identification of a DMD variant enables appropriate carrier testing, reproductive counseling, cascade testing, disease surveillance, and consideration of mutation-specific therapeutic strategies. Updated molecular characterization is increasingly relevant as therapeutic eligibility may depend on the precise molecular defect.

The potential neurological component of dystrophinopathy also provides an important context. Dystrophin is expressed in the central nervous system, and neurobehavioral and cognitive manifestations have been documented in DMD and BMD.[1,2] Studies such as BIND have specifically investigated the relationship between genotype, brain phenotype, neurobehavioral function, and MRI findings.[2] These observations suggest that the molecular characterization of dystrophinopathy has implications beyond skeletal muscle disease.

Interestingly, recent work on behavioral and emotional outcome measures in dystrophinopathies has emphasized the need for standardized assessment of neurobehavioral manifestations.[10] Although such outcomes were not systematically evaluated in our cohort, their recognition represents an important direction for future genotype–phenotype studies.

The present study therefore contributes a real-world molecular snapshot from a South Indian pediatric neurology practice, with a clear predominance of DMD deletions and a concentration in the central deletion-rich region.

Clinical Implications

The findings have several practical implications:

1. A deletion-first strategy remains highly relevant in children with a classical dystrophinopathy phenotype.
2. CNV analysis is essential because a substantial proportion of DMD pathogenic variants are exon-level deletions or duplications.[3],
3. Exon boundaries should not be equated automatically with phenotype. Reading-frame prediction and clinical correlation are necessary.
4. Broad NGS is valuable in atypical cases, particularly when the clinical phenotype overlaps with limb-girdle or congenital muscular dystrophies.[3]
5. A negative DMD result should prompt consideration of alternative neuromuscular genes, as demonstrated by the three non-DMD cases in this series.
6. Precise molecular characterization has increasing importance for genetic counseling and mutation-specific therapeutic planning.

Limitations

This study has several limitations.

First, the sample size was small and derived from a single tertiary pediatric neurology practice. Second, the study was retrospective, and clinical information was not uniformly available for every patient. Third, the genetic tests were performed at different diagnostic laboratories and using somewhat different platforms, potentially introducing methodological heterogeneity.

Fourth, MLPA or another orthogonal CNV-confirmation method was recommended by the reporting laboratories for several of the large deletions. Therefore, the molecular findings should be interpreted as laboratory-reported pathogenic/likely pathogenic results unless independent confirmatory testing has been performed.

Finally, dystrophin protein studies, RNA studies, and systematic reading-frame analysis were not available for all patients. Consequently, definitive genotype–phenotype conclusions should be avoided.

Future Directions

Future multicenter studies from India should incorporate:

- standardized DMD variant nomenclature;
- MLPA or orthogonal confirmation of WES-derived CNVs;
- transcript-level reading-frame analysis;
- dystrophin immunohistochemistry/Western blot where clinically indicated;
- systematic cardiac and respiratory phenotyping;
- standardized cognitive and neurobehavioral assessment;
- segregation and carrier studies;
- assessment of eligibility for mutation-specific therapies; and
- longitudinal genotype–phenotype correlation.

Such an approach could establish a more representative Indian DMD variant database and improve understanding of population-specific molecular patterns.

CONCLUSION

This case series demonstrates a deletion-dominant molecular spectrum of DMD gene mutations among children with genetically confirmed dystrophinopathy. Five children had pathogenic or likely pathogenic hemizygous DMD deletions, with four large deletions clustering between exons 45 and 52 and one smaller 176-bp deletion reported in the exon 45 region.

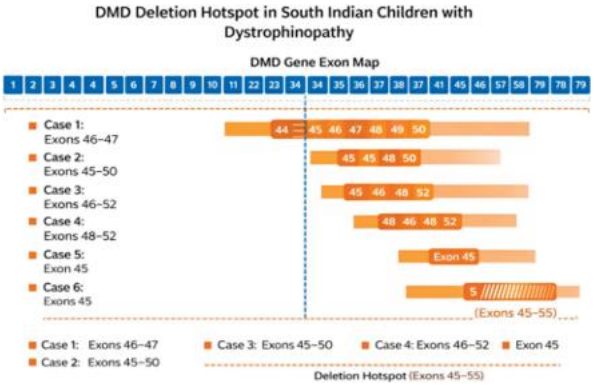
The findings reinforce the importance of comprehensive molecular testing incorporating CNV analysis in children suspected of having dystrophinopathy. The identification of alternative neuromuscular gene variants in three additional children further emphasizes that clinical phenotypes may overlap substantially and that broad genomic testing can prevent diagnostic misclassification.

Precise molecular diagnosis is increasingly central to genetic counseling, prognostication, disease surveillance, and emerging precision therapies for dystrophinopathies.

Table 4. Suggested Genotype–phenotype Interpretation

Molecular finding	Potential clinical implication
DMD multi-exon deletion	Strong molecular evidence for dystrophinopathy
Central-region deletion involving exons 45–52	Consistent with recognized DMD deletion-rich region
DMD deletion with reported BMD phenotype	Suggests residual dystrophin function; requires clinical/transcript-level correlation

DMD CNV identified by WES	Orthogonal confirmation should be considered
No pathogenic DMD variant	Consider other muscular dystrophy genes and alternative diagnoses
VUS in another neuromuscular gene	Should not be considered diagnostic without additional evidence
Pathogenic non-DMD variant	Reclassifies the molecular diagnosis away from dystrophinopathy



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