



Dystrophinopathies

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Created: September 5, 2000; Revised: January 20, 2022.

Summary

Clinical characteristics

The dystrophinopathies cover a spectrum of X-linked muscle disease ranging from mild to severe that includes Duchenne muscular dystrophy, Becker muscular dystrophy, and *DMD*-associated dilated cardiomyopathy (DCM). The mild end of the spectrum includes the phenotypes of asymptomatic increase in serum concentration of creatine phosphokinase (CK) and muscle cramps with myoglobinuria. 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 *DMD*-associated DCM when the heart is primarily affected.

Duchenne muscular dystrophy (DMD) usually presents in early childhood with delayed motor milestones including delays in walking independently and standing up from a supine position. Proximal weakness causes a waddling gait and difficulty climbing stairs, running, jumping, and standing up from a squatting position. DMD is rapidly progressive, with affected children being wheelchair dependent by age 12 years. Cardiomyopathy occurs in almost all individuals with DMD after age 18 years. Few survive beyond the third decade, with respiratory complications and progressive cardiomyopathy being common causes of death.

Becker muscular dystrophy (BMD) is characterized by later-onset skeletal muscle weakness. 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. Despite the milder skeletal muscle involvement, heart failure from DCM is a common cause of morbidity and the most common cause of death in BMD. Mean age of death is in the mid-40s.

DMD-associated DCM is characterized by left ventricular dilatation and congestive heart failure. Females heterozygous for a *DMD* pathogenic variant are at increased risk for DCM.

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Diagnosis/testing

The diagnosis of a dystrophinopathy is established in a proband with the characteristic clinical findings and elevated CK concentration and/or by identification of a hemizygous pathogenic variant in *DMD* on molecular genetic testing in a male and of a heterozygous pathogenic variant in *DMD* on molecular genetic testing in a female. Females may present with a classic dystrophinopathy or may be asymptomatic carriers.

Management

Treatment of manifestations: ACE inhibitors are used with or without beta blockers for cardiomyopathy in both DMD and BMD phenotypes. Congestive heart failure is treated with diuretics and oxygen as needed; cardiac transplantation is offered to persons with severe dilated cardiomyopathy and BMD with limited or no clinical evidence of skeletal muscle disease. Scoliosis is treated with bracing and surgery. Corticosteroid therapy improves muscle strength and function for individuals with DMD between ages five and 15 years; the same treatment is used in BMD, although the efficacy is less clear. Dystrophin restoration therapies have been developed by using synthetic antisense oligonucleotides to restore the reading frame by exon skipping for individuals with specific pathogenic variants in *DMD*.

Prevention of secondary complications: Evaluation by a pulmonologist and cardiologist before surgeries; pneumococcal and influenza immunizations annually; nutrition assessment; physical therapy to promote mobility and prevent contractures; sunshine and a balanced diet rich in vitamin D and calcium to improve bone density and reduce the risk of fractures; weight control to avoid obesity.

Surveillance: For males with DMD or BMD: annual or biannual evaluation by a cardiologist beginning at the time of diagnosis; monitoring for scoliosis; baseline pulmonary function testing before wheelchair dependence; frequent evaluations by a pediatric pulmonologist. For heterozygous females: cardiac evaluation at least once after the teenage years.

Agents/circumstances to avoid: Botulinum toxin injections; succinylcholine and inhalational anesthetics because of susceptibility to malignant hyperthermia or malignant hyperthermia-like reactions.

Evaluation of relatives at risk: Early identification of heterozygous females who are at increased risk for cardiomyopathy and, thus, need routine cardiac surveillance and prompt treatment.

Genetic counseling

The dystrophinopathies are inherited in an X-linked manner. The risk to the sibs of a proband depends on the genetic status of the mother. Heterozygous females have a 50% chance of transmitting the *DMD* pathogenic variant in each pregnancy. Sons who inherit the pathogenic variant will be affected; daughters who inherit the pathogenic variant are heterozygous and may have a range of clinical manifestations. Males with DMD usually do not reproduce. Males with BMD or *DMD*-associated DCM may reproduce: all of their daughters are heterozygotes; none of their sons inherit their father's *DMD* pathogenic variant. Carrier testing for at-risk females, prenatal testing, and preimplantation genetic testing are possible if the *DMD* pathogenic variant in the family is known.

GeneReview Scope

Dystrophinopathies: Included Phenotypes ¹

- Duchenne muscular dystrophy (DMD)
- Becker muscular dystrophy (BMD)
- *DMD*-associated dilated cardiomyopathy

For synonyms and outdated names see Nomenclature.

1. For other genetic causes of these phenotypes see Differential Diagnosis.

Diagnosis

The dystrophinopathies cover a spectrum of X-linked muscle disease that ranges from mild to severe and includes Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD), and *DMD*-associated dilated cardiomyopathy (DCM).

Suggestive Findings

A dystrophinopathy **should be suspected** in an individual with the following clinical and laboratory test findings that support the diagnosis of DMD, BMD, or *DMD*-associated DCM – especially when they occur in addition to a positive family history compatible with X-linked inheritance. Findings are most commonly noted in males, but females may also be affected.

Clinical Findings

Duchenne muscular dystrophy (DMD)

- Progressive symmetric muscle weakness (proximal > distal) often with calf hypertrophy
- Symptoms present before age five years
- Wheelchair dependency before age 13 years

Becker muscular dystrophy (BMD)

- Progressive symmetric muscle weakness (proximal > distal) often with calf hypertrophy; weakness of quadriceps femoris in some cases the only sign
- Activity-induced cramping (present in some individuals)
- Flexion contractures of the elbows (if present, late in the course)
- Wheelchair dependency (after age 16 years); although some individuals remain ambulatory into their 30s and in rare cases into their 40s and beyond
- Preservation of neck flexor muscle strength (differentiates BMD from DMD)

Note: The presence of fasciculations or loss of sensory modalities excludes a suspected diagnosis of a dystrophinopathy. Individuals with an intermediate phenotype (outliers) have symptoms of intermediate severity and become wheelchair dependent between ages 13 and 16 years.

DMD-associated dilated cardiomyopathy (DCM)

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

See also [Dilated Cardiomyopathy Overview](#).

Laboratory Testing

Serum creatine phosphokinase (CK) concentration. See Table 1.

