SUPPLEMENT TO
OBG MANAGEMENT
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Carrier Screening for Duchenne Muscular Dystrophy

Introduction

Duchenne muscular dystrophy (DMD), an X-linked condition, is the most common muscular dystrophy in children and affects families of all ethnicities.[1] Approximately two-thirds of clinically diagnosed cases of DMD are attributable to a carrier mother, who is likely unaware that she is a carrier. In addition to providing information about reproductive risks, carrier screening can identify women who are, themselves, at risk of health effects caused by defects in the *DMD* gene. However, population-wide carrier screening has not been available until now.

Although to date there have not been screening guidelines for DMD, the condition aligns with recommendations made in a 2015 Joint Statement by the American College of Medical Genetics and Genomics, the American Congress of Obstetricians and Gynecologists, the National Society of Genetic Counselors, the Perinatal Quality Foundation, and the Society for Maternal-Fetal Medicine regarding expanded carrier screening in reproductive medicine.[2] These recommendations advocate screening for those conditions involving cognitive disability, that have a need for medical intervention, and that have an effect on quality of life. DMD meets all of these criteria.

The *DMD* (Dystrophin) Gene

The *DMD* gene, which encodes the protein dystrophin, is located on the X chromosome (Xp21.2-p21.1) and is the largest protein-coding gene (**FIGURE 1**). Dystrophin is essential to the integrity of muscle fibers; it is part of a protein complex that provides protection to the muscles over time. Dystrophin helps to connect muscle cells to surrounding proteins, and may help to facilitate cell signaling between muscle cells. Mutations in the gene lead to an absence or decreased expression of dystrophin, causing progressive damage to muscle cells. Mutations are associated with DMD and Becker muscular dystrophy (BMD), as well as DMD-associated dilated cardiomyopathy.

DMD Incidence and Phenotype

DMD affects approximately 1/3500 male births. DMD has a similar male population incidence to fragile X syndrome (1/3600 males) and to cystic fibrosis (1/3700 births) (**FIGURE 2**).[3,4]

FIGURE 1 The *DMD* Gene

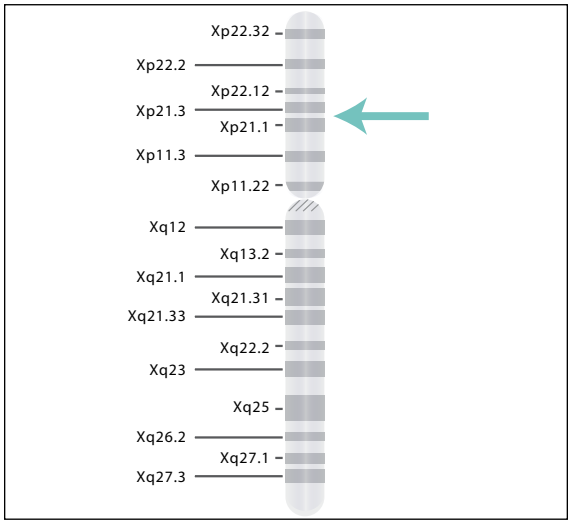
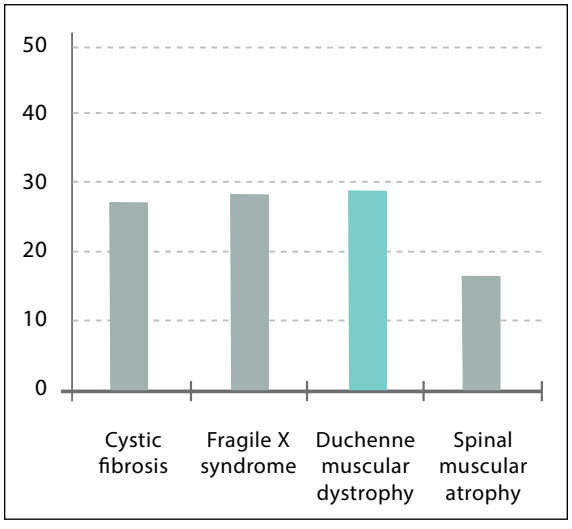


FIGURE 2 Incidence Per 100,000 Male Births



Boys with DMD present in early childhood with delayed milestones, such as sitting and standing. There is progressive symmetrical proximal muscle weakness and atrophy, calf hypertrophy, persistent toe walking, scoliosis, and an unsteady gait. Boys with DMD demonstrate a positive Gowers' sign, a maneuver used by individuals with proximal muscle weakness to rise from a seated position. Blood creatine kinase (CK) is elevated. Cognitive impairment is seen to varying degrees, particularly related to verbal working memory skills.[5,6] The incidence of attention deficit hyperactivity disorder and autism spectrum disorders are increased in this population.[6] Boys with DMD are wheelchair dependent by approximately 12 years of age. Cardiomyopathy has clinical onset in the early teen years or younger, is present in patients in the second decade of life, and is often the cause of death in early adulthood, along with respiratory failure.[7]

