R.C.P.U. NEWSLETTER

R.C. Philips Research and Education Unit

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A statewide commitment to the problems of intellectual disability **December 2022**

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Duchenne Muscular Dystrophy

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Introduction

Duchenne muscular dystrophy (DMD) is a severe neuromuscular disorder charactered by progressive weakness and loss of muscle resulting from the absence of the dystrophin protein. It is the most prevalent neuromuscular disorder, with an incidence of 10.72-28.78/100,000 male births worldwide. A number of cognitive disabilities have been seen in males with DMD, such as intellectual disability (20-30%), learning disability (44%), ADHD (32%), autism spectrum disorder (15%), and anxiety (27%), although the degree of severity of these impairments is widely variable. Boys without intellectual disability may show deficits in overall executive function, such as in multitasking, problem solving, and inhibition, and working memory in verbal and visuospatial domains. Currently, there is no cure for DMD, but proper management and treatment may improve overall prognosis and quality of life. Average life expectancy is close to 30 years of age.

Clinical Features

Motor Development

Individuals usually show delays in motor milestones, such as walking (mean age 18 months) and standing. When walking, children may display toe walking and flat-footedness, waddling gain, and trouble climbing stairs, running, jumping, and standing up. Children may use the Gower maneuver when rising from a supine position. As calf muscles begin to waste, deposition of fat and connective tissue leads to muscle hypertrophy. Boys are usually wheelchair bound by 12 years of age. This age for wheelchair dependency differentiates Duchenne muscular dystrophy from the milder Becker muscular dystrophy, in which males are usually still walking independently after 16 years of age. Motor dysfunction may be further compromised by the development of scoliosis.

Cardiac

Dilated cardiomyopathy with congestive heart failure, usually presenting between 20-40 years of life. This may present in females later in life. The progressive decline of cardiac and respiratory function are major causes of death.

While female carriers were originally thought to be asymptomatic, females are now recognized to present with muscle weakness (19%), myalgia (5%) left ventricle dilation (19%), and cardiac dilated cardiomyopathy (8%).

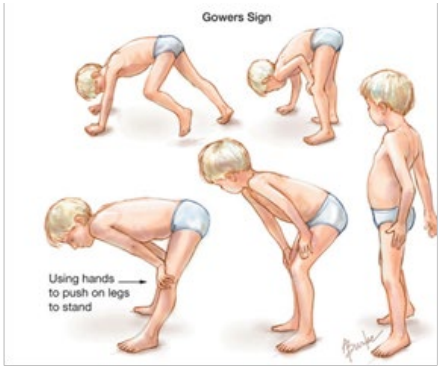

Image: https://www.viquepedia.com/archive/Duchenne-muscular-dystrophy

Molecular Etiology Duchenne muscular dystrophy is caused by a pathogenic variant in the *DMD* gene. The *DMD* gene encodes for dystrophin, a membrane bound protein present in muscle cells. The N-terminal domain binds to actin and the C-terminal domain binds to other membrane proteins. Therefore, dystrophin acts as part of a protein complex that links the cytoskeleton to the extracellular matrix. Pathogenic variants in *DMD* eliminate dystrophin expression, leading to muscle breakdown.

Pathogenic variants in *DMD* that lead to a lack of protein expression include deletions (65%), duplications (6-10%), missense, nonsense, splice site mutations, and small nucleotide insertions or deletions (25%) that disrupt the reading frame.

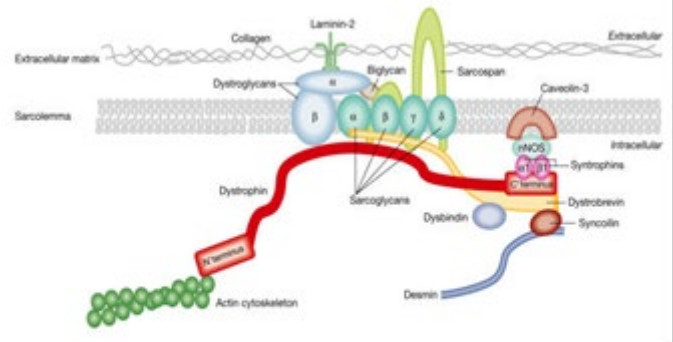

Image: https://doi.org/10.1038/sj.emboj.7600221

Diagnosis

Individuals are diagnosed based on the clinical findings of progressive symmetric muscle weakness and symptoms before age 5 years, wheelchair dependency by age 13 years, and a serum creatine phosphokinase (CK) concentration greater than 10 times the normal concentration. Identification of a hemizygous (males) or heterozygous (females) pathogenic variant in *DMD* can confirm the diagnosis.

Genetic Testing

The majority of *DMD* pathogenic variants involve deletions of one or more exons. Therefore, deletion/duplication analysis of *DMD* is the first line of testing before sequence analysis. Multigene panels for muscular dystrophies are appropriate when symptoms are non-specific. Sequence analysis detects 20-25% of pathogenic variants in people with DMD, while deletion/duplication analysis detects 65-80% of variants.

