Turkish Journal of Pediatric Disease

Original Article

# Clinical and demographic characteristics of Becker muscular dystrophy cases

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## ABSTRACT

**Objective:** Becker Muscular Dystrophy (BMD) is a rare and progressive muscle disease characterized by mutations in the dystrophin gene. Although similar to Duchenne Muscular Dystrophy (DMD), BMD usually has a milder course. The aim of this study was to analyze the clinical and genetic profiles of BMD.

**Material and Methods:** Evaluations were made of 67 patients diagnosed with BMD between 2006 and 2024. Clinical findings, laboratory tests, and genetic analysis of the patients were retrospectively analyzed.

**Results:** The study group consisted of 67 patients with a mean age of 11.6±4.1 years and age at diagnosis of 4.6±3.3 years. A total of 7.5% of the patients had a history of consanguineous marriage, and 35.8% had a family history of BMD. The most common clinical symptoms were exercise intolerance (44.8%), fatigue (19.4%), and exercise-related pain (14.9%). Cardiac involvement was detected in 11.9% of the patients, and mutations between exons 45-55 were most frequently detected in these patients. Psychiatric problems were detected in 22.4% of patients, and 66.7% of these patients had mutations involving the exon 45 region. There was no significant difference in the clinical and laboratory findings of patients with reading frame mutations.

**Conclusion:** Although patients with BMD usually have milder clinical features, it was observed that cardiac and psychiatric involvement in particular may be associated with certain genetic mutations. Genetic analysis is considered to be an important tool in the diagnosis and prognosis of BMD, which may reduce the need for muscle biopsy.

**Keywords:** Becker muscular dystrophy, Clinical characteristics, Genetic mutations, Reading frame mutations

## INTRODUCTION

Becker muscular dystrophy (BMD) is an inherited and progressive muscle disease characterized by muscle fibre degeneration and proximal muscle weakness due to a mutation in the dystrophin gene (1). The disease is clinically similar to Duchenne muscular dystrophy (DMD), but it is less common, clinical findings appear later, and the course is milder (2). BMD is caused by mutations in dystrophin protein. In the diagnosis, the evaluation of creatine kinase (CK) levels accompanied by physical examination findings compatible with clinical findings shows high sensitivity (3). Dystrophin has a recessive inheritance pattern linked to the X chromosome, although approximately 30% of cases are due to sporadic new mutations (4,5).

Studies in Europe and North America have shown that the prevalence of Duchenne muscular dystrophy ranges from one in 3500 to one in 5050 live male births, while Becker muscular dystrophy is about one-third of this prevalence (6,7).

Compared with DMD, the age of onset of symptoms in individuals with BMD is generally later, with a wide range from 5 to 60 years of age. Furthermore, the degree of clinical involvement is usually milder (8). Approximately 85% of patients with BMD have dystrophin of abnormal molecular weight, with smaller dystrophin in 80% of cases with deletions and larger dystrophin in 5% of cases with duplications. In these individuals, the amount of dystrophin is usually reduced. The remaining 15% have dystrophin of normal size but reduced quantity (9). Serum CK concentrations in patients with BMD typically rise to ≥5-fold the upper limit of normal (10).

Preserved muscle strength allows clinical distinctions to be made between BMD and DMD. People with BMD are usually able to stand until at least 16 years of age and often well into



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Received : 02.10.2024
Accepted : 23.12.2024
DOI: 10.12956/tchd.1557901

adulthood, with some retaining the ability to walk into old age. Furthermore, cognitive impairment, intellectual disability, behavioral disorders and contractures are less common or less severe in BMD compared to DMD (11). Cardiac involvement is often a prominent feature of the clinical picture in BMD, although muscle involvement is less severe than in DMD (12).

There is no complete cure for BMD, so treatment is based on supportive care and rehabilitation. Many clinical trials of gene therapy are still ongoing (9). BMD is a rare neuromuscular disorder and studies systematically addressing the clinical and laboratory findings of individuals with this disease are very limited in the literature. The main aim of this study was to provide new and in-depth information for a better understanding of the disease by detailing the clinical, demographic and genetic characteristics of patients diagnosed with BMD.

