Duchenne/Becker Muscular Dystrophy Deletion/Duplication With Reflex to Sequencing

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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.

Featured ARUP Testing

Duchenne/Becker Muscular Dystrophy (DMD) Deletion/Duplication with Reflex to Sequencing 2011241

Method: Multiplex Ligation-Dependent Probe Amplification (MLPA)/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

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate. Refer to the Laboratory Test Directory for additional test options.

Disease Overview

Symptoms

- DMD
  - Delayed childhood milestones (eg, sitting, standing, walking, climbing) due to progressive symmetrical muscular weakness
  - Cardiomyopathy onset: approximately 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: approximately 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: approximately 1/3 cases

Typical Diagnostic Testing Strategy

- 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

Analytic Sensitivity

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

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%)	Analytic 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

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