

Becker muscular dystrophy: an inimitable case

Gaurang M Sindhav¹, Jitendra J Mehta², Mandava V Rao¹

¹Department of Zoology, Gujarat Genetic Diagnostic Center (GenDiCe), School of Sciences, Gujarat University, Ahmedabad, Gujarat, India.

²Indian Muscular Dystrophy Society (IMDS), Ahmedabad, Gujarat, India.

Correspondence to: Mandava V Rao, E-mail: manvrao@gmail.com

Received January 30, 2015. Accepted February 5, 2015

Abstract

Muscular dystrophies (MDs) are broad group of muscle illness. Duchenne muscular dystrophy (DMD) and allelic Becker muscular dystrophy (BMD) are the most common forms of MDs, together termed as dystrophinopathy. A margin line between DMD and BMD is only justified by the presence of dystrophin protein along with muscle strength. Here, we report a first case of large deletion with BMD phenotype of an 11-year-old Gujarati boy. This inimitable case has been reported for its uniqueness and to attest the magnitude of molecular screening for diagnosis as well as hint for development of new therapeutics.

KEY WORDS: Becker muscular dystrophy, dystrophin gene, exon, deletion

Introduction

In India, millions of individuals are affected with various genetic diseases.^[1] Within these genetic disorders, muscular dystrophies (MDs) are a broad group of muscle illness, which affect humans as well as animals.^[2,3] In MDs, Duchenne muscular dystrophy (DMD; OMIM #310200) and milder allelic Becker muscular dystrophy (BMD; OMIM #300376) are most commonly observed forms in humans. In India including Gujarat, very less work is focused to view the burden of the condition. Therefore, the data on which to develop strategies for understanding D/BMD regarding Gujarati population are very essential. Hence, the study was undertaken with prime aim to uncover the genetic burden and pathophysiologic machinery of D/BMD by evaluating clinical, biochemical, and genetic indices in Gujarat population.

Case Report

An 11-year-old Gujarati boy was screened at our centers (Gujarat Genetic Diagnostic Center and Indian Muscular

Dystrophy Society, Ahmedabad, Gujarat, India) with complaints of walking difficulties and bilateral calf hypertrophy for the past 2 years. The painless hypertrophy was slow in progression. Proband have had weakness in distal muscles though self-ambulatory. On visual examinations, there were nonattendances of Gower's sign as well as scoliosis, which were found to be signs of BMD-type MDs [Figure 1]. Moreover, the boy did not experience any innate anomalies or no familial history for the same [Figure 2].



Figure 1: Phenotypic feature in the index case.

Access this article online

Website: <http://www.ijmsph.com>

DOI: 10.5455/ijmsph.2015.30012015187

Quick Response Code:



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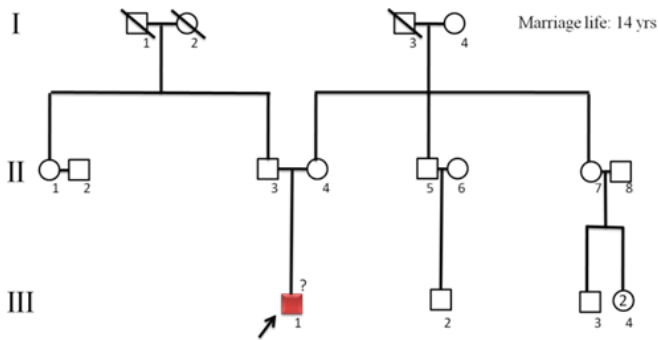


Figure 2: Pedigree analysis of the index case.

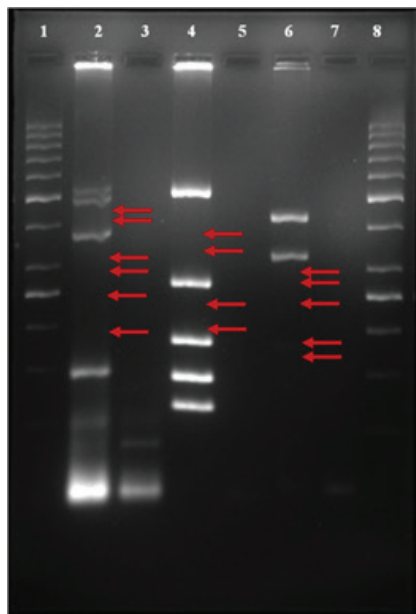


Figure 3: Electrophoresis of the dystrophin gene amplified using three sets of M-PCR. Interpretation of gel electrophoresis—Lane 1: Ladder (50 bp); Lane 2: Index case; Chamberlain set exon: 45,48,19,17,51,8,12,44,4,46; Lane 3: Negative (Chamberlain set); Lane 4: Index case; Beggs set exon: Dp427m,3,43,50,13,6,47,60,52; Lane 5: Negative (Beggs set); Lane 6: Index case; Kunkel set exon: 49,Dp427c,16,41,32,42,34; Lane 7: Negative (Kunkel set); Lane 8: Ladder (50 bp).