## MATERIALS and METHODS

The study retrospectively included 67 patients with BMD who were followed up at Tepecik Training and Research Hospital Muscle Center between 2006 and 2024. Ethical approval was granted by the Tepecik Training and Research Hospital Non-Interventional Ethics Committee (Decision No: 2024/08-05, Date: 02.09.2024). BMD was diagnosed based on clinical and genetic findings. Patients with Gowers sign and Functional Ambulation Scale score of <5 were evaluated as DMD and were excluded from the study. Muscle biopsy was performed in only one patient and the biopsy revealed findings consistent with BMD, which were confirmed by genetic testing. The genetic analysis was performed using the multiplex ligation-dependent probe amplification (MLPA) method for the DMD gene. This method was utilized to investigate large deletions and duplications. Additionally, Sanger sequencing was conducted to identify the presence of nonsense mutations. These analyses confirmed the patient's genetic diagnosis and revealed findings consistent with BMD. The patients were divided into two groups: In-Frame Deletion (-) and In-Frame Deletion (+). Demographic data, clinical symptoms, physical examination findings, laboratory tests and 6-minute walk test results were analyzed.

Muscle strength assessment of the patients was performed using the Medical Research Council (MRC) manual muscle strength scale, which grades muscle strength on a scale from 0 to 5 (13). Psychiatric comorbidities such as learning disabilities, speech delay and/or speech disorders, attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) were evaluated and questioned.

The patients were divided into two groups according to the genetic mutations of with and without in-frame mutations. The clinical and laboratory characteristics of patients with and without in-frame mutations were compared.

### Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA). Descriptive statistics were calculated for demographic, clinical, and laboratory data, including means, standard deviations, medians and interquartile ranges (IQR) for continuous variables, and frequencies and percentages for categorical variables. The comparison of continuous variables between two independent groups was conducted using the independent t-test or Mann-Whitney U test, depending on the distribution of data. The chi-square test or Fisher's exact test was used for the comparison of categorical variables. A p-value of <0.050 was considered statistically significant.

## RESULTS

Evaluation was made of 67 patients with BMD, all of whom were male (100%). The mean age of the patients was 11.6±4.1 years (median 12, IQR 9-15 years). The mean age at diagnosis was 4.6±3.3 years (median 4, IQR 2-6 years). There was a history of consanguineous marriage in 5 (7.5%) patients, and a family history of BMD in 24 (35.8%). A maternal carrier test was conducted on the mothers of 42 patients, and carrier status was identified in 34 (80.1%) of them.

Of the total 67 patients, 45 (67.2%) were diagnosed incidentally during the evaluation of elevations in liver function tests, 20 (29.9%) were diagnosed because of a family history of muscle disease, 1 (1.5%) from complaints of fatigue, and 1 (1.5%) during the investigation of chest pain.

The mean age at diagnosis was 4.9±3.5 years for patients with an incidental diagnosis and 3.9±2.9 years for those diagnosed through family history screening. Although patients diagnosed via family history had a lower mean age at diagnosis, the difference was not statistically significant (p=0.238).

The mean age at diagnosis was 4.5±3.4 years in patients with inframe mutations and 5.3±2.9 years in out of frame patients, there was no statistical difference between the two groups (p=0.443).

The most common symptoms were exercise intolerance, fatigue, exercise-induced pain and muscle cramps, respectively. On physical examination, calf hypertrophy was found in 64 patients (95.5%), but no patient had Gowers sign. Muscle strength examination revealed normal strength (5/5) in the upper extremities of all patients. Distal muscle weakness (4/5) in the lower extremities was observed in only two patients, aged 12 and 18 years. The 6-minute walk test results of 48 patients were available and the median value for walking distance was 555 (IQR 457-589) meters (Table I).