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

	Phenotype	% of Affected Individuals	Serum CK Concentration
Males	DMD	100% ¹	>10x normal
	BMD	100% ¹	>5x normal
	<i>DMD</i> -assoc DCM	Most individuals ²	"Increased"
Female carriers	DMD	~50% ^{3, 4}	2-10x normal
	BMD	~30% ^{3, 4}	2-10x normal

1. Serum CK concentration gradually decreases with advancing age as a result of 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. Serum CK concentrations are usually increased, but normal concentrations have been reported in *DMD*-associated DCM [Mestroni et al 1999].

3. Hoogerwaard et al [1999b]

4. Other investigations have confirmed a wide variability in serum CK concentration among *DMD*/*BMD* carriers with the mean serum CK concentration significantly higher in carriers age <20 years than in those age >20 years [Sumita et al 1998].

Establishing the Diagnosis

Male proband. The diagnosis of a dystrophinopathy **is established** in a male proband with the characteristic clinical findings and elevated CK concentration and/or by identification of a hemizygous pathogenic (or likely pathogenic) variant in *DMD* on molecular genetic testing (see Table 1).

Female proband. The diagnosis of a dystrophinopathy **is usually established** in a female proband with characteristic clinical findings and elevated CK concentration and/or by identification of a heterozygous pathogenic (or likely pathogenic) variant in *DMD* on molecular genetic testing (see Table 1).

Females may present with a classic dystrophinopathy or may be asymptomatic carriers.

- **Females with a classic dystrophinopathy.** The genetic mechanisms that can explain this rare occurrence (and testing to identify the cause) include the following:
 - A deletion involving Xp21.2 (microarray [CMA] studies)
 - An X-chromosome rearrangement involving Xp21.2 or complete absence of an X chromosome (i.e., Turner syndrome) (cytogenetic studies)
 - Uniparental disomy (UPD) of the X chromosome (UPD studies)
 - Compound heterozygosity for two *DMD* pathogenic variants [Soltanzadeh et al 2010] (deletion/duplication analysis and/or sequence analysis)
 - Nonrandom X-chromosome inactivation (XCI). See Genotype-Phenotype Correlations.
- **Carrier testing for at-risk female relatives.** Note: Carriers are heterozygotes for this X-linked disorder and may later develop clinical findings related to the disorder (see Clinical Characteristics and Management, Evaluation of Relatives at Risk for testing recommendations).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a hemizygous or heterozygous *DMD* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include **single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**:

- **Single-gene testing.** Because the majority of pathogenic variants involve deletions of one or more exons, gene-targeted deletion/duplication analysis of *DMD* is performed first and followed by sequence analysis if no pathogenic variant is found.
- **A multigene panel** that includes *DMD* and other genes of interest (see Differential Diagnosis) may be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

Note: (1) A **multigene panel** may be most appropriate for individuals with less severe clinical presentations. Men with the BMD phenotype and most women may not have findings clinically distinct enough to suggest single-gene testing of *DMD* as the initial test. (2) **Chromosomal microarray analysis (CMA)** may:

- Be appropriate if not already performed, to identify multiple gene deletions/duplications (including *DMD*);
 - Be considered first in an individual presenting with additional medical concerns associated with known X-linked disorders such as [retinitis pigmentosa](#), [chronic granulomatous disease](#), and McLeod red cell phenotype (see [McLeod neuroacanthocytosis syndrome](#)) [Francke et al 1985] or glycerol kinase deficiency and [adrenal hypoplasia](#) [Darras & Francke 1988] to suggest a contiguous gene disorder;
 - Detect an unexpected or incidental *DMD* deletion/duplication in an asymptomatic individual.
- **More comprehensive genomic testing** (when available) including exome sequencing and genome sequencing may be considered, particularly if the presentation is atypical. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

Exome array (when clinically available) may be considered if exome sequencing is nondiagnostic given the frequency of *DMD* deletions or duplications associated with dystrophinopathy.

Table 2. Molecular Genetic Testing Used in Dystrophinopathies

Gene ¹	Method	Proportion of Probands with a Pathogenic Variant ² Detectable by Method
<i>DMD</i>	Sequence analysis ³	20%-35%
	Gene-targeted deletion/duplication analysis ^{4, 5}	65%-80%

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on variants detected in this gene.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

4. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

5. Chromosomal microarray analysis (CMA) may detect *DMD* deletions or duplications either as part of a contiguous gene deletion syndrome or as an incidental or unexpected intragenic finding. Given that the sensitivity of CMA is not sufficient to detect all exon-level *DMD* deletions and duplications, CMA is not recommended as a primary assay for dystrophinopathies.

Note: If no *DMD* pathogenic variant is identified, skeletal muscle biopsy of individuals with suspected *DMD* or *BMD* is warranted for western blot and immunohistochemistry studies of dystrophin. Skeletal muscle biopsy continues to be used only rarely in the diagnosis of dystrophinopathies.

- **Muscle histology** early in the disease shows nonspecific dystrophic changes, including variation in fiber size, foci of necrosis and regeneration, hyalinization, increased internal nuclei, fiber splitting, inflammatory changes, and, later in the disease, deposition of fat and connective tissue.
- **Western blot and immunohistochemistry** are summarized in Table 3.

Table 3. Findings in the Dystrophin Protein from Skeletal Muscle Biopsy

	Phenotype	Western Blot		Immunohistochemistry ³
		Dystrophin mol wt ¹	Dystrophin quantity ²	
Males	DMD	Undetectable	0%-5%	Complete or almost complete absence
	Intermediate	Normal/abnormal	5%-20%	
	BMD	Normal	20%-50%	Normal appearing or reduced intensity ± patchy staining
		Abnormal	20%-100%	

Table 3. continued from previous page.

	Phenotype	Western Blot		Immunohistochemistry ³
		Dystrophin mol wt ¹	Dystrophin quantity ²	
Heterozygous females	DMD random XCI ⁴	Normal/abnormal	>60% ^{5,6} (70%±9%)	Normal or minor changes or mosaic pattern; dystrophin-negative fibers (9%±2%) ⁵
	DMD skewed XCI ⁷	Normal/abnormal	<30% on average (29%±25%) ⁵	Mosaic pattern; dystrophin-negative fibers (44%±33%) ⁵

mol wt = molecular weight; XCI = X-chromosome inactivation

1. Normal molecular mass is 427 kb.

2. The quantity of dystrophin is expressed in percent of control values. The reference ranges shown in this table are the ones currently used by clinical laboratories and reflect approximate and reconciled data from the literature.

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

4. Asymptomatic to mild disability

5. Pegoraro et al [1995]

6. Quantitative analysis of dystrophin in female carriers is not useful in clinical practice because of the wide range of values and the significant overlap with normal values.

