Inheritest® CARRIER SCREEN

Dystrophinopathies, including Duchenne and Becker muscular dystrophies and X-linked dilated cardiomyopathy

What are dystrophinopathies?

The dystrophinopathies are X-linked muscle disorders with variable severity that include Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD) and X-linked dilated cardiomyopathy. The dystrophinopathies are characterized by progressive muscle weakness and wasting and occur predominantly in males. Skeletal muscle is primarily affected in DMD and BMD. Heart muscle is primarily affected in X-linked dilated cardiomyopathy.[1,2] Signs and symptoms of the dystrophinopathies are due to the alterations of the protein dystrophin, which helps to stabilize and protect muscle fibers.[1]

What are the symptoms of dystrophinopathies and what treatment is available?

DMD and BMD differ in severity, age of onset, and rate of progression. Signs and symptoms of DMD and BMD may include:[1,2]

- Large calves
- Unusual gait and difficulty running, climbing, and getting up from the floor
- Problems with learning and memory
- Intellectual disability
- Progressive muscle weakness with associated delayed motor skills, leading to wheelchair dependence before age 13 (DMD), or after age 16 (BMD)
- Cardiomyopathy (progressive enlargement of the heart) leading to congestive heart failure

Individuals with DMD usually experience symptoms in early childhood and may live into their 20s. Individuals with BMD may have less severe symptoms with later onset and slower progression, and life expectancy into their 40s.[1,2]

There is no cure for Duchenne or Becker muscular dystrophies. Treatment is supportive and multidisciplinary. Genotype-targeted therapies may be available for some individuals.[2]

X-linked dilated cardiomyopathy may be a milder form of BMD in which there is heart disease, leading to congestive heart failure, and usually no obvious signs of skeletal muscle weakness Signs and symptoms are typically seen in males between ages 20 and 40 and in females later in life.[1,2]

How are dystrophinopathies inherited?

Dystrophinopathies are X-linked recessive disorders caused by pathogenic variants, usually deletions, in the *DMD* gene.[2] Approximately 67% of the time a *DMD* pathogenic variant is inherited, and approximately 33% of the time the variant is *de novo* and not previously been seen in the family.[2] A male with a pathogenic variant in the *DMD* gene is affected with a dystrophinopathy. A female with a pathogenic variant in one *DMD* gene is a carrier. Approximately 10% of carrier females may be at risk of developing cardiomyopathy, mild muscle weakness, and/or cognitive dysfunction.[3] A female who inherits two pathogenic variants, one from each parent, is affected with a dystrophinopathy, although this is an uncommon occurrence.

If a female is a carrier, the risk for each son to be affected is 50% and the risk for each daughter to be a carrier is 50%. If a male is affected, each son is unaffected and each daughter is an obligate carrier.

If a pathogenic variant is identified in the affected individual but not the mother it is considered to be *de novo*, and there is an increased risk for that mother to have another affected child due to germline mosaicism. 15-20% of mothers with affected sons have germline mosaicism, in which the pathogenic variant is present in some but not all egg cells.[2]

Who is at risk for dystrophinopathies?

Duchenne and Becker muscular dystrophies can occur in individuals of all races and ethnicities. Approximately 1 in 3500 – 1 in 5000 boys are born with these conditions worldwide.[1]

Having a relative who is a carrier or who is affected can increase an individual's risk of being a carrier. Consultation with a genetics health professional may be helpful in determining carrier risk and appropriate testing.

What does a positive test result mean?

If a gene mutation is identified, an individual should speak to a health care provider or a genetics professional about the implications of the result and appropriate testing for the reproductive partner and at-risk family members.

What does a negative test result mean?

A negative result reduces, but does not eliminate, the possibility that an individual carries a gene mutation. The likelihood of being a carrier is also influenced by family history, medical symptoms, and other relevant test results.

Where can I get more information?

Genetics Home Reference: https://ghr.nlm.nih.gov/condition/duchenne-and-becker-muscular-dystrophy

Muscular Dystrophy Association: https://www.mda.org/

Duchenne Family Support Group: https://www.dfsg.org.uk/index.php

References

1. Genetics Home Reference: Duchenne and Becker muscular dystrophy. Available at https://ghr.nlm.nih.gov/condition/duchenne-and-becker-muscular-dystrophy#. Accessed May 29, 2108.
2. Darras BT, Urion DK, Ghosh PS. Dystrophinopathies. *GeneReviews*. Available at https://www.ncbi.nlm.nih.gov/books/NBK1119. Accessed May 29, 2018.
3. Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. *Lancet.* 2009;Nov. DOI:10.1016/S1474-4422(09)70271-6.