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Dystrophinopathies

[Includes: Duchenne Muscular Dystrophy (DMD), Pseudohypertrophic Muscular Dystrophy), Becker Muscular Dystrophy (BMD), and X-Linked Dilated Cardiomyopathy (XLDCM)]

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Summary

Disease characteristics. The dystrophinopathies are characterized by a spectrum of muscle disease that ranges from mild to severe. The mild end of the spectrum includes the phenotypes of asymptomatic increase in serum concentration of creatine phosphokinase (CK); muscle cramps with myoglobinuria and isolated quadriceps myopathy. The severe end of the spectrum includes progressive muscle diseases that are classified as Duchenne/Becker muscular dystrophy when skeletal muscle is primarily affected and as X-linked dilated cardiomyopathy when the heart is primarily affected. Duchenne muscular dystrophy usually presents in early childhood with delayed milestones, including delays in sitting and standing independently. Proximal weakness causes a waddling gait and difficulty climbing. DMD is rapidly progressive, with affected children being wheelchair-bound by age 12 years. Cardiomyopathy occurs in all patients after age 18. Few survive beyond the third decade, with respiratory complications and cardiomyopathy being common causes of death. Becker muscular dystrophy is characterized by later-onset skeletal muscle weakness; patients remain ambulatory into their 20s. Despite the milder skeletal muscle involvement, heart failure from dilated cardiomyopathy (DCM) is a common cause of morbidity and the most common cause of death. Mean age of death is in the mid-40s. X-linked dilated cardiomyopathy is characterized by left ventricular dilation and congestive heart failure. Carrier females are at increased risk for dilated cardiomyopathy.

Diagnosis/testing. In approximately 70% of males with DMD and 85% of males with BMD, the presence of deletions or duplications involving one or more exons of the dystrophin (*DMD*) gene (chromosomal locus Xp21.3-p21.2) confirms the diagnosis of dystrophinopathy without muscle biopsy. Such testing is available in clinical laboratories. Small insertions, deletions, and point mutations in the *DMD* gene account for the remainder of disease-causing mutations in DMD and BMD and presumably a significant proportion of patients with XLDCM. Such testing is available in research laboratories only. In these patients, a combination of clinical findings, family history, serum CK concentration, and muscle biopsy with dystrophin studies confirms the diagnosis.

Genetic counseling. The dystrophinopathies are inherited in an X-linked recessive manner. The risk to the sibs of a proband depends upon the carrier status of the mother. Carrier females have 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. Males with DMD do not reproduce. Males with BMD and XLDCM may reproduce. All their daughters are carriers; none of the sons will inherit their father's *DMD* mutation. Prenatal testing for pregnancies at risk is possible if the *DMD* disease-causing mutation has been identified in a family member or if informative linked markers have been identified.

Diagnosis

The dystrophinopathies include a spectrum of muscle disease caused by mutations in the gene, *DMD*, that encodes the protein dystrophin. Molecular genetic testing of the *DMD* gene (chromosomal locus Xp21.3-p21.2) is available clinically and can establish the diagnosis of a dystrophinopathy without muscle biopsy in the majority of cases of Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD). In the remaining cases of DMD, BMD, and X-linked dilated cardiomyopathy (XLDCM), a combination of clinical findings, family history, serum CK concentration, and muscle biopsy with dystrophin studies confirms the diagnosis.

Clinical Diagnosis

In addition to a positive family history compatible with X-linked recessive inheritance, the clinical findings that support the diagnosis of Duchenne muscular dystrophy, Becker muscular dystrophy, and X-linked dilated cardiomyopathy in males are:

Duchenne Muscular Dystrophy (DMD)

- Progressive symmetrical muscular weakness, proximal greater than distal, often with calf hypertrophy
- Symptoms present before five years of age
- Wheelchair dependency before 13 years of age

Becker Muscular Dystrophy (BMD)

- Progressive symmetrical muscle weakness and atrophy, proximal greater than distal, often with calf hypertrophy; weakness of quadriceps femoris may be the only sign.
- Activity-induced cramping in some patients
- Flexion contractures of the elbows may occur late in the course.
- Wheelchair dependency, if present, after 16 years of age
- Preservation of neck flexor muscle strength in BMD differentiates it from DMD.

Note: The presence of fasciculations or loss of sensory modalities excludes the diagnosis of a dystrophinopathy.