7. Mild, intermediate, severe symptoms. Carriers with mild disease were young (age 5-10 years) [Pegoraro et al 1995].

Clinical Characteristics

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 creatine phosphokinase (CK) and muscle cramps with myoglobinuria. The severe end of the spectrum includes progressive muscle diseases that are classified as Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) when skeletal muscle is primarily affected and as *DMD*-associated dilated cardiomyopathy (DCM) when the heart is primarily affected [Beggs 1997, Cox & Kunkel 1997, Muntoni et al 2003].

DMD vs BMD vs *DMD*-associated DCM. The distinction between DMD and BMD is based on the age of wheelchair dependency: before age 13 years in DMD and after age 16 years in BMD. An intermediate group of individuals who become wheelchair bound between ages 13 and 16 years is also recognized. Additionally, some investigators have extended the mild end of the BMD spectrum to include individuals with elevated serum CK concentration and abnormal dystrophin on muscle biopsy, but with "subclinical" skeletal muscle involvement [Melacini et al 1996]. When these individuals with atypical disease develop severe cardiomyopathy, it is not possible to distinguish between BMD and *DMD*-associated DCM [Cox & Kunkel 1997].

Cardiac involvement is usually asymptomatic in the early stages of the disease, although sinus tachycardia and various EKG abnormalities may be noted. Echocardiography is normal or shows only regional abnormalities. Pericardial effusion with cardiac tamponade and myocardial inflammation precipitating heart failure has been described in people with DMD [Lin et al 2009, Mavrogeni et al 2010]. Subclinical or clinical cardiac involvement is present in approximately 90% of individuals with DMD or BMD; however, cardiac involvement is the cause of death in only 20% of individuals with DMD and 50% of those with BMD [Hermans et al 2010].

DMD-associated DCM generally presents with congestive heart failure secondary to an increase in ventricular size and impairment of ventricular function. In males, DCM is rapidly progressive with onset in teenage years,

leading to death from heart failure within one to two years after the diagnosis [Finsterer & Stollberger 2003]. Individuals with DCM may or may not have clinical evidence of skeletal muscle disease [Neri et al 2007].

DMD

Motor development. DMD usually presents in early childhood with delayed motor milestones, including delays in walking independently and standing up from the floor. The mean age of walking is approximately 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%). The mean age of diagnosis of boys with DMD without a family history of DMD is approximately four years ten months (range: 16 months - 8 years) [Bushby 1999, Zalaudek et al 1999]. A recent study reported a mean age of 41 months at diagnosis of DMD [D'Amico et al 2017]. Proximal weakness causes a waddling gait and difficulty climbing stairs, running, jumping, and standing up from a squatting position [Li et al 2012, Liang et al 2018]. 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 [Darras et al 2015].

Cardiomyopathy. Among children with DMD, the incidence of cardiomyopathy increases steadily in the teenage years, with approximately one third of individuals being affected by age 14 years, one half by age 18 years, and all individuals after age 18 years [Nigro et al 1990].

Cognitive abilities. Some degree of non-progressive cognitive impairment in boys with DMD has long been known. This was initially described as a general "leftward shift" in the spectrum of IQ scores of a population with DMD compared to the population at large. Earlier reports had suggested that verbal IQ was more affected than performance IQ on the Wechsler Intelligence Scales.

A retrospective study by Banihani et al [2015] demonstrated that in their sample, 27% of the boys had IQ <70, with 19% overall fulfilling all criteria for intellectual disability (ID). A learning disability was present in 44%, attention-deficit/hyperactivity disorder (ADHD) in 32%, autism spectrum disorder (ASD) in 15%, and anxiety in 27%. No significant correlation was seen between these neuropsychiatric conditions and dystrophin isoforms.

Ricotti et al [2016] assessed 130 males with DMD from four European centers and reviewed IQ assessment and a screening questionnaire. Of the original 130, 87 then underwent more extensive testing. Comparable rates of ID, ASD, ADHD, learning disability, and anxiety were observed.

These retrospective studies thus suggest increased rates of ID, ASD, ADHD, and learning disability in boys with DMD compared to the population at large.

Battini et al [2018] engaged in a prospective assessment of 40 boys with DMD. Their work showed that in boys without frank ID, executive functions such as multitasking, problem solving, inhibition, and working memory were affected out of proportion to overall cognitive function. They suggested that DMD was therefore associated with deficits in "executive function" in boys who did not demonstrate ID.

This confirms the retrospective work of Wicksell et al [2004], who demonstrated that boys with DMD who did not have ID showed deficits in active working memory in both verbal and visuospatial domains. It also confirms the retrospective study of Hinton et al [2001], who demonstrated short-term verbal memory issues in boys with DMD who did not have ID.

All of these studies thus suggest that the earlier allegation of poorer verbal function in boys with DMD and without ID was better explained by deficits in executive function, which could also lead to visuospatial difficulties in certain settings.

Mobility. DMD is associated with reduced mobility. Thus, boys with DMD have decreased bone density and are at increased risk for fractures. Corticosteroids further increase the risk of vertebral compression fractures, many of which are asymptomatic.

Life span. Despite improvement of survival, few affected individuals survive beyond the third decade [Passamano et al 2012]. Respiratory complications and progressive cardiomyopathy are common causes of death. A study of individuals with molecularly confirmed diagnoses has determined a median survival of 24 years, with ventilated patients reaching a median survival of 27 years [Rall & Grimm 2012]. In a cohort of affected individuals having both spinal surgery and nocturnal ventilation, the median survival was 30 years [Eagle et al 2007]. Because death frequently occurs outside the hospital setting, the cause of death is often difficult to determine [Parker et al 2005].

BMD

Motor development. BMD is characterized by later-onset skeletal muscle weakness. 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 [Yazaki et al 1999].

Mildly affected individuals with confirmatory *DMD* molecular genetic studies and/or dystrophin studies on muscle biopsy have been classified as having either of the following [Melacini et al 1996]:

- BMD with "subclinical" skeletal muscle involvement in the presence of elevated serum CK concentration, calf hypertrophy, muscle cramps, myalgia, and exertional myoglobinuria
- "Benign" skeletal muscle involvement when "subclinical" findings are accompanied by muscle weakness in the pelvic girdle and/or shoulder girdle

Cardiomyopathy. While skeletal muscle involvement is milder in BMD, heart failure from DCM is a common cause of morbidity and the most common cause of death [Cox & Kunkel 1997]. Mean age at cardiomyopathy diagnosis is 14.6 years, similar to that in DMD (14.4 years) [Connuck et al 2008]. Heart transplantation rate in BMD is high within five years after the diagnosis of cardiomyopathy [Connuck et al 2008, Kamdar & Garry 2016]. Mean age of death is in the mid-40s [Bushby 1999].