Current treatments for DMD are limited, but include supportive therapies and corticosteroid therapy to improve muscle strength and respiratory function and to prevent scoliosis.[6] There are several gene therapies under investigation, including ataluren to promote ribosomal readthrough of stop codons, and antisense oligonucleotides that induce exon skipping, which increases the expression of dystrophin and reduces the severity of disease.[6]

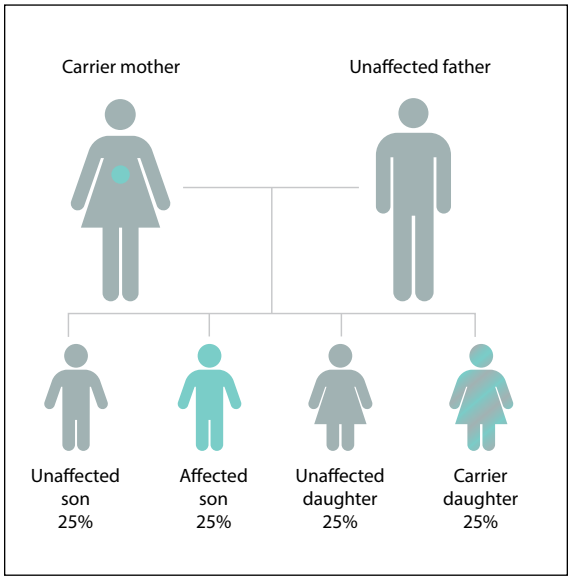
Becker Muscular Dystrophy

BMD is similar to DMD, although less prevalent. Affecting approximately 1/20,000 to 1/30,000 males, BMD is essentially a later-onset, milder form of DMD. Wheelchair dependency occurs after age 16 years, and the neck flexor muscle strength is generally preserved, which differentiates it from DMD. Very mild cases can occur. These men can remain ambulatory even into their 60s.[8] Cardiomyopathy is a common cause of morbidity and mortality in BMD, with the mean age of death in the mid-40s.[9]

Inheritance Patterns

Women have 2 copies of the *DMD* gene, 1 on each X-chromosome. As a result, DMD and related conditions are inherited in an X-linked pattern. A mutation in 1 copy of the *DMD* gene generally is not sufficient to cause disease (although carrier women may be at risk for some health effects, see next page). If a woman is a carrier of a mutation in the *DMD* gene, there is a 50% chance in each pregnancy that the fetus will inherit the *DMD* gene mutation. If the fetus is female, there is a 50% chance that she will be a carrier; if the fetus is male there is a 50% chance that he will be affected (**FIGURE 3**).

FIGURE 3 DMD Inheritance Patterns



Abbreviation: DMD, Duchenne muscular dystrophy.

Given the *DMD* gene's large size (79 exons), it is vulnerable to mutations.[6] Approximately 60% to 70% of mutations causing DMD are deletions of 1 or more exons, and about 5% to 7% are duplications.[10-12] Most of the remainder of patients have point mutations within the coding region of the gene—although approximately 7% do not (**FIGURE 4**).[10]

In boys diagnosed with DMD who have no family history of the condition, approximately 67% of

FIGURE 4 DMD Mutations

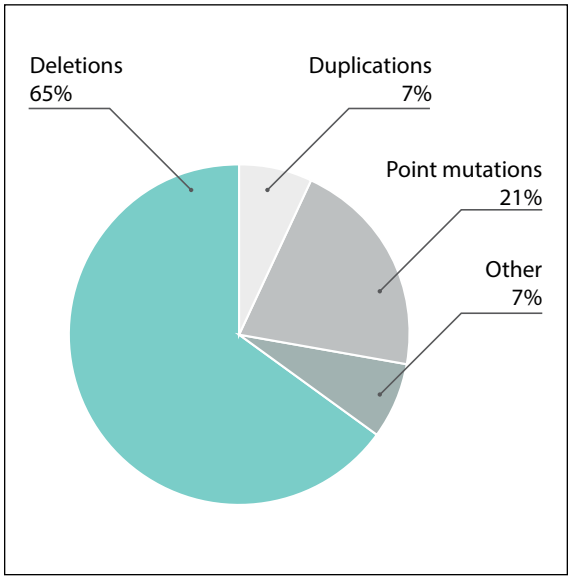


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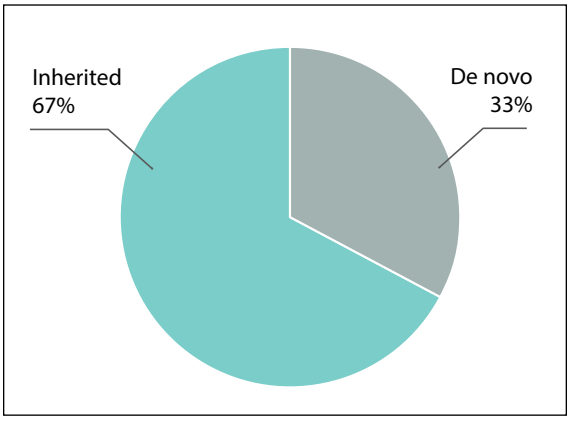
FIGURE 5 Inherited vs De Novo DMD Mutations