X-Linked Dilated Cardiomyopathy (XLDCM)

- Dilated cardiomyopathy (DCM) with congestive heart failure, with males typically presenting at age 20 to 40 years and females presenting later in life
- Usually no clinical evidence of skeletal muscle disease; may be classified as "subclinical" BMD [Angelini et al 1994]
- Rapid progression to death in several years in males and slower progression over a decade or more in females [Beggs 1997]

Testing

Serum Creatine Phosphokinase (CK) Concentration

Table 1. Serum Creatine Phosphokinase (CK) Concentration in the Dystrophinopathies

Males	% of Patients	Serum CK Concentration
DMD	100% ¹	> 10 X normal
BMD	100% ¹	> 5 X normal
XLDCM	Most patients ²	"increased"
Female Carriers		
DMD	~ 50% ^{3,4}	2-10 X normal
BMD	~ 30% ^{3,4}	2-10 X normal

1. It is known that serum CK concentration gradually decreases with advancing age due to the progressive elimination of dystrophic muscle fibers that are the source of the elevated serum CK concentration [Hoffman et al 1988, Zatz et al 1991].

2. CK levels are usually increased, but normal levels have been reported in XLDCM [Mestroni et al 1999].

3. [Hoogerwaard, van der Wouw et al 1999]

4. Other investigations have confirmed a wide variability in serum CK concentration among DMD/BMD carriers with the mean serum CK concentration significantly increased in carriers younger than 20 years compared with those older than 20 years [Sumita et al 1998].

Electromyography (EMG) EMG is useful in distinguishing a myopathic process from a neurogenic disorder. This is done by demonstrating short-duration, low-amplitude, polyphasic, rapidly recruited motor unit potentials; as the disease progresses, the interference pattern becomes incomplete due to reduced recruitment and eventually the muscle becomes electrically silent. However, these findings are non-specific, occurring in all myogenic disorders.

Skeletal Muscle Biopsy

Histology. Muscle histology early in the disease shows non-specific dystrophic changes, including variation in fiber size, foci of necrosis and regeneration, hyalinization, and, later in the disease, deposition of fat and connective tissue.

Western blot and immunohistochemistry are summarized in Table 2.

Table 2. Findings in the Dystrophin Protein from Skeletal Muscle Biopsy

Males	Western Blot		Immunohistochemistry ¹
	Dystrophin Molecular Weight ²	Dystrophin Quantity ³	
DMD	Non-detectable	0-3%	Complete/almost complete absence
Intermediate		3-20%	
BMD	Abnormal	> 20%	Normal appearing or reduced intensity ± patchy staining
Female Carriers			
DMD			Mosaic pattern [Arahata et al 1989]

1. Uses monoclonal antibodies to the C-terminus, N-terminus, and rod domain of dystrophin [Hoffman et al 1988]

2. Normal molecular mass is 427 kb.

3. The quantity of dystrophin is expressed in % of control values.

Cytogenetic Analysis

Males. In rare instances boys with DMD are found to have other X-linked disorders including retinitis pigmentosa, chronic granulomatous disease, and McLeod red cell phenotype [Francke et al 1985] or glycerol kinase deficiency and adrenal hypoplasia [Dunger et al 1986] as part of contiguous gene deletion syndromes. Such boys warrant high-resolution chromosome studies.

Females. Girls with classical DMD may have an X chromosome rearrangement or deletion involving Xp21, or complete absence of an X chromosome (i.e., Turner syndrome), or complete uniparental disomy of the X chromosome. Girls with findings of typical DMD warrant high-resolution chromosome studies.

Molecular Genetic Testing

Males and females with classical DMD. Approximately 70% of males with DMD and 85% of males with BMD have deletions or duplications involving one or more exons of the *DMD* gene (chromosomal locus Xp21.3-p21.2) [Den Dunnen et al 1989].