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

DMD-associated DCM

In 1987, a five-generation, 63-member family with DCM but no evidence of skeletal myopathy was reported. Males present in their teens and twenties; the disease course is rapidly progressive and associated ventricular arrhythmias are common. Heterozygous females develop mild dilated cardiomyopathy in the fourth or fifth decade, with slow progression. The only biochemical abnormality is elevation in serum CK concentration. Towbin et al [1993] demonstrated linkage to the dystrophin locus in this family and one other.

Subsequent study demonstrated that in individuals with the most severe cardiac phenotype the cardiac muscle is usually unable to produce functional dystrophin in the heart, while in skeletal muscle reduced levels of virtually normal dystrophin transcript and protein are present [Ferlini et al 1999, Neri et al 2007, Neri et al 2012]; see Molecular Genetics.

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

DMD is a relatively infrequent cause of DCM. In a cohort of 99 Japanese unrelated adult males and females with familial and sporadic DCM, *DMD* pathogenic variants were identified in only three males [Shimizu et al 2005].

Females

In some instances females can have classic *DMD* (see Establishing the Diagnosis).

Signs and symptoms of *DMD* and *BMD* were studied among confirmed heterozygous females [Hoogerwaard et al 1999a, Hoogerwaard et al 1999b] (Table 4). In contrast, Nolan et al [2003] found no cardiac abnormalities in 23 proven heterozygotes age 6.2 to 15.9 years (see Penetrance). The prevalence of cardiomyopathy depends on its definition and can vary from 3% to 33% [McCaffrey et al 2017]. No correlation of phenotype (*DMD* vs *BMD*), age, CK level, or muscle symptoms was noted. In another study, however, DCM was more common in functionally symptomatic heterozygous females [Schade van Westrum et al 2011].

Table 4. Signs and Symptoms in Females Heterozygous for a *DMD* Pathogenic Variant

Signs/Symptoms	In Families w/ <i>DMD</i>	In Families w/ <i>BMD</i>
None	76%	81%
Muscle weakness ¹	19%	14%
Myalgia/cramps	5%	5%
Left ventricular dilatation	19%	16%
Dilated cardiomyopathy	8%	0

From Hoogerwaard et al [1999b]

1. Mild-to-moderate weakness

Genotype-Phenotype Correlations

If a pathogenic variant is identified, the diagnosis of a dystrophinopathy is established, but the distinction between *DMD* and *BMD* can be difficult in some cases. For example, deletion of exons 3-7, the most extensively investigated deletion associated with both phenotypes, has been found in males with *DMD* and also with *BMD* [Aartsma-Rus et al 2006].

Reading frame rule. This "rule" states that pathogenic variants that do not alter the reading frame (in-frame deletions/duplications) generally correlate with the milder *BMD* phenotype, whereas those that alter the reading frame (out-of-frame) generally correlate with the more severe *DMD* phenotype [Monaco et al 1988]. Therefore, the type of deletion/duplication can distinguish between the *DMD* and *BMD* phenotypes with 91%-92% accuracy in young children who represent simplex cases (i.e., a single occurrence in a family) [Aartsma-Rus et al 2006], and in many cases a muscle biopsy is not needed to address the issue of *BMD* vs *DMD*.

Although exceptions to the "reading frame rule" have been documented to occur at a rate below 10% [Aartsma-Rus et al 2006], more recent studies suggest that this may only hold true for the *DMD* phenotype, and that the rate of exception may be higher with the *BMD* phenotype for both deletions and duplications [Kesari et al 2008, Takeshima et al 2010]. Correlation of clinical features with molecular test results is thus very important.

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. Pathogenic variants that disrupt the reading frame include stop variants, some splicing variants, 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 rule": deletions in protein-binding domains that may severely affect function even when 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]. The accuracy of phenotype prediction using this rule is in the range of 91%-92% [Aartsma-Rus et al 2006]. More recent studies suggest that duplications, which occur more commonly in BMD, may result in exceptions to the reading frame rule in a higher proportion of cases, perhaps up to 30% [Kesari et al 2008, Takeshima et al 2010]. Correlation of clinical features with molecular test results is thus very important.

Wingeier et al [2011] showed that there was no clear relationship between pathogenic variants seen in males with DMD and specific aspects of cognitive function, or overall performance on standard measures of cognitive abilities. They did note, however, that the lack of the dystrophin isoform Dp140 was associated with greater impairments overall; this observation confirms the findings of a previous study that suggested that dystrophin deletions involving the brain distal isoform Dp140 are associated with intellectual impairment [Felisari et al 2000]. Mild intellectual disability is significantly more common in males with pathogenic variants affecting Dp140; also, most males with pathogenic variants involving the Dp71 isoform are cognitively disabled [Daoud et al 2009, Taylor et al 2010]. Recent work from the French Neuromuscular Network suggests that pathogenic variants in the distal parts of the dystrophin gene are more likely to be associated with cognitive impairment [Mercier et al 2013].

Dp71 and Dp140 are the shorter isoforms of dystrophin and are highly expressed in fetal brain with gradual increase from the embryonic stage to adult. Dp71 is very abundant in the hippocampus and some layers of the cerebral cortex with sublocalization in synaptic membranes, microsomes, synaptic vesicles, and mitochondria. The location of the pathogenic variant appears to correlate with full-scale IQ (FSIQ) values (e.g., pathogenic variants affecting the Dp140 isoform 5' UTR affect FSIQ less than those affecting the Dp140 promoter or coding region) [Taylor et al 2010]. Further, the cumulative loss of isoforms expressed in the central nervous system increases the risk of cognitive deficit [Taylor et al 2010].

- **BMD.** The BMD phenotype occurs when some dystrophin is produced, usually resulting from deletions or duplications that juxtapose in-frame exons, some splicing variants, and most nontruncating 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 [Deburgrave et al 2007].

Exceptions to the reading frame rule occur more commonly in BMD than in DMD. In one large cohort, a BMD phenotype failed to follow the reading frame rule in approximately 15% of cases caused by deletion, and approximately 34% of cases caused by duplication [Takeshima et al 2010]. Another study also reported exceptions to the reading frame rule in 30% of males with BMD with a duplication [Kesari et al 2008]. Correlation of clinical features with molecular test results is crucial; affected males and their families should be informed that using this rule, phenotype prediction may be less accurate.