The comorbid conditions of the BMD patients were analyzed, and muscular dystrophy-related cardiac involvement was present in 8 patients (11.9%), and psychiatric problems were

**Table I: The demographic and clinical characteristics of patients with BMD**

| Characteristics | Values |
|---|---|
| Age (years)* | 11.6±4.1 (9-15) |
| Age at diagnosis (years)* | 4.6±3.3 (2-6) |
| Consanguineous marriage† | 5 (7.5) |
| Family history of BMD† | 24 (35.8) |
| Brother | 9 (13.4) |
| Grandfather | 1 (1.5) |
| Uncle | 11 (16.4) |
| Cousin | 3 (4.5) |
| Maternal carrier† | 34 (80.1) |
| Neuromotor development stages | |
| Age of starting to walk (years)‡ | 1 (1-2.5) |
| Delay in walking† | 2 (3) |
| Age of onset of speech (years) ‡ | 1 (1-5) |
| Delay in speech† | 9 (13.4) |
| Clinical symptoms† | |
| Exercise intolerance | 30 (44.8) |
| Early fatigue | 13 (19.4) |
| Pain with exercise | 10 (14.9) |
| Cramp | 9 (13.4) |
| Leg pain | 6 (9) |
| Physical examination findings | |
| Pseudohypertrophy of calf muscles† | 64 (95.5) |
| Gowers sign | - |
| Scoliosis† | 18 (26.9) |
| Distal muscle strength of the upper extremity§ | 67/0/0/0/0/0 |
| Proximal muscle strength of upper extremity§ | 67/0/0/0/0/0 |
| Distal muscle strength of the lower extremity§ | 67/0/0/0/0/0 |
| Proximal muscle strength of lower extremity§ | 65/2/0/0/0/0 |
| 6 minutes walking test (m) (n=48)‖ | 555 (457-589) |

***:** *mean±SD ( Inter Quantile Range)* ,**†:** *n(%)*, **‡:** *median (min-max)* **§:** *Medical Research Council (MRC) manual muscle strength scale (5/5-4/5-3/5-2/5-1/5-0/5),* **‖:** *median (Inter Quantile Range)*

detected in 15 patients (22.4%). Psychiatric comorbidities included learning disabilities in 7 patients, speech delay and/or speech disorder in 5, ADHD in 2, and ASD in 1. Mutation involving exon 45 was detected in 10 (66.7%) of the patients with psychiatric problems, but this finding was not statistically significant (p=0.622).

Furthermore, no difference in the frequency of psychiatric problems was observed between the two groups when the upstream and downstream regions of DMD exon 45 were compared (p=0.471).

Of the 8 patients with cardiac involvement, 4 had exon 45-48, 3 had exon 45-53 and 1 had exon 45-55 deletion. The genetic mutations and comorbidities of the patients are summarized in Table II.

The patients were divided into two groups as complying and non-complying with the reading frame rule. When the clinical and laboratory findings of these groups were compared, no significant difference was found between them (Table III).

**Table II: Genetic mutations and comorbidities of the patients**

| Mutation region (exon) | n (%) | LD | SD | ASD | ADHD | CI |
|---|---|---|---|---|---|---|
| 45-47 deletion (+) | 13 (19.4) | 2/13 | 1/13 | | | |
| 45-48 deletion (+) | 12 (17.9) | | 1/12 | | | 4/12 |
| 45-55 deletion (+) | 7 (10.4) | | 1/7 | | 1/7 | 1/7 |
| 45-53 deletion (+) | 5 (7.5) | 2/5 | | | | 3/5 |
| 3-4 deletion (+) | 3 (4.5) | | | | | |
| 3-4 duplication (+) | 3 (4.5) | | 2/3 | | | |
| 46-47 deletion (-) | 2 (3) | | | | | |
| 48-51 deletion (+) | 2 (3) | | | | | |
| 19-30 deletion (+) | 2 (3) | | | | 1/2 | |
| 43-53 deletion (+) | 2 (3) | | | | | |
| 52-53 deletion(+) | 1 (1.5) | | | | | |
| 51-53 deletion (-) | 1 (1.5) | | | | | |
| 48-53 deletion (+) | 1 (1.5) | 1/1 | | | | |
| 45-49 deletion (+) | 1 (1.5) | | | 1/1 | | |
| 44-45 deletion (+) | 1 (1.5) | | | | | |
| 6,7,42-44 duplication (-) | 1 (1.5) | | | | | |
| 22-29 deletion (-) | 1 (1.5) | 1/1 | | | | |
| 13-15 deletion (+) | 1 (1.5) | | | | | |
| 11 deletion (-) | 1 (1.5) | | | | | |
| 5-7 deletion (-) | 1(1.5) | | | | | |
| 3-5 deletion (+) | 1(1.5) | | | | | |
| 3-9 deletion (+) | 1(1.5) | 1/1 | | | | |
| 2-7 duplication (+) | 1(1.5) | | | | | |
| 2 duplication(-) | 1(1.5) | | | | | |
| Non-sense mutation | 2 (3) | | | | | |