- **Deletions** are detected in DNA from affected males by hybridization of cDNA probes to Southern blots of restriction enzyme-digested DNA [Koenig et al 1987]. PCR analysis greatly simplifies the testing and allows testing to be done rapidly at low cost [Multicenter Study Group 1992]. Multiple primer sets can be used to simultaneously amplify several exons in the same reaction (multiplex PCR) and determine the presence or absence of an exon by separating the PCR products by agarose gel electrophoresis and staining the DNA in the gel [Chamberlain et al 1988, Beggs et al 1990]. Examination of 18 exons in this way detects up to 98% of the deletions identifiable by cDNA hybridization [Beggs et al 1990].
- **Duplications** may lead to in-frame or out-of-frame transcripts and account for the disease-causing mutations in about 6% of males with DMD [Hu et al 1990].
- **Other mutations** including small deletions or insertions, single base changes, or splicing mutations account for the remaining 34% of patients with DMD or BMD [Gardner et al 1995, Prior et al 1995]. Currently, analysis of nondeletion mutations is available on a research basis only.

Table 3. Molecular Genetic Testing Used in the Diagnosis of the Dystrophinopathies

% of Males with DMD	% of Males with BMD	% of Males with XLDCM	Genetic Mechanism	Test Type	Test Availability
~65%	~85%	?	Deletion of one or more exons of <i>DMD</i> gene	PCR or Southern blotting	Clinical ¹
~6%	?	?	Duplication of one or more exons of <i>DMD</i> gene	Southern blotting or quantitative PCR	GENETests
~30%	?	?	Small insertions/deletions/point mutations/splicing mutations of <i>DMD</i> gene	Various	Research

1. For DMD/BMD only

Carrier females.

- **Proband's DMD mutation is known.** Carrier testing may be performed using molecular diagnosis. Analysis of deletions and duplications in females, however, requires quantitative analysis for gene dosage, which may be difficult to perform and interpret [[Prior et al 1990](#), [Abbs and Bobrow 1993](#)].
- **Proband's DMD mutation is not known.** Linkage analysis can be offered to at-risk females to determine carrier status in families with more than one affected male with the unequivocal diagnosis of DMD/BMD/XLDCM. Linkage studies are based upon accurate clinical diagnosis of DMD/BMD/XLDCM in the affected family members and accurate understanding of the genetic relationships in the family. Linkage analysis is dependent on the availability and willingness of family members to be tested. The markers used for linkage in DMD/BMD/XLDCM are highly polymorphic, informative, and both within and flanking the *DMD* locus; thus, they can be used in most families with DMD/BMD/XLDCM [[Darras, Harper et al 1987](#)]. However, the large size of the *DMD* gene leads to an appreciable risk of recombination. It has been estimated that the gene itself spans a genetic distance of 12 centimorgans [[Abbs et al 1990](#)]. Multiple recombination events among different members of a family therefore may complicate the interpretation of a linkage study. Linkage testing is not available to families in which there is a single affected male.

Testing Strategy for Patients Suspected of Having a Dystrophinopathy

For patients with clinical findings suggesting a dystrophinopathy and an elevated serum CK concentration, the first step in diagnosis is molecular genetic testing of the *DMD* gene.

- If a disease-causing mutation is identified, the diagnosis is established; evaluation of muscle tissue in this instance may be considered to help distinguish between the DMD and BMD phenotypes in younger patients with a negative family history.
- If no *DMD* disease-causing mutation is identified, skeletal muscle biopsy of patients with suspected DMD or BMD is warranted for western blot and immunohistochemistry studies of dystrophin.

Genetically Related Disorders

No other phenotypes are associated with mutations in the *DMD* gene.

Clinical Description

Males

The dystrophinopathies cover a spectrum of muscle disease that ranges from mild to severe. The mild end of the spectrum includes the phenotypes of asymptomatic increase in serum concentration of CK, muscle cramps with myoglobinuria, and isolated quadriceps myopathy. The severe end of the spectrum includes progressive muscle diseases that are classified as Duchenne/Becker muscular dystrophy when skeletal muscle is primarily affected and as X-linked dilated cardiomyopathy (XLDCM) when the heart is primarily affected [[Beggs 1997](#), [Cox and Kunkel 1997](#)].

The distinction between Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) is based on the age of wheelchair dependency, which is less than 13 years in DMD and greater than 16 years in BMD. An intermediate group of patients who become wheelchair bound between 13 years and 16 years is also recognized. Additionally, some investigators have extended the mild end of the BMD spectrum to include patients with elevated serum CK concentration and abnormal dystrophin on muscle biopsy, but with "subclinical" skeletal muscle involvement [[Angelini et al 1994](#), [Melacini et al 1996](#)]. When these patients with atypical disease develop severe cardiomyopathy, it is not possible to distinguish between BMD and XLDCM [[Cox and Kunkel 1997](#)]. Dilated cardiomyopathy (DCM) generally presents with congestive heart failure secondary to an increase in ventricular size and impairment of ventricular function. Individuals with DCM may or may not have clinical evidence of skeletal muscle disease.