In men with BMD, deletions involving the amino-terminal domain correlate with early-onset dilated cardiomyopathy (DCM; mid-20s), whereas deletions affecting part of the rod domain and hinge 3 result in a later-onset DCM (mid-40s) [Kaspar et al 2009].

DMD-associated DCM is caused by pathogenic variants in *DMD* 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 dystrophin expression sufficient to prevent manifestation of skeletal muscle symptoms [Beggs 1997, Towbin 1998, Yoshida et al 1998]. Other types of pathogenic variants including a novel rod domain duplication of exons 13-16 [Chamberlain et al 2015], missense variants, and deletions in the exon 45-53 region of *DMD* [Shimizu et al 2005] have been reported in *DMD*-associated DCM.

DMD-associated DCM 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 pathogenic variants in hypothetical cardiac-specific exons.

Abnormalities in cardiac conduction noted in persons with dystrophinopathies may be related to reduced expression of cardiac sodium channel NA(v)1.5 secondary to dystrophin deficiency [Gavillet et al 2006].

See also [Dilated Cardiomyopathy Overview](#). The occurrence of either cardiomyopathy or BMD in the same family raises the possibility of modification of the phenotypic expression of a specific pathogenic variant by epigenetic factors [Palmucci et al 2000].

Penetrance

Penetrance of dystrophinopathies is complete in males.

Penetrance in heterozygous females varies, and may depend in part on patterns of X-chromosome inactivation (XCI).

- Some studies have shown no clear correlation between the active-to-inactive X-chromosome ratio observed in XCI studies in leukocytes and serum CK concentration, clinical signs, or the proportion of dystrophin-negative fibers observed on muscle biopsy [Sumita et al 1998].
- In another study of seven symptomatic heterozygous females, the XCI pattern was skewed toward non-random in the four with deletions or duplications but was random in the three with pathogenic nonsense variants [Soltanzadeh et al 2010].
- In contrast, Pegoraro et al [1995] showed that more than 90% of heterozygous females with skewed XCI (defined as $\geq 75\%$ of nuclei containing the *DMD* pathogenic variant on the active X-chromosome) as demonstrated from a blood sample develop mild, moderate, or severe muscular dystrophy. Heterozygous females with a mild phenotype were young (i.e., age 5-10 years).
- Direct correlation with a skewed XCI pattern was also observed recently in cohorts of symptomatic and asymptomatic *DMD*/*BMD* carriers [Giliberto et al 2014, Viggiano et al 2016, Viggiano et al 2017]. However, because the methylation status of the androgen receptor (*AR*) gene in white blood cells or muscle may not always reflect the methylation status of *DMD*, the use of the *AR* methylation assay has limited prognostic value in clinical practice [Juan-Mateu et al 2012].

Nomenclature

The term "pseudohypertrophic muscular dystrophy" was used in the past; however, it is not used currently because pseudohypertrophy is not unique to the *DMD* or *BMD* phenotype.

Prevalence

Prevalence data are not available.

The overall incidence of *DMD* in Canada (Nova Scotia) is one in 4,700 live male births and has remained stable from 1969 to 2008 [Dooley et al 2010a].

The incidence of *BMD* in northern England is 1:18,450 live male births [Bushby et al 1991].

During the years 1968 to 1978, the incidence of *DMD* in southeast Norway was 1:3,917 live male births [Tangsrud & Halvorsen 1989].

Genetically Related (Allelic) Disorders

Intellectual disability without muscle weakness. In-frame deletion of *DMD* exons 56-57 (with different dystrophin isoforms Dp424m, Dp260, Dp140, and Dp116) has been associated with intellectual disability (ID) without muscle weakness. In addition, three asymptomatic heterozygous females (with duplication of exons 13-27, partial deletion of exon 46, and deletion of 46-55) were found to have isolated cognitive impairment and no evidence of muscle weakness, suggesting that dystrophinopathy with isolated ID and no evidence of muscle weakness may be more common than had been previously thought [Juan-Mateu et al 2013]. Another case of X-linked ID without muscle weakness was reported in a family with a 3-base pair, in-frame, single amino-acid deletion in the brain-specific Dp71 isoform of dystrophin. Creatine phosphokinase was mildly elevated [de Brouwer et al 2014].

Differential Diagnosis

Limb-girdle muscular dystrophy (LGMD) is a group of autosomal recessive and autosomal dominant disorders that are clinically similar to DMD but occur in both sexes. Limb-girdle dystrophies are caused by mutation of genes that encode sarcoglycans and other proteins associated with the muscle cell membrane that interact with dystrophin [Mohassel & Bönnemann 2015]. Testing for deficiency of proteins from the transmembrane sarcoglycan complex and of other proteins is indicated in individuals with dystrophin-positive dystrophies. LGMD type 2I phenotypically resembles DMD and BMD and is caused by biallelic pathogenic variants in *FKRP* (encoding fukutin-related protein).

Emery-Dreifuss muscular dystrophy (EDMD) is characterized by the clinical triad of joint contractures that begin in early childhood, slowly progressive muscle weakness and wasting initially in a humero-peroneal distribution that later extends to the scapular and pelvic girdle muscles, and cardiac involvement that may include palpitations, presyncope and syncope, poor exercise tolerance, and congestive heart failure. Age of onset, severity, and progression of the muscle and cardiac involvement show intra- and interfamilial variation. Clinical variability ranges from early and severe presentation in childhood to a late onset and slowly progressive course. In general, joint contractures appear during the first two decades, followed by muscle weakness and wasting. Cardiac involvement usually occurs after the second decade. Pathogenic variants in three genes are known to cause EDMD: *EMD* and *FHL1*, which cause X-linked EDMD; and *LMNA*, which causes autosomal dominant EDMD and autosomal recessive EDMD.

Spinal muscular atrophy (SMA) is suspected in individuals with poor muscle tone, 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. The onset of weakness ranges from before birth to adolescence or young adulthood. The weakness is symmetric, proximal > distal, and progressive. Poor weight gain with growth failure, restrictive lung disease, scoliosis, joint contractures, and sleep difficulties are common complications. SMA is caused by pathogenic variants in *SMN1* and inherited in an autosomal recessive manner.

Dilated cardiomyopathy (DCM) can be familial or nonfamilial. In a large series in which family studies were performed, one third to one half of individuals had nonfamilial DCM and two thirds had familial DCM. Familial DCM may be inherited in an autosomal dominant, an autosomal recessive, or an X-linked manner. Most familial DCM (probably 80%-90%) appears to be autosomal dominant; X-linked and autosomal recessive forms are less common [Watkins et al 2011].

