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# Duchenne/Becker Muscular Dystrophy Deletion/Duplication with Reflex to Sequencing

Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are X-linked degenerative muscle disorders caused by pathogenic variants in the *DMD* gene. Testing for *DMD* variants can be used to confirm a diagnosis of DMD/BMD in symptomatic individuals or to determine carrier status for females with a family history of DMD/BMD or dilated cardiomyopathy (DCM). Prenatal testing for familial *DMD* variants is also available.

## DISEASE OVERVIEW

### Symptoms

- DMD
  - Delayed childhood milestones (eg, sitting, standing, walking, climbing) due to progressive symmetrical muscular weakness
  - Cardiomyopathy onset – ~14 years
    - 95% have cardiovascular involvement
  - Wheelchair dependence – typically by 12 years
  - Laboratory findings
    - No observable dystrophin expression
    - Serum CK levels – significantly increased
- BMD
  - Later-onset muscle weakness
  - Cardiomyopathy onset – ~15 years
  - Wheelchair dependence – 20s-30s
  - Laboratory findings
    - Dystrophin expression – 20-100%
    - Serum CK levels – increased
- *DMD*-Associated Dilated Cardiomyopathy (DCM)
  - Rapidly progressive disease course in the absence of skeletal myopathy
  - Male age of onset – teens and 20s
  - Female age of onset – 30s and 40s

### Incidence

- DMD – 1/3,500 male births worldwide
- BMD – 1/19,000 male births worldwide

### Genetics

Gene – *DMD*

Inheritance – X-linked

Penetrance

- Males – 100%
- Females – varies with X-chromosome inactivation

De novo variants – ~1/3 cases

### Typical Diagnostic Testing Strategy

## TESTS TO CONSIDER

Duchenne/Becker Muscular Dystrophy (DMD) Deletion/Duplication with Reflex to Sequencing 2011241
Method: Multiplex Ligation-dependent Probe Amplification/Massively Parallel Sequencing

- Most comprehensive *DMD* gene test for DMD or BMD
- Deletion/duplication analysis is performed first
  - If no large deletions or duplications are detected and/or results do not explain the clinical scenario, sequencing of the *DMD* gene is performed
- Deletion/duplication and sequencing components are also orderable separately, see below

Duchenne/Becker Muscular Dystrophy (DMD) Deletion/Duplication 2011235
Method: Multiplex Ligation-dependent Probe Amplification

- Appropriate first-tier genetic test for diagnostic testing or carrier screening for DMD or BMD; does not detect sequence variants
- Recommended test for a known familial *DMD* large deletion or duplication previously identified in a family member
- A copy of the family member's test result documenting the known familial variant is required

Duchenne/Becker Muscular Dystrophy (DMD) Sequencing 2011153
Method: Massively Parallel Sequencing

- Appropriate second-tier test for diagnostic or carrier screening for DMD or BMD after result of deletion/duplication analysis is negative

- Initial testing for DMD/BMD
  - Serum creatine kinase (CK) concentration
  - Muscle biopsy with dystrophin studies
- Molecular testing
  - Deletion/duplication analysis
  - Sequencing analysis

**Typical Carrier Testing Strategy**

- For a known familial *DMD* variant, targeted testing is recommended.
- If there is a family history of DMD/BMD but the causative familial variant is unknown, test an affected relative then perform targeted testing for the identified variant in at-risk relatives.
- If an affected relative cannot be tested, at-risk relatives should be tested by deletion/duplication analysis first because most *DMD* variants are large deletions and duplications.
  - If negative, consider *DMD* sequencing.

**Recommended Follow-Up Testing**

Cardiac evaluation for affected individuals and carriers

## TEST DESCRIPTION

**Clinical Sensitivity**

- DMD
  - Deletion/duplication – 55-75%
  - Sequencing – 20-35%
- BMD
  - Deletion/duplication – 75-90%
  - Sequencing – 10-20%

**Results**

- Positive
  - One pathogenic variant detected in *DMD* gene
    - Causative for DMD/BMD in males
    - Female carriers are variably affected
- Negative
  - No pathogenic variants identified
    - Risk for being affected with, or a carrier of, DMD/BMD, is reduced but not excluded.
- Inconclusive
  - Variants of uncertain clinical significance detected
  - Whether variants are benign or pathogenic is unknown

**Limitations**

- A negative result does not exclude a heritable form of muscular dystrophy.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if the individual has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of the targeted gene(s)
  - Regulatory region variants and deep intronic variants
  - Breakpoints of large deletions/duplications
  - Noncoding transcripts
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic variants

**Analytical Sensitivity**

Familial Mutation, Targeted Sequencing 2001961
Method: Polymerase Chain Reaction/Sequencing

- Recommended test for a known familial *DMD* sequence variant previously identified in a family member.
- A copy of the family member's test result documenting the known familial variant is required.

Duchenne/Becker Muscular Dystrophy (DMD) Deletion/Duplication, Fetal 2011231
Method: Multiplex Ligation-dependent Probe Amplification

- This test is performed on prenatal samples at risk for a known familial *DMD* deletion or duplication.
- A copy of the family member's test result documenting the known familial variant is required.

Familial Mutation, Targeted Sequencing, Fetal 2001980
Method: Polymerase Chain Reaction/Sequencing

- This test is performed on prenatal samples at risk for a known familial sequence variant.
- A copy of the family member's test result documenting the known familial variant is required.

See Related Tests

- For MLPA – greater than 99%
- For massively parallel sequencing:

| Variant Class | Analytical Sensitivity (PPA) Estimate[a] (%) | Analytical Sensitivity (PPA) 95% Credibility Region[a] (%) |
|---|---|---|
| SNVs | 99.2 | 96.9-99.4 |
| Deletions 1-10 bp | 93.8 | 84.3-98.2 |
| Deletions 11-44 bp | 100 | 87.8-100 |
| Insertions 1-10 bp | 94.8 | 86.8-98.5 |
| Insertions 11-23 bp | 100 | 62.1-100 |

*DMD* gene is a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

## REFERENCES

Darras B, Urion D, Ghosh P. Dystrophinopathies. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews, University of Washington, 1993-2017. Seattle, WA [Last Update: Apr 2018; Accessed: Nov 2018]

## RELATED TESTS

Creatine Kinase, Total, Serum or Plasma 0020010
Method: Quantitative Enzymatic

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