DMD usually presents in early childhood with delayed milestones, including delays in sitting and standing independently. The mean age of walking is about 18 months (range 12-24 months). The first symptoms of DMD as identified by parents are typically: general motor delays (42%), gait problems, including persistent toe-walking and flat-footedness (30%), delay in walking (20%), learning difficulties (5%), and speech problems (3%) [[Marshall and Galasko 1995](#)]. The mean age of diagnosis of boys with DMD without a family history of DMD is about four years 10 months, with a range of 16 months to eight years [[Bushby et al 1999](#), [Zalaudek et al 1999](#)]. Proximal weakness causes a waddling gait and difficulty climbing. Boys use the Gower maneuver to rise from a supine position, using the arms to supplement weak pelvic girdle muscles. The calf muscles are hypertrophic and firm to palpation. Occasionally there is calf pain. DMD is rapidly progressive, with affected children being wheelchair-bound by age 12 years.

Among children with DMD, the incidence of cardiomyopathy increases steadily in the teenage years, with approximately 1/3 of patients being affected by age 14 years, 1/2 by age 18, and all patients after age 18 [[Nigro et al 1990](#)]. Few survive beyond the third decade, with respiratory complications and cardiomyopathy being common causes of death.

Some degree of nonprogressive cognitive impairment is common in children with DMD [[Liebowitz and Dubowitz 1981](#), [Bresolin et al 1994](#), [Moizard et al 1998](#)] and affects the verbal ability more than nonverbal performance (i.e., verbal IQ < performance IQ on tests such as WISC-III).

BMD is characterized by later-onset skeletal muscle weakness; patients remain ambulatory into their 20s. Despite the milder skeletal muscle involvement, heart failure from DCM is a common cause of morbidity and the most common cause of death [[Cox and Kunkel 1997](#)]. Mean age of death is in the mid-40s [[Bushby and Gardner-Medwin 1993](#), [Bushby 1999](#)]. With improved diagnostic techniques it has been recognized that the mild end of the spectrum includes men with onset of symptoms after age 30 years who remain ambulatory even into their 60s [[Heald et al 1994](#), [Quinlivan et al 1995](#), [Yazaki et al 1999](#)].

Mildly affected patients with confirmatory *DMD* molecular genetic studies and/or dystrophin studies on muscle biopsy have been classified as having either: 1) BMD with "subclinical" skeletal muscle involvement in the presence of elevated serum CK concentration, calf hypertrophy, muscle cramps, myalgia, and exertional myoglobinuria or 2) "benign" skeletal muscle involvement when "subclinical" findings are accompanied by muscle weakness in the pelvic girdle and/or shoulder girdle [[Angelini et al 1994](#), [Melacini et al 1996](#)].

Cognitive impairment is not as common or as severe as in DMD.

XLDCM. In 1987 a five-generation, 63-member family was reported who had dilated cardiomyopathy, but no evidence of skeletal myopathy [Berko and Swift 1987]. Males present in their teens and twenties, the disease course is rapidly progressive, and associated ventricular arrhythmias are common. Female carriers develop mild cardiomyopathy in the fourth or fifth decade with slow progression. The only biochemical abnormality is an elevation in CK. Towbin et al. (1993) demonstrated linkage of XLDCM to the dystrophin locus at Xp21 in this family and one other. Subsequent work has demonstrated that in patients with the most severe cardiac phenotype, the cardiac muscle is usually unable to produce dystrophin, while skeletal muscle is unaffected [Ferlini et al 1999].

XLDCM may be the presenting finding in individuals with BMD who have little or no clinical evidence of skeletal muscle disease. Some investigators classify such patients as subclinical or benign BMD [Melacini et al 1996], whereas others may classify such patients having DCM with increased serum CK activity [Towbin 1998]. In one study of 28 patients with subclinical and benign BMD ranging in age from six to 48 years, 19 (68%) had myocardial involvement, although only two were symptomatic [Melacini et al 1996]. In another study of 21 patients ranging in age from three to 63 years (mean age 40 years), 33% had cardiac failure despite relatively mild skeletal muscle findings [Saito et al 1996].