The study was approved by the institutional ethics board and written informed consent was taken before sample collection. Initial biochemical screening of the blood serum for creatine phosphokinase, myoglobin, lactate dehydrogenase, and calcium (Ca) was conducted, which showed elevated levels compared to normal or reference ranges except Ca [Table 1]. DNA was also extracted at the same time for the dystrophin gene deletion study using M-PCR (26 exons incorporate; Chamber, Beggs and Kunkel set, available at: <http://www.dmd.nl>). The deletion mutation in the proband was observed as del3-44. In this study, this is the longest deletion

Table 1: Biochemical indices in the index case

Biochemical indices	Index BMD case	References range
CPK (U/L)	2461.00	38.00–174.00
Mb (ng/mL)	257.00	0.0–110.0
LDH (U/L)	518.24	135.00–225.00
CA (mg/dL)	8.18	8.10–10.0

CPK, creatine phosphokinase; Mb, myoglobin, LDH, lactate dehydrogenase; Ca, calcium; BMD, Becker muscular dystrophy.

found [Figure 3]. Moreover, proband was suspected to be of BMD type on basis of onset age, absence of various signs, as well as severity of condition.

Discussion

In India, wide spectra of MDs are routinely encountered.^[4] Lack of availability of large-scale laboratory facilities, especially in the fields of genetic analysis, limits the molecular testing of D/BMD observed in India. Hence, we have assessed the levels of clinical severity, biochemical markers, and dystrophin gene deletion pattern in indexed BMD proband by visual examination, fully automated biochemical analyzer, and M-PCR using 26 exons multiplex reaction, respectively.

BMD is an allelic, less severe muscular dystrophy with symptoms that can mimic lethal DMD condition. Various studies from India and abroad have documented deletions in the main “hot spot” region between exons 45-53 in majority of cases.^[5–8] In this clinically suspected BMD case, we found exceptional deletion exons 3-44 of both actin-binding and the rod domain, which is approximately 50% deletion for targeted dystrophin gene containing 79 exons for translation fully functional dystrophin protein. Despite the fact that half deletion or missing of dystrophin gene, severity, and symptoms of the index case compared to DMD is paradoxical puzzle. So, one can suspect that there is no apparent correlation between the size and/or location of the deletion and the severity or succession of the condition.^[7,8] Large deletions mutation spanning >35 exons usually were associated with DMD condition.^[6] From Gujarat, India, this is the first case reported of BMD with large-scale (>40) exon deletions.

In milder BMD, the reading frame remains intact (IN-frame), though a coding segment of the gene has been lost or reduced. In present case, by the reading frame rule we can hypothesize shortened and only partially functional dystrophin protein. However, due to lack of flanking exon (exon 2), deletion needs to be studied in-depth (del (?2)-3-44); IN-/OUT-frame).^[9] Moreover, deletion results are only at a gene level and in fact concur with the reading frame on the RNA and/or protein level.^[6,7]

Because of X-linked inheritance of the DMD gene, deletions are easily identified by conventional M-PCR method in male patients only. However, due to lack of flank-

ing exons of hot spot region in this study, it is worthwhile or recommended to confirm the deletion mutation by latest high-throughput next-generation techniques, namely, MLPA, direct sequencing or arrayCGH; the functional properties of the dystrophin proteins and to correlate such important cases for further appraisal.

Conclusion

In sum, this is the first report for such large deletion of BMD case in Gujarat, India. Undiagnosed or untreated BMD cases can result in severe condition due to missing of proper management as well worthless therapeutics. This case emphasizes the importance of taking a detailed medical history using specific diagnosis parameters and makes physicians and patients aware that condition can result in less severe symptoms with prolong life span compared to DMD. Prompt and proper diagnosis with molecular study is important in establishing screening, diagnosis, and management of such condition. The study outcome opens up new areas for potential research in D/BMD specially.

References

1. Verma IC. Burden of genetic disorders in India. *Indian J Pediatr* 2000;67(12):893–8.
2. Mercuri E, Muntoni F. Muscular dystrophies. *Lancet* 2013; 381:845–60.
3. Cohn RD, Campbell KP. Molecular basis of muscular dystrophies. *Muscle Nerve* 2000;23:1456–71.
4. Khadilkar SV, Wagh S. Practice patterns of neurology in India: fewer hands, more work. *Neurol India* 2007;55(1):27–30.
5. Rao MV, Sindhav GM, Mehta JJ. Duchenne/Becker muscular dystrophy: a report on clinical, biochemical, and genetic study in Gujarat population, India. *Ann Indian Acad Neurol* 2014;17(3):303–7.
6. Dastur RS, Gaitonde PS, Khadilkar SV, Nadkarni JJ. Becker muscular dystrophy in Indian patients: analysis of dystrophin gene deletion patterns. *Neurol India* 2008;56:374–8.
7. Aartsma-Rus A, Van Deutekom JC, Fokkema IF, Van Ommen GJ, Den Dunnen JT. Entries in the Leiden Duchenne muscular dystrophy mutation database: an overview of mutation types and paradoxical cases that confirm the reading-frame rule. *Muscle Nerve* 2006;34:135–44.
8. Pandey GS, Kesari A, Mukherjee M, Mittal RD, Mittal B. Re-evaluation of reading frame-shift hypothesis in Duchenne and Becker muscular dystrophy. *Neurol India* 2003;51: 367–9.
9. Monaco AP, Bertelson CJ, Liechti-Gallati S, Moser H, Kunkel LM. An explanation for the phenotypic differences between patients bearing partial deletions of the DMD locus. *Genomics* 1988;2:90–5.

How to cite this article: Sindhav GM, Mehta JJ, Rao MV. Becker muscular dystrophy: an inimitable case. *Int J Med Sci Public Health* 2015;4:1027-1029

Source of Support: Nil, **Conflict of Interest:** None declared.