Barth syndrome, an X-linked disorder caused by mutation of *TAFAZZIN* (formerly *TAZ*), is characterized in affected males by cardiomyopathy, neutropenia, skeletal myopathy, prepubertal growth delay, and distinctive facial gestalt (most evident in infancy); not all features may be present in a given affected individual. Cardiomyopathy, which is almost always present before age five years, is typically dilated cardiomyopathy with or without endocardial fibroelastosis or left ventricular non-compaction. Heart failure is a significant cause of

morbidity and mortality; risk of arrhythmia and sudden death is increased. The non-progressive myopathy predominantly affects the proximal muscles, and results in early motor delays. Prepubertal growth delay is followed by a postpubertal growth spurt with remarkable "catch-up" growth.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with a dystrophinopathy, the following evaluations are recommended if they have not already been completed:

- Physical therapy assessment
- Developmental evaluation before entering elementary school for the purpose of designing an individualized educational plan, as necessary
- At the time of diagnosis or by age six years, evaluation for cardiomyopathy by electrocardiography, cardiac echocardiography, and/or MRI [Towbin 2003, Bushby et al 2010b]
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Appropriate management of individuals with a dystrophinopathy can prolong survival and improve quality of life.

Duchenne Muscular Dystrophy (DMD) / Becker Muscular Dystrophy (BMD) Phenotypes

Cardiomyopathy in DMD and BMD. Recommendations are based on an American Academy of Pediatrics policy statement and various additional publications [American Academy of Pediatrics Section on Cardiology and Cardiac Surgery 2005, Jefferies et al 2005, Viollet et al 2012] and apply to patients with the DMD or BMD phenotype.

- The authors' institution commonly treats children with DMD or BMD early with an ACE inhibitor and/or beta blocker.
- When used in combination, these appear to lead to initial improvement of left ventricular function; however, ACE inhibitors are also used without beta blockers, with similar results [Viollet et al 2012].
- The optimal time to start treatment in DMD is unknown, but most cardiologists will initiate treatment when the left ventricle ejection fraction drops below 55% and fractional shortening is less than 28% [Jefferies et al 2005, Viollet et al 2012].
- Angiotensin II-receptor blockers (ARBs) such as losartan are similarly effective and can be used in cases of poor tolerability of ACE inhibitors [Allen et al 2013].
- In cases of overt heart failure, other heart failure therapies including diuretics and digoxin are used as needed.
- Cardiac transplantation is offered to persons with severe dilated cardiomyopathy and BMD with limited or no clinical evidence of skeletal muscle disease.

Scoliosis in DMD and BMD. Treatment as needed is appropriate. The management of scoliosis involves bracing and surgery. Most patients end up getting a spinal fusion. The use of rods is not contraindicated; therefore, rod and bone grafts are used to fuse the spine. A minority of patients do not develop significant scoliosis and may not require a spinal fusion.

Corticosteroid therapy in DMD. Studies have shown that corticosteroids improve the muscle strength and function of individuals with DMD. This therapy remains the treatment of choice for affected individuals older

than age four years. Although steroids have been used in younger individuals with DMD, efficacy has not been proven in controlled studies. Corticosteroid therapy is not recommended in children before age two years [Bushby et al 2010a].

The following published recommendations for corticosteroid therapy are in accordance with the national practice parameters developed by the American Academy of Neurology and the Child Neurology Society [Moxley et al 2005] ([full text](#)), as well as the DMD Care Considerations Working Group [Bushby et al 2010a].

- Boys with DMD should be offered treatment with prednisone (0.75 mg/kg/day, maximum daily dose: 30-40 mg) or deflazacort (0.9 mg/kg/day, maximum daily dose: 36-39 mg) as soon as plateauing or decline in motor skills is noted, which usually occurs at age 4-8 years. Prior to the initiation of therapy, the potential benefits and risks of corticosteroid treatment should be carefully discussed with each individual.
- To assess benefits of corticosteroid therapy, the following parameters are useful: timed muscle function tests, pulmonary function tests, and age at loss of independent ambulation.
- To assess risks of corticosteroid therapy, maintain awareness of the potential corticosteroid therapy side effects (e.g., weight gain, cushingoid appearance, short stature, decrease in linear growth, acne, excessive hair growth, gastrointestinal symptoms, behavioral changes). There is also an increased frequency of vertebral and long bone fractures with prolonged corticosteroid use [King et al 2007].
- The optimal maintenance dose of prednisone (0.75 mg/kg/day) or deflazacort (0.9 mg/kg/day) should be continued if side effects are not severe. Significant but less robust improvement can be seen with gradual tapering of prednisone to as low as 0.3 mg/kg/day (or ~0.4 mg/kg/day of deflazacort).
- If excessive weight gain occurs (>20% above estimated normal weight for height over a 12-month period), the prednisone dose should be decreased by 25%-33% and reassessed in a few months. If excessive weight gain continues, the dose should be further decreased by an additional 25% to the minimum effective dose cited above after three to four months.
- If significant weight gain or intolerable behavioral side effects occur in patients treated with prednisone, change to deflazacort on a ten-day-on / ten-day-off schedule or a high-dose weekend schedule. In patients on deflazacort, side effects of asymptomatic cataracts and weight gain should be monitored.

Many clinicians continue treatment with glucocorticoids after loss of ambulation for the purpose of maintaining upper limb strength, delaying the progressive decline of respiratory and cardiac function, and decreasing the risk of scoliosis. Retrospective data suggest that the progression of scoliosis can be reduced by long-term daily corticosteroid treatment; however, an increased risk for vertebral and lower-limb fractures has been documented [King et al 2007]. Individuals on steroid therapy were less likely to require spinal surgery [Dooley et al 2010b]. The dose is allowed to drift down to 0.3-0.6 mg/kg/day of prednisone or deflazacort, which is still effective [Bushby et al 2010a].

Corticosteroid therapy in BMD. Information about the efficacy of prednisone in treating individuals with BMD is limited, but this treatment could be used to treat weakness in individuals with BMD.

Dystrophin Restoration Therapies in DMD

Exon-skipping therapy in DMD restores the reading frame using synthetic antisense oligonucleotides (ASO) targeted to the dystrophin pre-messenger RNA to skip out-of-frame variants [Datta & Ghosh 2020]. Approximately 70% of pathogenic variants in DMD are located between exons 45 and 55.