Females

Occasionally, females have clinical features of DMD as the result of X chromosome rearrangements involving the DMD locus (Xp21.3-21.2). In other instances, females who have a disease-causing DMD mutation have DMD because of Turner syndrome (i.e., complete or partial absence of an X chromosome), or nonrandom X chromosome inactivation [Bodgug et al 1987, Richards et al 1990]. Recent studies have shown no clear correlation between X-inactivation ratios in leukocytes with serum CK activity, clinical signs, or the proportion of dystrophin-negative fibers observed on muscle biopsy [Sumita et al 1998].

Signs and symptoms of DMD and BMD were studied among confirmed carriers [Hoogerwaard, van der Wouw et al 1999, Hoogerwaard, Bakker et al 1999] (Table 4).

Table 4: Signs and Symptoms in Carrier of Duchenne and Becker Muscular Dystrophy

	DMD Carriers	BMD Carriers
No symptoms/signs	76%	81%
Muscle weakness ¹	19%	14%
Myalgia/cramps	5%	5%
Left ventricle dilation	19%	16%
Dilated cardiomyopathy	8%	0

From Hoogerwaard, van der Wouw et al 1999

1. Mild to moderate weakness

Genotype-Phenotype Correlations

In males with DMD and BMD, phenotypes are best correlated with the degree of expression of dystrophin, which is largely determined by the reading frame of the spliced message obtained from the deleted allele [Monaco et al 1988, Koenig et al 1989].

DMD. Very large deletions may lead to absence of dystrophin expression. Mutations that disrupt the reading frame include stop mutations, some splicing mutations, and deletions or duplications; they produce a severely truncated dystrophin protein molecule that is degraded, leading to the more severe DMD phenotype. Exceptions to this "reading frame hypothesis," are deletions in protein-binding domains that may severely affect function even if in-frame [Hoffman et al 1991], and exon-skipping events in which apparently out-of-frame deletions behave as in-frame deletions or vice versa [Chelly et al 1990]. Data suggest that dystrophin deletions involving the brain distal isoform Dp140 are associated with intellectual impairment [Felisari et al 2000].

BMD. The BMD phenotype occurs when there is some dystrophin, usually resulting from deletions or duplications that juxtapose "in-frame" exons, some splicing mutations, and most non-truncating single base changes that result in translation of a protein product with intact N and C termini. The shorter than normal dystrophin protein molecule, which retains partial function, produces the milder BMD phenotype.

XLDCM. X-linked cardiomyopathy (XLDCM) is caused by mutations in the DMD gene that affect the muscle promoter (P_M) and the first exon (E1), resulting in no dystrophin transcripts being produced in cardiac muscle; however, two alternative promoters that are normally only active in the brain (P_B) and Purkinje cells (P_P) are active in the skeletal muscle, resulting in sufficient dystrophin expression to avoid skeletal muscle symptoms [Beggs 1997, Towbin 1998, Yoshida et al 1998]. XLDCM may also be caused by alteration of epitopes in a region of the protein of particular functional importance to cardiac muscle [Ortiz-Lopez et al 1997] or possibly by mutations in hypothetical cardiac-specific exons.

Prevalence

The birth incidence in northern England of DMD is one in 5,618 live male births, and that of BMD is one in 18,450 live male births [Bushby et al 1991].

Differential Diagnosis

Limb-girdle muscular dystrophy is a group of disorders that is clinically similar to DMD, but occurs in both sexes due to autosomal recessive and autosomal dominant inheritance. Limb-girdle dystrophies are caused by mutations in genes that encode sarcoglycans and other proteins associated with the muscle cell membrane that interact with dystrophin [Bushby 1999]. Testing for deficiency of proteins from the transmembrane sarcoglycans complex is indicated in patients with dystrophin-positive dystrophies.

Emery-Dreifuss muscular dystrophy is associated with limb contractures and cardiac arrhythmia. There are X-linked recessive and autosomal dominant forms [Zacharias et al 1999]. Autosomal recessive forms also exist [Rafaele Di Barletta et al 2000] due to mutations in the LMNA gene. For laboratory testing information on Emery-Dreifuss muscular dystrophy, see [GENETests](#).