***LD:** Learning disabilities,* ***SD:** Speech delay and/or speech disorder,* ***ASD:** Autism spectrum disorder,* ***ADHD:** Attention deficit hyperactivity disorder,* ***CI:** Cardiac involvement,* **(+):** *In-Frame Deletion,* **(-):** *In-Frame Deletion*

## DISCUSSION

This study analyzed the genetic and clinical characteristics of patients with BMD, focusing on the association between specific genetic mutations and comorbidities. In particular, cases with out-of-frame mutations were identified and some deletions were found to be associated with cardiac or psychiatric involvement. The study also provides new insights into the phenotypic spectrum of BMD, highlighting the earliest age at which certain comorbidities are detected.

In a previous study in literature, the overall carrier frequency in mothers with carrier mutation types of DMD and BMD was found in 80 of 139 mothers (57.6%), and this carrier rate was significantly higher at 89.5% for BMD (14 ). In the current study,

**Table III: Comparisons of the clinical and laboratory findings of BMD patients according to the reading frame rule**

| | In-Frame Deletion (+) (n=59) | In-Frame Deletion (-) (n=8) | Total (n=67) | p |
|---|---|---|---|---|
| Clinical symptoms* | | | | |
| Exercise intolerance | 24 (40.7) | 6 (76) | 30 (44.8) | 0.126‡ |
| Early fatigue | 10 (16.9) | 3 (37.5) | 13 (19.4) | 0.179‡ |
| Pain with exercise | 8 (13.6) | 2 (25) | 10 (14.9) | 0.341‡ |
| Cramp | 8 (13.6) | 1 (12.5) | 9 (13.4) | 0.705‡ |
| Leg pain | 6 (9) | - | 6 (9) | - |
| Scoliosis* | 14 (23.7) | 4 (50) | 18 (26.9) | 0.127‡ |
| Cardiac involvement* | 8 (14) | - | 8 (11.9) | - |
| Psychiatric symptoms* | 14 (23.7) | 1 (12.5) | 15 (22.4) | 0.672‡ |
| Creatinine kinase (U/L)† | | | | |
| Highest value | 9343 (3400-12751) | 16435 (9341-18890) | 9422 (3579-13759) | 0.069§ |
| Lowest value | 2590 (1464-4900) | 3476 (1813-7481) | 2810 (1482-4900) | 0.686§ |

**: n(%), †: median (Inter Quantile Range), ‡:* Chi-square test, *§:* Mann-Whitney U test

the carrier rate was found to be 80.1%, which was lower than in the literature. This difference was thought to be because, for various reasons, carrier tests could not be performed on all the mothers.

Preserved muscle strength facilitates the differentiation of clinical features between BMD and DMD. BMD patients typically retain ambulation until at least 16 years of age and, in many cases, well into adulthood, with some maintaining this ability into advanced age (9). Diagnosis is most often established incidentally through the detection of elevated CK levels (15).

In the literature, the mean age of diagnosis for DMD is reported to be approximately 5 years; however, due to the milder clinical symptoms in BMD, it is generally expected to be diagnosed at a later age (1,16). In our study, the mean age at diagnosis was 5 years, which is earlier than the age typically observed in BMD patients. Age at diagnosis was lower among patients screened for a family history of the disease; however, this difference was not statistically significant. These findings underscore the critical role of CK screening and emphasize the importance of early diagnostic evaluation in patients with a positive family history.

