Duchenne Muscular Dystrophy

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Key Points

- Duchenne muscular dystrophy (DMD) is an X-linked condition that causes progressive muscle weakness and cardiomyopathy, with death by the third decade in affected males.
- Approximately one-third of affected individuals have a new mutation in the *DMD* gene and two-thirds of affected individuals have inherited a *DMD* mutation from their mothers, who are carriers.
- Both carrier testing and prenatal diagnosis are possible after DMD has been diagnosed in a family. The first step in the testing process is identification of the specific disease-causing mutation in the affected family member. Once the specific familial mutation is known, female relatives can be tested for carrier status and prenatal diagnosis can be performed.

Learning Objectives

Participants will be able to:

- Calculate the pre-test probability that a woman whose brother has DMD will be a carrier;
- Explain a genetic testing strategy that clarifies the reproductive risks for a carrier;
- Describe how linkage analysis can be used to clarify reproductive risks when a mutation cannot be identified in a family.

Family History Issues

Duchenne muscular dystrophy is inherited in an X-linked manner. One-third of affected males have a new mutation causing the condition, and the remaining two-thirds have inherited a mutation from their mother. When inherited, the condition always is passed from the maternal side of the family.

Red Flags 

The first symptoms of DMD usually identified by parents are gross motor delays and gait problems. Proximal weakness causes a tendency for toe-walking, and eventually a waddling gait and difficulty climbing stairs. Affected boys use the Gower maneuver to rise from a supine position, using the arms to supplement weak pelvic girdle muscles. In a minority of cases, the first symptom identified by parents is some degree of cognitive impairment, usually in verbal ability, and presenting as speech delay or learning difficulties.

Case 23. A Young Woman with a Family History of Duchenne Muscular Dystrophy

Mrs. M is a 26-year-old woman who seeks care with a new primary care provider. She is hoping to get pregnant soon. She is in good health but is concerned about the possibility of having a child with Duchenne muscular dystrophy (DMD). Her 17-year-old brother is in the late stages of this disease. He became wheelchair bound at age ten years and is currently on full-time ventilator support at home. Her experience watching her younger brother grow up with DMD has convinced her that she would like to avoid having an affected child. However, she is uncertain of her options. She notes no other history of DMD in the family.

Clinical Care Issues

In Duchenne muscular dystrophy (DMD), progressive muscle weakness begins in early childhood, usually presenting with delays in gross motor milestones, especially delays in sitting and standing independently. Proximal weakness causes a waddling gait and difficulty climbing stairs. Boys are usually wheelchair bound by age 12 years. Cardiomyopathy occurs in all patients after age 18 years. Few survive beyond the third decade, with respiratory complications and cardiomyopathy being common causes of death (see *GeneReview*: Dystrophinopathies). Another muscular dystrophy, Becker muscular dystrophy (BMD), is also caused by mutation of the *DMD* gene. BMD is by definition a milder disorder with later-onset muscle weakness and slower progression. In BMD, patients remain ambulatory until their 20s and survive until their mid-40s. Cardiomyopathy also causes significant morbidity in BMD, but at a later age than in males with DMD.

Testing for the presence of a *DMD* mutation using DNA-based technology is now

the first diagnostic step for individuals suspected to have DMD. If the molecular test does not identify a mutation, a muscle biopsy is performed to quantitate the amount of the dystrophin protein present; DMD is associated with absence or near-absence of the dystrophin protein from muscle tissue.

Risk Assessment

DMD is inherited in an X-linked manner. Approximately one-third of individuals with DMD have a new mutation within the family; the other two-thirds inherit the condition through their mothers, who are carriers.

Mrs. M's risk of being a carrier for DMD is dependent on whether her brother has a new mutation in the *DMD* gene or whether he inherited it from his mother. In some families, this question can be answered by the family pedigree:

- If Mrs. M had one other male biological relative with DMD on her mother's side of the family, her mother would be an obligate carrier. Mrs. M would then have a 50% chance of having inherited the X chromosome carrying the familial *DMD* mutation from her mother.

- However, in Mrs. M's family, no other males are known to have DMD, so no conclusions can be made about her mother's carrier status:

    - If her brother has inherited his mutation from their mother, as is the case in two-thirds of individuals with DMD, there is a 50% chance that Mrs. M has also inherited the mutation from her mother and is a carrier herself. If Mrs. M is a carrier, she has a 50% chance of transmitting the *DMD* mutation in each pregnancy. Sons who inherit the mutation will be affected; daughters who inherit the mutation are carriers. Thus, with each pregnancy, a woman who is a carrier has a 25% chance of having an affected male.

      In this instance (and in the absence of any molecular genetic testing information), the risk of having an affected child can be roughly calculated as: 2/3 (chance of her brother having an inherited mutation) x 1/2 (chance Mrs. M inherited the mutation and is a carrier) X 1/4 (chance of a carrier having an affected child) = 1/12 = 8.3%. However, genetic testing may be helpful in clarifying Mrs. M's carrier status.