Spinal muscular atrophy. The diagnosis of SMA is suspected in individuals with poor muscle tone, symmetric muscle weakness that spares the face and ocular muscles, and evidence of anterior horn cell involvement, including fasciculations of the tongue and absence of deep tendon reflexes. SMA is caused by mutations in the SMN gene (chromosomal locus 5q11-q13). Molecular genetic testing is clinically available and is used to confirm the diagnosis of SMA and to provide genetic counseling to at-risk family members.

Dilated cardiomyopathy can be sporadic or familial. In a large series in which family studies were performed, 1/3 of patients had sporadic DCM and 2/3 had familial DCM. Causes of familial DCM included: autosomal dominant (56%), autosomal recessive (16%), X-linked recessive with DMD mutation (10%), autosomal dominant with subclinical muscle disease (7.7%), DCM with conduction defects (2.6%), and unclassified (7.7%) [Mestroni et al 1999]. For laboratory testing information on familial dilated cardiomyopathy, see [GENETests](#).

The spectrum of X-linked infantile dilated cardiomyopathies caused by mutations in the *G4-5* gene (chromosomal locus Xq28) includes Barth syndrome, X-linked endocardial fibroelastosis, left ventricular non-compaction, and severe X-linked cardiomyopathy [D'Adamo et al 1997]. For laboratory testing information on Barth syndrome, see [GENETests](#).

Management

Males with DMD/BMD. No definitive treatment exists for Duchenne or Becker muscular dystrophy. Appropriate management can prolong survival and improve quality of life. Major issues are:

- Weight control to avoid obesity
- Physical therapy to promote mobility and prevent contractures
- Monitoring and surgical intervention, as needed, for orthopedic complications, especially scoliosis.
- Routine monitoring for evidence of cardiomyopathy, particularly for individuals with BMD who have relatively mild skeletal muscle involvement. Aggressive medical management with anti-congestive medications.

Prednisone therapy in DMD is controversial. Some authors have reported improvement in strength and function in patients given a single dose of 0.75 mg/kg/day [Griggs et al 1993]. Improvement begins within ten days and plateaus after three months. Long-term benefit has not been demonstrated.

Myoblast transfer is under investigation but remains experimental [Cussoni et al 1997].

Females. A complete cardiac evaluation is recommended at least once in all carriers [Hoogerwaard, Bakker et al 1999]. If left ventricular dilatation or DCM is present, close follow-up is warranted.

XLDCM. Symptomatic management with anti-congestive medications as needed. Cardiac transplantation has been utilized in severe cases.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal or cultural issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see [GENETests](#). —ED.

Mode of Inheritance

The dystrophinopathies are inherited in an X-linked recessive manner.

Risk to Family Members

Parents of a proband.

- A woman who has an affected son and one other affected relative in the maternal line is an obligate heterozygote.
- A woman with more than one affected son and no other family history of a dystrophinopathy can have: 1) a germline mutation (i.e., a *DMD* disease-causing mutation present in each of her cells); or 2) germline mosaicism (i.e., mosaicism for a *DMD* disease-causing mutation which includes her germline) [Darras and Francke 1987].
- If pedigree analysis reveals that the proband is the only affected family member, the question that must be resolved is whether the mother and other females in her family are carriers of a disease-causing *DMD* gene mutation. Possible genetic mechanisms [Van Essen et al 1997] are:
 - The proband has a *de novo DMD* -disease-causing gene mutation. Possible mechanisms are:
 - The mutation occurred in the egg at the time of the proband's conception and, therefore, is present in every cell of the proband's body. In this instance, the proband's mother does not have a *DMD* disease-causing gene mutation and no other family member is at risk.
 - The mutation occurred after conception and therefore is present in some, but not all, cells of the proband's body (somatic mosaicism). In this instance the likelihood that the mother is a heterozygote is low.
 - The proband's mother has a *de novo DMD* disease-causing gene mutation. Approximately 2/3 of mothers of sporadically occurring males with *DMD* are carriers. The mechanisms by which a *de novo DMD* disease-causing gene mutation could have occurred in the mother are:
 - The mutation occurred in the egg or sperm at the time of her conception (germline mutation), and therefore is present in every cell of her body and is detectable in white blood cells.
 - The mutation is present in some, but not all cells of her body (somatic mosaicism), and may or may not be detectable in white blood cells.
 - The mutation is present only in her egg cells (termed "germline mosaicism") and is not detectable in a blood sample. In all instances, each of her offspring has a risk of inheriting the *DMD* disease-causing gene mutation [Darras and Francke 1987].
 - The proband's mother has inherited a *DMD* mutation from:
 - Her mother who is a carrier;
 - Her mother or her father who has somatic mosaicism; or
 - Her mother or her father who has a germline mosaicism.

