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Case report

# Duchenne muscular dystrophy in a female with compound heterozygous contiguous exon deletions

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**Abstract**

Females with Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) mutations rarely exhibit clinical symptoms from childhood, although potential mechanisms for symptoms associated with DMD and BMD in females have been reported. We report the case of a female DMD patient with a clinical course indistinguishable from that of a male DMD patient, and who possessed compound heterozygous contiguous exon deletions in the dystrophin gene. She exhibited Gowers' sign, calf muscle hypertrophy, and a high serum creatine kinase level at 2 years. Her muscle pathology showed most of the fibers were negative for dystrophin immunohistochemical staining. She lost ambulation at 11 years. Multiplex ligation-dependent probe amplification analysis of this gene detected one copy of exons 48–53; she was found to be a BMD carrier with an in-frame deletion. Messenger RNA from her muscle demonstrated out-of-frame deletions of exons 48–50 and 51–53 occurring on separate alleles. Genomic DNA from her lymphocytes demonstrated the accurate deletion region on each allele. To our knowledge, this is the first report on a female patient possessing compound heterozygous contiguous exon deletions in the dystrophin gene, leading to DMD.


*Keywords:* Compound heterozygous; Duchenne muscular dystrophy; Dystrophin; Exon deletion; Female

## 1. Introduction

Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder caused by mutations in the dystrophin gene located at Xp21.2. It affects approximately 1 in 3500 boys and causes progressive muscle weakness. DMD patients generally carry frame-shift dystrophin mutations, whereas a milder form called Becker muscular dystrophy (BMD) is due to in-frame mutations. Deletions of one or more exons account for approximately 60%–70% of mutations in individuals with DMD and BMD and duplications are found in approximately 5%–10%. The remaining 25%–35% of DMD cases and 10%–20% of BMD cases are caused by point mutations or other subtle changes in the dystrophin gene [1]. Most heterozygous carrier females with dystrophin mutations exhibit no clinical symptoms, and it is very rare for females with DMD and BMD mutations to exhibit symptoms from childhood. In this study, we report the case of female DMD patient with a clinical course indistinguishable from that of a male DMD patient; the female possessed compound heterozygous contiguous exon deletions in the dystrophin gene.

## 2. Case report

The proband (III-2) was a 21-year-old female, who was the first child of non-consanguineous parents (Fig. 1A). Her mother (II-4) lost an unborn child (III-1) before the patient was born. In addition, her mother was addicted to alcohol and divorced from her father (II-2). She had a half-brother (III-3); however, it was not clear if he was healthy or not. She was born uneventfully; her body weight was 3490 g and body length was 48 cm at birth. At 1 year, she began walking alone but was likely to fall. At 2 years and 2 months, she was referred to the hospital for a heart murmur. The possible existence of heart disease was excluded; however, she exhibited Gowers' sign,