    - If her brother has a new mutation, Mrs. M is not at risk of being a

carrier.

Genetic Counseling and Testing

Molecular genetic testing to identify carrier status

More definitive information about Mrs. M's carrier status may be provided by molecular testing. Duchenne muscular dystrophy is caused by mutations in the *DMD* gene, which encodes the protein dystrophin. About 95% of patients with DMD have an identifiable mutation in the *DMD* gene. About 70% of mutations are deletions or inversions identified with a widely available test; about 25% are point mutations, identified by sequencing the *DMD* gene, a test available in only a few centers. [The fact that the *DMD* gene has many different mutations (alleles) that can give rise to Duchenne muscular dystrophy is called allelic heterogeneity.] These same methods are used to identify a mutation in two different contexts: to confirm diagnosis in a person with clinical findings suggesting DMD, especially if the clinical presentation is atypical, and to perform carrier testing for at-risk female family members once a mutation has been identified in the affected male(s) in that family.

If her brother has undergone molecular testing and if a *DMD* mutation has been identified, this same test can be used to determine whether Mrs. M is a carrier. Thus, the next step in clarifying Mrs. M's carrier status is a review of her brother's molecular genetic testing results. If a specific *DMD* mutation cannot be identified in her brother, no direct test is available to determine her carrier status. Carrier females can have elevated serum CK levels, as do affected males. Before molecular testing became widely available, measurement of serum CK levels of at-risk female relatives was used to assess their risk of being a carrier; however, this testing approach had limited sensitivity and specificity. Now that molecular testing can identify the majority of mutations, it is the preferred approach to identify carriers.

If her brother has an identifiable mutation in the *DMD* gene, Mrs. M can be offered testing to determine her carrier status. If the test is negative — that is, if she does not have the mutation present in her brother — she can be reassured that she is not at risk of having an affected child. If she has the mutation present in her brother, she is a carrier, which means that her sons will have a 50% chance of having DMD and her daughters will have a 50% chance of being DMD carriers.

Linkage analysis when a mutation cannot be identified

In some families, a mutation cannot be identified in the *DMD* gene but **linkage analysis** may be helpful in clarifying the carrier status of at-risk females. Such an approach is only possible if at least two affected family members with DMD are available for testing.

For example, if the patient (individual III-1 in the figure below) had an affected brother (III-2) and an affected maternal uncle (II-1), her mother (II-2) would be an obligate carrier for DMD (Note: Given such a situation, the patient would be at 50% risk of being a carrier). Linkage analysis uses DNA markers near or within the *DMD* gene to track the mutation in a particular family. Linkage analysis relies on variable regions of DNA flanking the gene, which allows for the identification of markers on the chromosome with the *DMD* mutation. In this example, the DNA markers a1, b1 are found in both of the affected males and in the patient's mother (II-2) (who is an obligate carrier). Therefore, the markers a1, b1 identify the X chromosome with the *DMD* mutation. The markers a2, b1 identify the X chromosome that does not have the *DMD* mutation.