Sibs of a proband. The risk to sibs of a proband depends upon the carrier status of the mother. Carrier females have 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 child.

Offspring of a proband. Males with *DMD* usually die before reproductive age or are too debilitated to reproduce. Males with *BMD* and *XLDCM* may reproduce. All the daughters are carriers. None of the sons will inherit their father's *DMD* mutation.

Carrier testing. Carrier testing is clinically available for at-risk females. See Molecular Genetic Testing, [carrier females](#).

Related Genetic Counseling Issues

- Females who are identified as carriers of a *DMD* disease-causing mutation need to be advised of their risk for dilated cardiomyopathy and the recommended surveillance.
- Because both *BMD* and *XLDCM* have been observed in some families [Palmucci et al 2000], the spectrum of possible muscle disease should be considered when obtaining a family history.

Prenatal Testing

Prenatal testing for pregnancies at increased risk is available. The usual procedure is to karyotype fetal cells obtained by chorionic villus sampling (CVS) at about 10-12 weeks gestation or amniocentesis at 16-18 weeks' gestation for sex determination. If the fetus is 46, XY and if the *DMD* disease-causing mutation has been identified in a family member, DNA from fetal cells can be analyzed for the known *DMD* disease-causing mutation. Linkage analysis may be considered in families in which the *DMD* disease-causing mutation has not been identified and in which informative linked markers have been identified.

Molecular Genetics

Table 5. Molecular Genetics of the Dystrophinopathies

Gene Symbol	Locus	Normal Gene Product	Genomic Databases
<i>DMD</i>	Xp21.3-p21.2	Dystrophin	OMIM HGMD LocusLink DMD

The Dystrophinopathies

- **Gene:** [DMD](#)
- **Pathologic allelic variants:** Disease-causing alleles are highly variable, including deletion of the entire gene, deletion or duplication of one or more exons, and small deletions, insertions, or single base changes. In both DMD and BMD, partial deletions and duplications cluster in two recombination hot spots, one proximal at the 5' end of the gene, comprising exons 2-20 (30%), and one more distal, comprising exons 44-53 (70%) [[Den Dunnen et al 1989](#)].
- **Abnormal product:** Mutations that lead to lack of dystrophin expression tend to cause DMD, whereas those that lead to abnormal quality or quantity of dystrophin lead to BMD.

Gene Involved: ***DMD***

- **Locus:** Xp21.3-p21.2
- **Normal allelic variants:** The dystrophin gene spans 2.4 mb of DNA and is comprised of 79 exons. It has at least four promoters. It is the largest known human gene. Innumerable intragenic variants have been described, many of which are useful as markers for genetic linkage analysis.
- **Normal product:** Dystrophin is a membrane-associated protein present in muscle cells and some neurons [[Ahn and Kunkel 1993](#)]. The N-terminal domain binds to actin. There is a large rod domain including 24 homologous repeats forming an α -helical structure, a cysteine-rich calcium-binding region near the C-terminus, and a C-terminal domain that binds with other membrane proteins. Dystrophin is therefore part of a protein complex that links the cytoskeleton with membrane proteins that in turn bind with proteins in the extracellular matrix.

Resources

GeneClinics provides information about selected national organizations and resources for the benefit of the reader. GeneClinics is not responsible for information provided by other organizations. —ED.

- **Muscular Dystrophy Association**
3300 East Sunrise Drive
Tucson, AZ 85718-3208
Phone: 520-529-2000; 800-572-1717
Fax: 520-529-5300
Email: mda@mdausa.org
www.mdausa.org
- **Muscular Dystrophy Campaign**
7-11 Prescott Place
London, SW4-6BS
Phone: +44 (0) 020 7720 8055
Fax: +44 (0) 020 7498 0670
Email: info@muscular-dystrophy.org
www.muscular-dystrophy.org
- **NCBI Genes and Disease Webpage**
www.ncbi.nlm.nih.gov/disease/DMD.html

References

Articles on The Dystrophinopathies [MEDLINE](#)

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