The first line of testing for individuals with autism and intellectual disability is Fragile X testing along with a chromosome microarray, which may detect deletions/duplications in the *DMD* gene.

Genotype-Phenotype Correlations

The lack of the dystrophin isoform Dp140 is associated with greater intellectual impairments. Dp140 is expressed in the brain, kidney, and retina, with the promoter region just upstream to exon 45. Individuals with deletions in exons 45-52 have increased incidence of cognitive impairment, most likely resulting from Dp140 lack of expression. Most males with pathogenic variants involving Dp71, where the promoter is just upstream to exon 63, are cognitively disabled.

Genetic Counseling

DMD is an X linked disorder. Women who are carriers have a:

•25% chance of having a daughter who is a carrier
•25% chance to have daughter who is unaffected
•25% chance to have a son that is affected
•25% chance to have a son that is unaffected

Affected men will always have a daughter who is a carrier, and never an affected son.

If a *DMD* pathogenic variant identified in a child is not identified in either parent, this could result from either a *de novo* variant that was not inherited from either parent, or germline mosaicism in the mother. The rate of germline mosaicism for DMD is 15-20%. About 2/3 of mothers of affected males with no family history of DMD are carriers.

Treatment and Management

Individuals with DMD should be enrolled in physical therapy and receive developmental evaluation to evaluate if an individualized educational plan is needed.

Treatments include:

Concern		Treatment
Cardiac	Cardiomyopathy	Ace Inhibitors with or without beta blockers
	Congestive Heart Failure	Diuretics and oxygen
Scoliosis		Bracing and surgery
Muscle		Corticosteroid therapy after 4 years of age

Gene Therapies

Exon skipping therapy is a treatment with the goal to restore the reading frame in *DMD* with the hope to increase dystrophin expression. While exon skipping still leads to a truncated protein, this is thought to still improve clinical symptoms and reduce the severe DMD phenotype to a milder phenotype comparable to Becker muscular dystrophy. Exon skipping utilizes a synthetic antisense oglionucelotide (ASO) to target dystrophin pre-mRNA to skip out-of-frame variants. Four exon skipping therapies currently exist, including Exondys 51 (eteplirsen), Vyondys 53 (golodirsen), Amondys 45 (casimersen), and Viltepso 53 (viltolarsen). As 70% of pathogenic variants in *DMD* are located between exons 45 and 55, exon skipping therapies focus on this region of the gene.

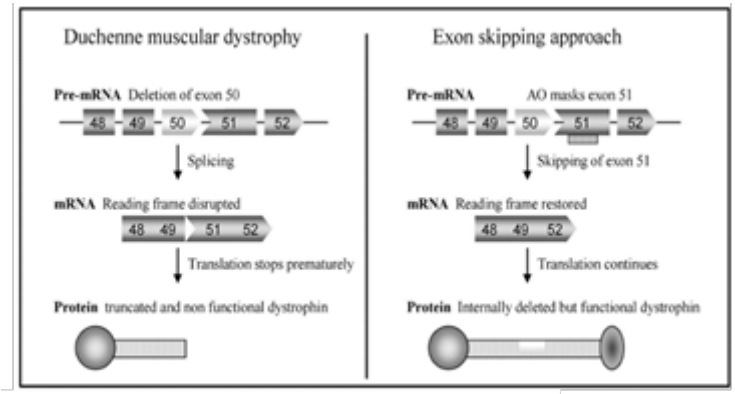

Image: https://doi.org/10.1186/2044-5040-1-8

Agents to Avoid

People with DMD should **not** receive succinylcholine (suxamethonium) as a depolarizing muscle relaxant, as this can cause severe, life threatening or fatal increases in blood potassium in people with muscular atrophy. Inhaled anesthetic agents should be avoided to prevent rhabdomyolysis. Safe anesthetics and medications are listed on the Parent Project Muscular Dystrophy website.

Patient Support Resources

- Muscular Dystrophy Association: https://www.mda.org/
- Parent Project Muscular Dystrophy: https://www.parentprojectmd.org/
- Cure Duchenne: https://www.cureduchenne.org/

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About the RCPU:

The Raymond C. Philips Research and Education Unit began in 1978 when the legislature established section 393.20, F.S., of what is now known as the "prevention" legislation. It is named after Raymond C. Philips, who was the Superintendent of Gainesville's Tacachale (formerly Sunland) Center for 38 years, and was an acknowledged state and national leader in services for mentally retarded persons. The Unit is located on the Tacachale campus and is funded through a contract with the Department of Children and Families and the Department of Health.

The purpose of the R.C.P.U. is to treat, prevent, and/or ameliorate disorders of intellectual disability through medical evaluations, education and research. The unit provides direct evaluations and counseling to families and promotes service, education, and prevention projects. Some of the conditions currently under study at the RCPU involve Angelman, Velo-Cardio-Facial, Prader-Willi, Fragile X, Williams and Smith-Lemli-Opitz syndromes.

The R.C. Philips Unit is a resource for all Floridians interested in the diagnosis, treatment and prevention of mental retardation. Staff members are available for consultation and for educational programs for health.

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