Abbreviation: DMD, Duchenne muscular dystrophy.

the mothers are subsequently found to be carriers. Because diagnosis is often delayed, and boys do not receive a definitive diagnosis until approximately age 5 years, these women often have more children without knowing they carry a DMD mutation.[13] Approximately 33% of cases of DMD are de novo—they occurred in the affected male child, and were not inherited from a carrier mother (**FIGURE 5**). These cases cannot be picked up by carrier screening of the mother. Of the apparently de novo cases, some are due to germline mosaicism in the mother.[11,14]

Female Carriers

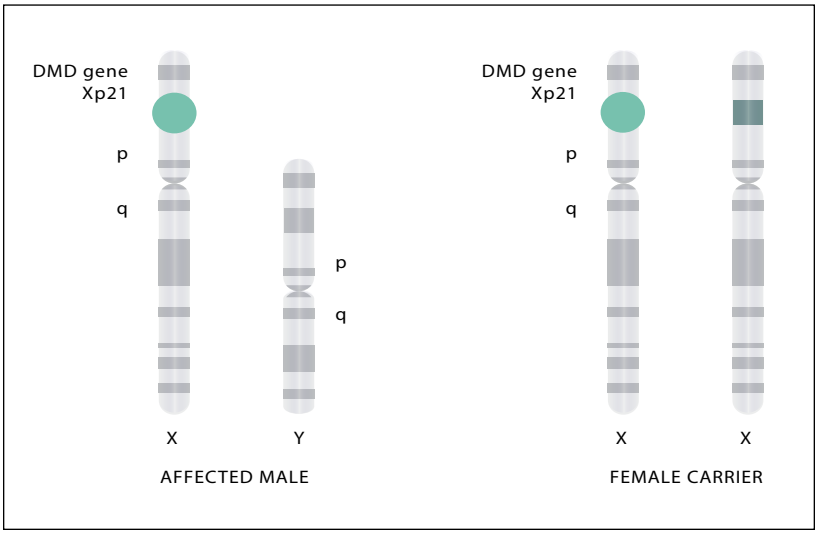
Some female carriers may exhibit symptoms, which range in severity. Up to 20% of carriers may have some degree of muscle weakness, ranging from mild to moderate.[6] Approximately 8% to 10% of carriers are reported to have dilated cardiomyopathy that is progressive.[6,15] Historically, skewed X-inactivation was the accepted mechanism for the development of symptoms in carriers. Newer studies have shown, however, that this is not necessarily the case, and in fact the reason for variability in symptoms among carriers is not well known.[16] In rare cases, presentation in female carriers can be very severe.[17]

The American Academy of Pediatrics provides guidelines for education and surveillance for female carriers of DMD-related conditions. Recommendations include education about the signs and symptoms of heart failure, including that complete cardiac evaluations by a specialist begin in late adolescence or early adulthood and be performed at least every 5 years. Treatment recommendations for symptomatic women are similar to recommendations for affected males.[7] Female carriers should consider being evaluated for cardiac symptoms during pregnancy, and symptomatic women should be followed closely by a high-risk obstetrician.[18]

Testing Technology

With the introduction of next generation sequencing, the ability to investigate large genes such as the *DMD* gene (79 exons) has become more time and cost effective. Techniques for testing for deletions and duplications also have improved in recent years, making high-throughput population-based screening possible. To detect deletions and duplications, two effective techniques are used: qPCR, which amplifies and quantifies a region of DNA, and multiplex ligation-dependent probe amplification (MLPA), a similar technique to qPCR that uses fluorescence to determine the relative quantity of DNA sequence. These techniques—next generation sequencing, qPCR, and MLPA—allow for a greater than 90% detection rate for deletions, duplications, and point mutations in the *DMD* gene. Population-based carrier screening can identify greater than 90% of women who are carriers of a mutation in the *DMD* gene, and therefore, at risk of having a child with DMD (**FIGURE 6**).

FIGURE 6 *DMD* Gene in Affected Males and Female Carriers



Conclusion

DMD, a severe, early-onset disease, and its related conditions, are relatively common in the population. Historically, broad-population DMD carrier screening has been unavailable. Many women who have had children with DMD were unknowingly carriers of the condition. With newer technologies and reduced costs, DMD carrier screening makes it possible to detect greater than 90% of carriers in advance of having an affected child. Because female carriers of DMD are also at risk for health problems, carrier screening can be beneficial for a woman's own health care by allowing the proactive monitoring of symptoms.

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