- **Exon 51 variants.** Exon 51 skipping restores the reading frame in these variants and is applicable to about 13% of individuals with DMD [Aartsma-Rus et al 2009]. The first clinical trials involving exon 51 skipping therapy used the compounds drisapersen and eteplirsen [Mendell et al 2013, Goemans et al 2018]. Eteplirsen received accelerated conditional United States Food and Drug Administration (FDA) approval in 2016 based on a clinical trial of 12 individuals with DMD who demonstrated a 23% increase in dystrophin-positive muscle fibers, an increase of dystrophin quantity by Western blot (0.08% to 0.93%),

and a 151-meter difference in the decline of the six-minute walking distance (6MWD) compared to matched historical controls [Mendell et al 2013]. Eteplirsen is the first drug to get FDA approval using dystrophin quantification as a surrogate outcome measure for DMD.

- **Exon 53 variants.** Golodirsen, an ASO for individuals amenable to exon 53 skipping, was approved by the FDA in December 2019 and is applicable to about 10% of individuals with DMD. Viltolarsen, also an exon 53 skipping ASO, was approved in August 2020 [Clemens et al 2020].
- **Exon 52 deletion.** Individuals with deletion of exon 52 (accounts for ~2% of those with DMD) are amenable to either exon 51 or 53 skipping [Datta & Ghosh 2020].
- **Exon 45 variants.** Casimersen, an ASO for individuals with variants amenable to exon 45 skipping, was approved by the FDA in February 2021.

Table 5 compares dystrophin restoration therapies by mechanism of action. (Note: Some of the therapies listed are still in development.)

Table 5. Dystrophin Restoration Therapies

Treatments	Mechanism of Action	Pros	Cons
ASOs (current US FDA-approved therapies): <ul style="list-style-type: none"> • Eteplirsen (exon skip 51 amenable) • Golodirsen (exon skip 53 amenable) • Viltolarsen (exon skip 53 amenable) • Casimersen (exon skip 45 amenable) 	Restoration of reading frame by exon skipping in deletions	Currently approved treatments apply to ~30% of persons w/DMD; well tolerated; good safety profile	Weekly intravenous infusions; variant specific
Ataluren (approved by European Medicines Agency; not FDA approved)	Stop codon read-through strategy for nonsense variants	Orally administered; well tolerated; good safety profile	Variant specific
Gene transfer therapy (currently in clinical trials)	Micro-dystrophin constructs are inserted into AAV vectors to drive high levels of transgene expression & produce enough potentially functional micro-dystrophin.	Variant nonspecific; single intravenous administration	Cannot restore full-length dystrophin; durability of therapeutic response; safety concerns (possibility of integration into host genome & risk of mutagenesis)
CRISPR/Cas9-mediated gene editing (preclinical phase)	Programmable nucleases to correct a gene defect	Variant nonspecific	Off-target effects; safety & tolerability concerns

AAV = adeno-associated virus; ASO = antisense oligonucleotide; FDA = Food and Drug Administration

DMD-Related Dilated Cardiomyopathy (DCM) Phenotype

Cardiomyopathy management is similar to the management of DMD- or BMD-associated cardiomyopathy.

Prevention of Secondary Complications

Cardiorespiratory

- Evaluation by pulmonary and cardiac specialists before surgeries [Finder et al 2004]
- Administration of pneumococcal vaccine and annual influenza vaccination [Finder et al 2004]

Nutritional. Assessment if:

- Planning to commence steroids [Davidson & Truby 2009]
- Dysphagia is present
- Patient is chronically constipated
- Major surgery has been planned
- Patient is malnourished

Muscular

- Physical therapy to promote mobility and prevent contractures
- Exercise
 - All ambulatory boys with DMD or those in early non-ambulatory phase should participate in regular gentle exercise to avoid contractures and disuse atrophy.
 - Exercise can consist of a combination of swimming pool and recreation-based activities. Swimming can be continued in non-ambulatory patients under close supervision, if medically safe.
 - If patients complain of muscle pain during or after exercise, the activity should be reduced and monitoring for myoglobinuria should be carried out. Myoglobinuria within 24 hours after exercise indicates overexertion leading to rhabdomyolysis.

Bone health. Assessments [Bushby et al 2010b, Darras 2018]:

- Blood
 - Measurement of serum concentrations of calcium and phosphorus, and activity of alkaline phosphatase
 - 25-hydroxyvitamin D (25-OHD) level in springtime or biannually
 - Consideration of magnesium and parathyroid hormone levels
- Urine (calcium, sodium, creatinine)
- Dual-energy x-ray absorptiometry (DXA) scanning
 - At baseline (age ≥ 3 years) or at start of corticosteroid therapy
 - Repeated annually in those at risk (history of fractures, chronic corticosteroid therapy) and those with DXA Z score < -2
- Spine radiograph
 - If back pain is present
 - To exclude vertebral compression fracture
 - To assess degree of kyphoscoliosis if present on physical examination
- Bone age if growth failure occurs (height for age < 5 th percentile or if linear growth is faltering) in persons on or off corticosteroids

Interventions:

- Exposure to sunshine and a balanced diet rich in vitamin D and calcium to improve bone density and reduce the risk of fractures. Supplementation should be carried out in consultation with a dietician.
- Vitamin D supplementation should be initiated if the vitamin D serum concentration is < 20 ng/mL [Bachrach 2005, Biggar et al 2005, Quinlivan et al 2005] and should be considered in all children if levels cannot be maintained [Bushby et al 2010b]. Supplementation should be carried out in consultation with an endocrinologist and in accordance with country-specific pediatric guidelines.
- Intravenous bisphosphonates; recommended in persons with symptomatic vertebral fracture(s). A bone health expert should be consulted.
- Note: Use of oral bisphosphonates for prophylaxis or treatment remains controversial.

Surveillance

Cardiac

The American Academy of Pediatrics (AAP) has published recommendations for optimal cardiac care in persons with dystrophinopathy [American Academy of Pediatrics Section on Cardiology and Cardiac Surgery 2005] ([full text](#)) and consensus guidelines [Bushby et al 2010b].

DMD

- Complete cardiac evaluation at least every two years, beginning at the time of diagnosis
- Note: At minimum, the evaluation should include an electrocardiogram and a noninvasive cardiac imaging study such as echocardiography or cardiac MRI.
- At approximately age ten years, or at the onset of cardiac signs and symptoms, annual complete cardiac evaluation
- Note: Most individuals with DMD demonstrating cardiac signs and symptoms are relatively late in their course.
- If evaluation reveals ventricular dysfunction, initiation of pharmacologic therapy and surveillance at least every six months [Bushby et al 2010a]

BMD. Complete cardiac evaluation at least every two years, beginning at the time of diagnosis. Evaluations should continue at least every two years.

