Genetics and Emerging Treatments for Duchenne and Becker Muscular Dystrophy

Nicolas Wein, PhD[a], Lindsay Alfano, DPT[a,b], Kevin M. Flanigan, MD[a,c,d,*]

KEYWORDS

• Duchenne • Becker • Muscular dystrophy • *DMD* gene • Dystrophin • Gene therapy • Exon skipping • Nonsense suppression

KEY POINTS

- Duchenne and Becker muscular dystrophy (DMD and BMD) are X-linked disorders that occur because of mutations in the *DMD* gene, encoding the dystrophin protein, which provides an important part of the protein complex that provides a link between the cytoskeleton the extracellular matrix.
- In most cases, DMD occurs because of mutations that result in the production of no dystrophin, and BMD occurs because of mutations that result in the production of partially functional dystrophin; this concept is being used for novel potential therapies directed at DMD.
- DMD typically presents at ages 2 to 5 years with gait abnormalities or motor performance that falls behind peers, but clinicians must be aware it may present with delayed motor milestones, early cognitive impairment, or elevated serum transaminases, any of which should lead to testing serum creatine kinase.
- Treatment with systemic corticosteroids (prednisone and deflazacort) is the only therapy that has definitively been shown to alter the course of DMD; careful monitoring and counseling are required to minimize side effects.
- Promising potential therapies, such as exon skipping or nonsense suppression, are directed toward specific mutations or mutation classes; definitive mutation analysis of the *DMD* gene from genomic DNA is widely available and detects approximately 95% of mutations.

Disclosures: Dr K.M. Flanigan receives research support from the National Institutes of Health (NS085238); the Association Francaise contre les Myopathies; and the CureDuchenne foundation. He has served as a site investigator or subinvestigator on trials funded by Prosensa Therapeutics; Sarepta Therapeutics; PTC Therapeutics; and Akashi Therapeutics. He has served on advisory boards for Prosensa, Sarepta, PTC, and Italofarmaco, Inc. Dr L. Alfano serves as a consultant for PTC Therapeutics, Eli Lilly and Company, and Pfizer Inc. Dr N. Wein has no disclosures.
[a] The Center for Gene Therapy, The Research Institute, Nationwide Children's Hospital, 700 Children's Drive, Columbus, OH 43205, USA; [b] Department of Physical Therapy, Nationwide Children's Hospital, 700 Children's Drive, Columbus, OH 43205, USA; [c] Department of Pediatrics, Ohio State University, 700 Children's Drive, Columbus, OH 43205, USA; [d] Department of Neurology, Ohio State University, 700 Children's Drive, Columbus, OH 43205, USA
* Corresponding author. Center for Gene Therapy, Rm 3014, Nationwide Children's Hospital, 700 Children's Drive, Columbus, OH 43205.
E-mail address: kevin.flanigan@nationwidechildrens.org

Pediatr Clin N Am 62 (2015) 723–742
http://dx.doi.org/10.1016/j.pcl.2015.03.008 **pediatric.theclinics.com**
0031-3955/15/$ – see front matter

The videos, showing a boy with DMD climbing stairs and a boy with DMD arising from the floor, accompany this article at http://www.pediatric.theclinics.com/

INTRODUCTION

Duchenne and Becker muscular dystrophy (DMD and BMD) are related disorders that occur because of mutations in the *DMD* gene, encoding the dystrophin protein. DMD is more severe, and more common, with newborn screening studies showing an incidence ranging from 1:3802 to 1:6291 live male births[1] (rather than the 1:3500 that is commonly cited),[2] and BMD is about one-third as common.[2,3] Because the gene is X-linked, the diseases affect only boys (except in those rare cases explained by unusual genetic mechanisms such as balanced chromosomal translocations).

The dystrophin protein consists of an N-terminal actin-binding domain, a long central rod domain consisting of 24 spectrin-like repeats, and a C-terminal dystroglycan-binding domain. Within the central rod domain is a second actin-binding domain as well as a binding site for neuronal nitric oxide synthase; additional proteins, including dystrobrevin and syntrophin, bind dystrophin distal to the dystroglycan-binding domain. These partners suggest a role for dystrophin in signaling, but it is clear that dystrophin plays a critical role as a structural linker between the cytoskeletal F-actin and β-dystroglycan, one of the proteins of the membrane-bound dystroglycan-associated glycoprotein complex. Another of these proteins, α-dystroglycan, is located externally, where it binds with the extracellular matrix. The deformational forces generated by muscle contraction are significant, and in the absence of dystrophin, which is typically the case with DMD, the muscle membrane is damaged. This damage leads to elevations of creatine kinase (CK) in the serum and to calcium influx within the muscle fiber, leading in turn to activation of calcium-dependent proteases. Cycles of muscle fiber necrosis, degeneration, and regeneration follow, with increasing endomysial fibrosis and fatty replacement of muscle over time, and loss of muscle contractile function. In BMD, a partially functional dystrophin is typically produced, leading to an attenuated clinical course and attenuated muscle pathologic abnormality.

At the level of gene mutations, the difference between an absent or a partially functional dystrophin (and hence DMD or BMD) is explained by the concept of the "reading frame rule."[4] Mutations that ablate the open reading frame (or "out-of-frame" mutations) lead to translation termination and DMD. In contrast, those that maintain an open reading frame (or "in-frame" mutations) lead to BMD, via translation of an internally truncated protein that still has domains critical to binding F-actin and β-dystroglycan. This reading frame rule is generally accurate, being 90% specific in DMD cases,[5] and it is important for the pediatrician ordering and interpreting genetic tests to be familiar with it, but as discussed later exceptions to the rule occur. Nevertheless, restoration of an open reading frame is a key goal of new molecular therapies now in clinical trials.

CLINICAL FEATURES

Duchenne Muscular Dystrophy

Typically, parents of boys with DMD seek attention when their boys are between ages 2 and 5 years old. They frequently describe altered gait, often with toe walking that leads to a referral to a physical therapist or orthopedic surgeon even before a serum CK is tested. Parents frequently describe a diagnostic odyssey, with diagnosis taking more than a year from presentation,[6] but serum CK elevations that are typically 50 to 100 times the normal levels lead quickly to a diagnosis of muscular dystrophy. Gait