All patients included in this study were ambulatory, with none exhibiting a positive Gowers sign. Upper extremity muscle strength was entirely preserved in all participants, while only two patients demonstrated mild proximal lower extremity weakness. This finding likely reflects the fact that the study cohort comprised individuals at an age when the initial manifestations of BMD typically emerge.

The most common symptoms in BMD are leg pain, cramping, exercise intolerance and exercise-induced pain (9,17). The most common symptoms in the current study were exercise intolerance, rapid fatigue, exercise-induced pain, cramps, and leg pain, respectively.

A small proportion of patients with dystrophinopathy do not have pathogenic variants in the coding region, which can make the mutation difficult to detect (10). In many cases, molecular genetic testing can confirm a definitive diagnosis of dystrophinopathy without the need for a muscle biopsy (9).

A muscle biopsy may be necessary to differentiate BMD and DMD and for prognostic evaluation. Immunohistochemical analyses have shown a complete absence of dystrophin in patients with DMD, whereas BMD patients have 10% to 40% of the normal amount of dystrophin or a partially functional form of the subsarcolemmal protein (1,18). In severe cases, dystrophin protein levels are usually below 10%, whereas in mild cases with dystrophin levels above 70%, symptoms may be of late onset or even remain asymptomatic (19–22). However, muscle biopsy is not current widely used because it is an invasive method. This increases the importance of studies on BMD. Identifying which mutations lead to which clinical picture and adding them to the literature may have the potential to reduce the need for biopsy.

A muscle biopsy was performed in only 1 patient in the current study, and the results were compatible with BMD. In all the patients, the diagnosis was confirmed by genetic analysis. Monaco et al.(23) first proposed a theory known as the “reading frame rule” based on patient examinations in 1988.

In-frame deletions/duplications in the DMD gene that do not alter the reading frame are generally associated with BMD phenotypes, with exceptions (23). Kesari et al. (24) observed a higher frequency of duplications, a different mutation distribution, and more exceptions to the reading frame rule in BMD patients. Additionally, in the study by Zambon et al. (25), which examined the phenotypic spectrum of dystrophinopathies associated with exon 2 duplications, 30% of the patients exhibited a BMD phenotype. These findings suggest that clinical manifestations can be heterogeneous even in cases with out-of-frame mutations. In the present study, eight patients with out-of-frame mutations were identified, further supporting these observations in the literature.

In patients with BMD, serum CK concentrations can often rise to a level ≥5-fold above the upper limit of normal (9). Consistent

with the literature, the CK levels in this study were ≥5-fold higher. Furthermore, no statistically significant difference was found between patients with and without in-frame mutations.

The most common mutations in BMD are deletions in exons 45-47 (26). In the current study, consistent with the literature, the most common deletions were found in exons 45-47. In addition, most mutations were clustered in the region between exons 45-55.

Although muscle involvement is milder in BMD than in DMD, cardiac involvement is often a prominent feature of the disease (27). The ability of patients with BMD to perform strenuous exercise may cause damage to myocardial cells with abnormal dystrophin by increasing mechanical stress on the heart (9). It has been reported in the literature that cardiac involvement is caused by mutations especially in exons 48 and 49 (28). Mutations involving exons 48 and 49 were found in all the patients with cardiac involvement in this study. Although life-threatening arrhythmias have been reported in patients with exon 3-4 duplications, no arrhythmia was observed in any of the current study patients with exon 3-4 duplication (29).

Different isoforms of dystrophin are also found in the cerebral cortex and Purkinje cells, but the function of all dystrophin isoforms in the brain is not yet fully understood. However, they appear to be involved in myelination during neuronal development, synaptic modulation, neuronal differentiation, and cellular energy metabolism. While cognitive abnormalities in DMD have been well documented, there is limited information on the cognitive profile of BMD patients (30–33).

Although the risk of intellectual disability is increased in children and adults affected by BMD, the average IQ does not differ from the general population (34). BMD has a higher incidence of learning disabilities and behavioral comorbidities compared to the general population, and learning disabilities have been reported in 32% of BMD patients (34). In the current study, psychiatric problems were detected in 15 (22.4%) patients, of which 7 were found to have learning disabilities.

