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

Indications for Ordering

- Confirm diagnosis of Duchenne or Becker muscular dystrophy (DMD/BMD) in symptomatic individual
- Determine carrier status for females with a family history of DMD/BMD or isolated dilated cardiomyopathy (DCM)
- Prenatal diagnosis when a *DMD* gene variant has been previously identified in a parent

Test Description

- Multiplex ligation-dependent probe amplification for large deletion/duplication analysis of the *DMD* gene
- Massively parallel sequencing of the entire *DMD* coding region and intron/exon borders
- Sanger sequencing is performed as necessary to fill in regions of low coverage and confirm reported variants

Tests to Consider

Typical testing strategy

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

Primary tests

Duchenne/Becker Muscular Dystrophy (*DMD*) Deletion/Duplication with Reflex to Sequencing 2011241
- Preferred test for confirming carrier status or diagnosis of DMD/BMD

Duchenne/Becker Muscular Dystrophy (*DMD*) Deletion/Duplication 2011235
- Appropriate first-tier genetic test for DMD/BMD
- Useful when familial deletion is known
- Does not detect sequence variations

Duchenne/Becker Muscular Dystrophy (*DMD*) Sequencing 2011153
- Order only if previous *DMD* gene deletion/duplication testing did not identify a causative variant

Duchenne/Becker Muscular Dystrophy (*DMD*) Deletion/Duplication, Fetal 2011231
- Prenatal test for known *DMD* gene deletions/duplications previously identified in a family member

Related tests

Familial Mutation, Targeted Sequencing 2001961
- Useful when a pathogenic familial variant identifiable by sequencing is known

Creatine Kinase, Total, Serum or Plasma 0020010
- Nonspecific indicator of muscle inflammation or damage
- Initial screening test when clinical features suggest muscular dystrophy

Disease Overview

Incidence

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

Symptoms

DMD
- Delayed childhood milestones (eg, sitting, standing, walking, climbing) due to progressive symmetrical muscular weakness
- Cardiomyopathy onset – ~14 years of age
  - 95% have cardiovascular involvement
- Wheelchair dependence – by 12 years of age
- Laboratory findings
  - No observable dystrophin expression
  - Serum CK levels – significantly increased

BMD
- Later-onset muscle weakness
- Cardiomyopathy onset – ~15 years of age
- Wheelchair dependence – 20s-30s
- Laboratory findings
  - Dystrophin expression – 20-100%
  - Serum CK levels – increased

DMD-associated 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

Recommended follow-up testing

Cardiac evaluation for affected individuals and carriers

Genetics

Gene – *DMD*

Inheritance – X-linked

Penetrance

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

Variants – >5,000 identified

De novo variants – ~1/3 cases

Test Interpretation

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 reduced but not excluded
- Inconclusive
  - Variants of uncertain clinical significance detected
    - Whether variants are benign or pathogenic is unknown

Limitations

- Diagnostic errors can occur due to rare sequence variations
- Regulatory region and deep intronic variants will not be detected
- Deletion/duplication breakpoints will not be determined
- Small deletions or insertions may not be detected by massively parallel sequencing

Reference

Darras BT, Miller DT, Urion DK. Dystrophinopathies. 2000 Sep 5 [Updated 2014 Nov 26]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015 (www.ncbi.nlm.nih.gov/books/NBK1119/)