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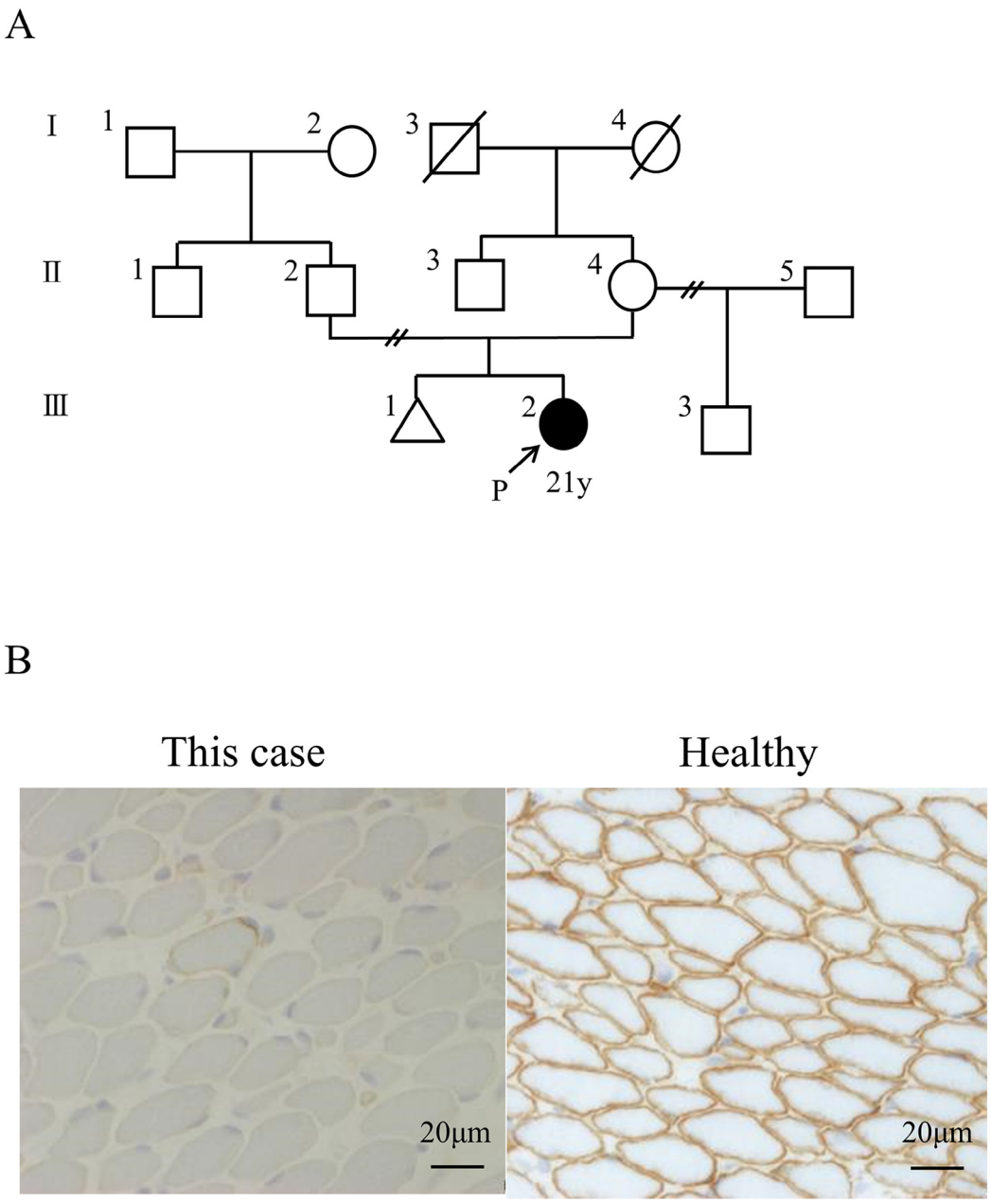


Fig. 1. (A) Family tree of the patient (P: proband). (B) Muscle pathology of the patient (at 400-fold magnification). Immunohistochemical staining for dystrophin. Most of the fibers were negative for dystrophin by immunohistochemical staining in this case.

calf muscle hypertrophy, and high serum creatine kinase level (CK 18,280 IU/L). A muscle biopsy was performed at 2 years and 4 months and most of the fibers were negative for dystrophin immunohistochemical staining; thus she was diagnosed with DMD (Fig. 1B). At 9 years, she experienced more difficulty going up and down stairs, and she lost ambulation at 11 years. Now, at over 21 years, she can operate her mobility scooter but has difficulty rolling over by herself, and her condition has progressed to deformity of the trunk due to scoliosis. Multiplex ligation-dependent probe amplification (MLPA) analysis of the dystrophin gene detected one copy of exons 48–53, which suggested that an in-frame exon deletion was present in a BMD carrier (Fig. 2A). However, her clinical course and muscle pathology were inconsistent with a BMD carrier and her condition was more similar to female DMD. Chromosomal study by G-banding determined 46 chromosomes with XX, i.e., a normal karyotype. The patterns of X-chromosome inactivation were assessed based on the methylation status at the androgen receptor locus, where the results showed that she possessed a random (non-skewed) X-chromosome inactivation pattern (38.7: 61.3%). These data excluded some possible known mechanisms for female DMD, which we consider later. Thus, we proceeded with additional gene analysis. Messenger RNA was amplified from her muscle by reverse transcription polymerase chain reaction (PCR) using primers located outside the exons of a deletion region (P1 and P2), where the two fragments amplified