In our study, the lower frequency of psychiatric disorders observed in patients with BMD compared to the general literature was attributed to the relatively short follow-up period and the lack of routine psychiatric evaluations. These limitations may have contributed to an underestimation of the prevalence of psychiatric comorbidities in this patient group (35,36).

Thangarajh et al. (37) reported that psychiatric problems such as ASD, ADHD, and LD were statistically more frequent in the upstream region of DMD exon 45. However, in the present patient group, no significant difference was observed between the two groups (37).

In conclusion, this study highlights the diversity of clinical and psychiatric challenges linked to genetic mutations in BMD patients. The impact of out-of-frame mutations on the phenotypic spectrum reinforces the heterogeneity described in the literature. Our findings emphasize the critical role of early diagnosis and the need for a multidisciplinary approach in the care of these patients. To further improve management strategies, we recommend prioritizing the systematic assessment of comorbidities to inform personalized care. The identification of mutation-specific clinical patterns may improve diagnostic and prognostic tools, reduce dependence on invasive procedures such as muscle biopsies, and ultimately improve the overall quality of care for BMD patients.

### Limitations of the study

As this was a retrospective chart review, maternal carrier status could not be examined in all the patients and 6-minute walk test results were not available for all patients. In addition, accurate data on the ages at which comorbid conditions were detected were not available.

### Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. Ethical approval was granted by the Tepecik Training and Research Hospital Non-Interventional Ethics Committee (Decision No: 2024/08-05, Date: 02.09.2024).

### Contribution of the authors

***Güzin Y:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***Doğan SD:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***Sarıkaya Uzan G:*** Organizing, supervising the course of progress and taking the responsibility of the research/study. ***Doğan G:*** Taking responsibility in logical interpretation and conclusion of the results. ***Özyılmaz B:*** Taking responsibility in logical interpretation and conclusion of the results. ***Tuncay B:*** Reviewing the article before submission scientifically besides spelling and grammar. ***Baydan F:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments.

### Source of funding

The authors declare the study received no funding.

### Conflict of interest

The authors declare that there is no conflict of interest.