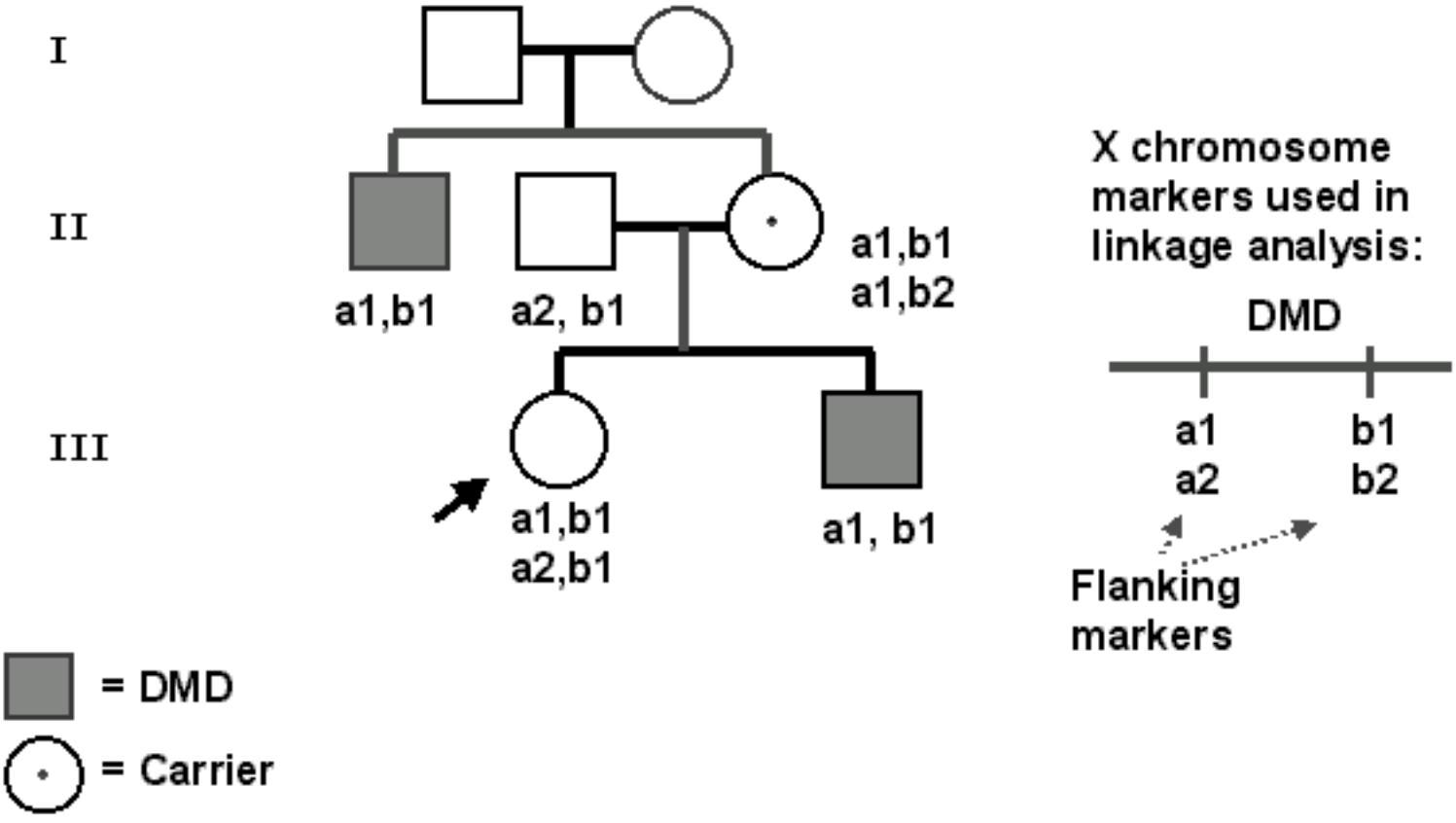

Figure 1. Use of linkage analysis to determine carrier status

Assessment of markers in the patient who is concerned about her carrier status (indicated by arrow) indicates that she has inherited a1, b1 markers, indicating

that she inherited from her mother the X chromosome with the DMD mutation.

Linkage analysis does not always lead to informative results. In the case of the *DMD* gene, many highly variable markers are available for study, both within the gene and flanking the gene. However, the large size of this gene can lead to a risk of recombination. Recombination can complicate the interpretation of the linkage analysis and make carrier determination impossible.

Interventions

Clinical care for carriers

Occasionally females who are DMD carriers have mild clinical features of DMD, either as a result of X-chromosome rearrangements or because of non-random X-chromosome inactivation. Some symptoms include mild to moderate muscle weakness, myalgia, left ventricle dilation, or dilated cardiomyopathy. For this reason, a cardiac evaluation should be performed at least once for female carriers, and any sign of ventricle dilation or cardiomyopathy should be followed yearly.

Reproductive options for carriers

A DMD carrier can choose to accept the 25% risk with each pregnancy of having a child with DMD. If, like Mrs. M, a DMD carrier wishes to avoid having a child with DMD, she has several potential options:

- Decide not to have children
- Adopt a child
- Use assisted reproductive technologies (ART) with a donated egg
- Use preimplantation genetic diagnosis (PGD) to assure that the embryos implanted are not affected males
- Use prenatal diagnosis with termination of the pregnancy if the fetus is a male with DMD.

Decisions about these options are morally weighted and couples differ in the choices they find acceptable. In addition, some of these options have limited availability. For example, couples wishing to adopt are not always able to do so; ART and PGD are expensive clinical services that are available only in certain specialty centers and are not usually covered by health insurance. Termination of a pregnancy in the second trimester, after prenatal testing results are available, may also not be a covered service.

Ethical/Legal/Social/Cultural Issues

Because her brother is already in the late stages of DMD and is not likely to survive much longer, Mrs. M may find that choosing to undergo carrier testing, in an attempt to avoid having a child with DMD, brings up difficult issues between the two of them. In order to determine her carrier status, she may need to request that he undergo genetic testing (if he has not already been tested), in order to identify the *DMD* mutation in the family, and may be reluctant to explain her interest in testing. Because she is healthy and about to start a family, she may feel guilty that her brother will not have the same chances that she has, and may also have mixed feelings about undergoing testing and about discussing it with her family.

Resources

- **Muscular Dystrophy Association - USA**
  3300 East Sunrise Drive
  Tucson, AZ 85718-3208
  Phone: 520-529-2000; 800-572-1717
  Fax: 520-529-5300
  Email: mda@mdausa.org

- **National Library of Medicine Genetics Home Reference**
  Duchenne and Becker muscular dystrophy

- **NCBI Genes and Disease Webpage**
  Duchenne muscular dystrophy

- **NINDS Muscular Dystrophy Information Page**

- ***GeneReview:* Dystrophinopathies**

- **GeneTests Resources for Dystrophinopathies**

- **GeneTests Online Medical Genetics Information Resource**

References

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