## REFERENCES

1. Thada PK, Bhandari J, Forshaw KC, Umapathi KK. Becker Muscular Dystrophy. Published online 2024:1-10.

2. Andrew LaPelusa; Ria Monica D. Asuncion; Michael Kentris . Muscular Dystrophy. Published online 2024:1-31.
3. Fox H, Millington L, Mahabeer I, van Ruiten H. Duchenne muscular dystrophy. BMJ 2020;368:l7012.https://doi.org/10.1136/bmj.l7012.
4. Cai A, Kong X. Development of CRISPR-Mediated Systems in the Study of Duchenne Muscular Dystrophy. Hum Gene Ther Methods 2019;30:71-80.https://doi.org/10.1089/hgtb.2018.187.
5. Landrum Peay H, Fischer R, Tzeng JP, Hesterlee SE, Morris C, Martin AS, et al. Gene therapy as a potential therapeutic option for Duchenne muscular dystrophy: A qualitative preference study of patients and parents. PLoS One 2019;14:e0213649. https://doi.org/10.1371/journal.pone.0213649.
6. Romitti PA, Zhu Y, Puzhankara S, James KA, Nabukera SK, Zamba GK, et al. Prevalence of Duchenne and Becker muscular dystrophies in the United States. Pediatrics 2015;135:513-21. https://doi.org/10.1542/peds.2014-2044.
7. Ryder S, Leadley RM, Armstrong N, Westwood M, de Kock S, Butt T, et al. The burden, epidemiology, costs and treatment for Duchenne muscular dystrophy: an evidence review. Orphanet J Rare Dis 2017;12:79. https://doi.org/10.1186/s13023-017-0631-3.
8. Bradley WG, Jones MZ, Mussini JM, Fawcett PR. Becker-type muscular dystrophy. Muscle Nerve 1978;1:111-32. https://doi.org/10.1002/mus.880010204.
9. Basil T Darras M. Duchenne and Becker muscular dystrophy: Clinical features and diagnosis. UpToDate Published online 2023.
10. Darras BT, Urion DK, Ghosh PS. Dystrophinopathies Summary Genetic counseling GeneReview Scope. GeneReviews Published online 2018:1-35.
11. Banihani R, Smile S, Yoon G, Dupuis A, Mosleh M, Snider A, et al. Cognitive and Neurobehavioral Profile in Boys With Duchenne Muscular Dystrophy. J Child Neurol 2015;30:1472-82. https://doi.org/10.1177/0883073815570154.
12. Mavrogeni S, Markousis-Mavrogenis G, Papavasiliou A, Kolovou G. Cardiac involvement in Duchenne and Becker muscular dystrophy. World J Cardiol 2015;7:410-4. https://doi.org/10.4330/wjc.v7.i7.410
13. Paternostro-Sluga T, Grim-Stieger M, Posch M, Schuhfried O, Vacariu G, Mittermaier C, et al. Reliability and validity of the Medical Research Council (MRC) scale and a modified scale for testing muscle strength in patients with radial palsy. J Rehabil Med. 2008;40:665-71. https://doi.org/10.2340/16501977-0235.
14. Lee T, Takeshima Y, Kusunoki N, Awano H, Yagi M, Matsuo M, et al. Differences in carrier frequency between mothers of Duchenne and Becker muscular dystrophy patients. J Hum Genet 2014;59:46-50. https://doi.org/10.1038/jhg.2013.119.
15. Zimowski JG, Pilch J, Pawelec M, Purzycka JK, Kubalska J, Ziora-Jakutowicz K, et al. A rare subclinical or mild type of Becker muscular dystrophy caused by a single exon 48 deletion of the dystrophin gene. J Appl Genet 2017;58:343-7. https://doi.org/10.1007/s13353-017-0391-8.
16. Ciafaloni E, Fox DJ, Pandya S, Westfield CP, Puzhankara S, Romitti PA, et al. Delayed diagnosis in duchenne muscular dystrophy: data from the Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STARnet). J Pediatr 2009;155:380-5. https://doi.org/10.1016/j.jpeds.2009.02.007.
17. Angelini C, Marozzo R, Pegoraro V. Current and emerging therapies in Becker muscular dystrophy (BMD). Acta Myol 2019;38:172-9.
18. Hoffman EP, Fischbeck KH, Brown RH, Johnson M, Medori R, Loike JD, et al. Characterization of dystrophin in muscle-biopsy specimens from patients with Duchenne's or Becker's muscular dystrophy. N Engl J Med 1988;318:1363-8. https://doi.org/10.1056/NEJM198805263182104.
19. Gao QQ, McNally EM. The Dystrophin Complex: Structure, Function, and Implications for Therapy. Compr Physiol 2015;5:1223-39. https://doi.org/10.1002/j.2040-4603.2015.tb00638.x.
20. van den Bergen JC, Wokke BH, Janson AA, van Duinen SG, Hulsker MA, Ginjaar HB, et al. Dystrophin levels and clinical severity in Becker muscular dystrophy patients. J Neurol Neurosurg Psychiatry 2014;85:747-53. https://doi.org/10.1136/jnnp-2013-306350.
21. Angelini C, Fanin M, Pegoraro E, Freda MP, Cadaldini M, Martinello F. Clinical-molecular correlation in 104 mild X-linked muscular dystrophy patients: characterization of sub-clinical phenotypes. Neuromuscul Disord 1994;4:349-58. https://doi.org/10.1016/0960-8966(94)90071-X.
22. Angelini C, Fanin M, Freda MP, Martinello F, Miorin M, Melacini P, et al. Prognostic factors in mild dystrophinopathies. J Neurol Sci 1996;142:70-8. https://doi.org/10.1016/0022-510X(96)00144-X.
23. 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. https://doi.org/10.1016/0888-7543(88)90113-9.
24. Kesari A, Pirra LN, Bremadesam L, McIntyre O, Gordon E, Dubrovsky AL, et al. Integrated DNA, cDNA, and protein studies in Becker muscular dystrophy show high exception to the reading frame rule. Hum Mutat 2008;29:728-37. https://doi.org/10.1002/humu.20722.
25. Zambon AA, Waldrop MA, Alles R, Weiss RB, Conroy S, Moore-Clingenpeel M, et al. Phenotypic Spectrum of Dystrophinopathy Due to Duchenne Muscular Dystrophy Exon 2 Duplications. Neurology 2022;98:e730-e8. https://doi.org/10.1212/WNL.0000000000013246.
26. Vengalil S, Preethish-Kumar V, Polavarapu K, Mahadevappa M, Sekar D, Purushottom M, et al. Duchenne Muscular Dystrophy and Becker Muscular Dystrophy Confirmed by Multiplex Ligation-Dependent Probe Amplification: Genotype-Phenotype Correlation in a Large Cohort. J Clin Neurol 2017;13:91-7. https://doi.org/10.3988/jcn.2017.13.1.91.
27. Silvestri NJ, Ismail H, Zimetbaum P, Raynor EM. Cardiac involvement in the muscular dystrophies. Muscle Nerve 2018;57:707-15. https://doi.org/10.1002/mus.26014.
28. Melacini P, Fanin M, Danieli GA, Fasoli G, Villanova C, Angelini C, et al. Cardiac involvement in Becker muscular dystrophy. J Am Coll Cardiol 1993;22:1927-34. https://doi.org/10.1016/0735-1097(93)90781-U.
29. Ishizaki M, Fujimoto A, Ueyama H, Nishida Y, Imamura S, Uchino M, et al. Life-threatening Arrhythmias in a Becker Muscular Dystrophy Family due to the Duplication of Exons 3-4 of the Dystrophin Gene. Intern Med 2015;54:3075-8. https://doi.org/10.2169/internalmedicine.54.3986.
30. Aranmolate A, Tse N, Colognato H. Myelination is delayed during postnatal brain development in the mdx mouse model of Duchenne muscular dystrophy. BMC Neurosci 2017;18:63. https://doi.org/10.1186/s12868-017-0381-0.
31. Rae MG, O'Malley D. Cognitive dysfunction in Duchenne muscular dystrophy: a possible role for neuromodulatory immune molecules. J Neurophysiol 2016;116:1304-15. https://doi.org/10.1152/jn.00248.2016.

32. García-Cruz C, Merino-Jiménez C, Ceja V, Aragon J, Siqueiros-Marquez L, Reyes-Grajeda JP, et al. The dystrophin isoform Dp71e(Δ71) is involved in neurite outgrowth and neuronal differentiation of PC12 cells. J Proteomics 2019;191:80-7. https://doi.org/10.1016/j.jprot.2018.03.027.
33. Pezzoni L, Brusa R, Difonzo T, Magri F, Velardo D, Corti S, et al. Cognitive abnormalities in Becker muscular dystrophy: a mysterious link between dystrophin deficiency and executive functions. Neurol Sci 2024;45:1691-8. https://doi.org/10.1007/s10072-023-07169-x.
34. Young HK, Barton BA, Waisbren S, Portales Dale L, Ryan MM, Webster RI, et al. Cognitive and psychological profile of males with Becker muscular dystrophy. J Child Neurol 2008;23:155-62. https://doi.org/10.1177/0883073807307975.
35. Lambert JT, Darmahkasih AJ, Horn PS, Rybalsky I, Shellenbarger KC, Tian C, et al. Neurodevelopmental, behavioral, and emotional symptoms in Becker muscular dystrophy. Muscle Nerve 2020;61:156-62. https://doi.org/10.1002/mus.26750.
36. Mori-Yoshimura M, Mizuno Y, Yoshida S, Yoshida S, Ishihara N, Minami N, et al. Psychiatric and neurodevelopmental aspects of Becker muscular dystrophy. Neuromuscul Disord 2019;29:930-9. https://doi.org/10.1016/j.nmd.2019.09.006.
37. Thangarajh M, Hendriksen J, McDermott MP, Martens W, Hart KA, Griggs RC. Relationships between DMD mutations and neurodevelopment in dystrophinopathy. Neurology 2019;93:e1597-e604. https://doi.org/10.1212/WNL.0000000000008363.