DMD-related DCM. There are no consensus guidelines regarding the optimal cardiac care of patients with DMD-related DCM. However, once the diagnosis of DCM is made, patients will need complete cardiac evaluations at intervals defined by experienced cardiac specialists.

Asymptomatic females. The AAP recommendations for optimal cardiac care of asymptomatic females with a heterozygous DMD pathogenic variant [American Academy of Pediatrics Section on Cardiology and Cardiac Surgery 2005] include the following:

- Education about the risk of developing cardiomyopathy and about the signs and symptoms of heart failure
- Complete cardiac evaluation by a cardiac specialist with experience in the treatment of heart failure and/or neuromuscular disorders, with the initial evaluation to take place in late adolescence or early adulthood, or earlier at the appearance of cardiac signs and symptoms
- Starting at age 25 to 30 years, screening with a complete cardiac evaluation at least every five years
- Treatment of cardiac disease similar to that for boys with dystrophinopathy

Pulmonary

Perform baseline pulmonary function testing before confinement to a wheelchair (usually age ~9-10 years)

Twice-yearly evaluation by a pediatric pulmonologist is indicated after ANY of the following [Finder et al 2004]:

- Confinement to a wheelchair
- Reduction in vital capacity below 80% predicted
- Age 12 years

The 2010 consensus guidelines [Bushby et al 2010b] make detailed recommendations regarding pulmonary care, including:

- Use of self-inflating manual ventilation bag or mechanical insufflation-exsufflation device;
- Manual and mechanically assisted cough techniques;
- Indications for nocturnal and then daytime noninvasive ventilation as well as for tracheostomy.

Orthopedic

Monitor for orthopedic complications, especially contractures and scoliosis in those with DMD and BMD phenotypes.

Evaluate for surgical interventions as needed.

Agents/Circumstances to Avoid

Individuals with dystrophinopathy should avoid botulinum toxin injections.

Although it is recommended that triggering agents like succinylcholine and inhalational anesthetics be avoided in patients with dystrophinopathy because of susceptibility to malignant hyperthermia or malignant hyperthermia-like reactions (rhabdomyolysis, cardiac complications, hyperkalemia), it should be noted that an extensive literature search did not find an increased risk for malignant hyperthermia susceptibility in individuals with dystrophinopathy when compared with the general population [Gurnaney et al 2009]. However, individuals with DMD have been reported to have severe reactions to anesthesia (malignant hyperthermia-like) that did not meet the criteria for true malignant hyperthermia [Bamaga et al 2016].

Evaluation of Relatives at Risk

It is appropriate to evaluate at-risk female family members (i.e., the sisters or maternal female relatives of an affected male and first-degree relatives of a known or possible heterozygous female) in order to identify as early as possible heterozygous females who would benefit from cardiac surveillance (see Surveillance). Evaluations can include the following:

- Molecular genetic testing if the *DMD* pathogenic variant in the family is known
- Serum creatine phosphokinase (CK) testing if the pathogenic variant in the family is not known. Although serum CK concentration can be normal in carrier females, if elevated, it will support heterozygosity status in a female relative.
- Molecular genetic testing of the at-risk female if an affected male is not available for testing:
- By deletion/duplication analysis first
- If no pathogenic variant is identified, by sequence analysis
- Linkage analysis to determine carrier status in at-risk females if (1) the *DMD* pathogenic variant in the proband is not known, (2) no *DMD* pathogenic variant or serum CK elevation is identified in a carrier female, and (3) the family has more than one affected male with the unequivocal diagnosis of DMD/BMD/*DMD*-associated DCM
- Linkage studies are based on accurate clinical diagnosis of DMD/BMD/*DMD*-associated DCM in the affected family members and accurate understanding of the genetic relationships in the family.
- Linkage analysis relies on the availability and willingness of family members to be tested.
- Because the markers used for linkage in DMD/BMD/*DMD*-associated DCM are highly informative and lie both within and flanking the *DMD* locus, they can be used in most families with DMD/BMD/*DMD*-associated DCM [Kim et al 2002].

Note: (1) The large size of *DMD* 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]; thus, multiple recombination events among different members of a family may complicate the interpretation of a linkage study.

- (2) Testing by linkage analysis is not possible for families in which there is a single affected male. (3) Testing by linkage analysis may not be widely available on a clinical basis.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management for Heterozygous Females

Symptomatic heterozygous women should undergo an evaluation for dilated cardiomyopathy ideally prior to conceiving a pregnancy or as soon as the pregnancy is recognized. Asymptomatic heterozygous women should consider undergoing a cardiac evaluation prior to conception or when a pregnancy is recognized. Those with evidence of dilated cardiomyopathy should be treated and/or monitored by a cardiologist and a high-risk obstetrician.

Therapies Under Investigation

See also Table 5.

Gene therapy. Clinical studies in gene therapy currently focus on restoring dystrophin expression by administering recombinant adeno-associated virus vectors that deliver either functional dystrophin transgene (micro- or minidystrophin genes) [Mendell et al 2010, Konieczny et al 2013, Bengtsson et al 2016] or gene-editing components [Calos 2016, Long et al 2016, Nelson et al 2016, Tabebordbar et al 2016].

Gene repair. CRISPR (clustered regularly interspaced short palindromic repeats)-associated protein 9 (CRISPR/Cas9)-mediated genome editing in *mdx* mice has been shown to partially restore dystrophin protein expression in cardiac and skeletal muscle by cutting the noncoding introns that flank the mutated sequence-containing exon 23 [Long et al 2016, Nelson et al 2016, Tabebordbar et al 2016].

Ataluren. Ten to 15 percent of individuals with DMD have nonsense (stop) pathogenic variants, which the investigational drug ataluren may treat by promoting ribosomal read-through, allowing bypass of the pathogenic variant and continuation of the translation process to production of a functioning protein [Finkel 2010].

Preclinical efficacy studies showed production of dystrophin in primary muscle cells from humans and *mdx* mice [Welch et al 2007]. Studies in humans have shown increased full-length dystrophin expression in vitro and in vivo, and decreased serum muscle enzyme levels within 28 days of treatment [Bönnemann et al 2007]. Affected individuals on low doses of ataluren had a 30-meter lower decline in the six-minute walk distance than those on high doses or placebo [Bushby et al 2014]. Based on these results, the drug Translarna™ was granted conditional approval from the European Medicines Agency in August 2014 to treat DMD caused by a nonsense variant; Translarna™ is not approved for treating DMD in the US.

A Phase III multicenter 48-week double-blind placebo-controlled trial (ACT DMD) showed no significant benefit of ataluren for the primary endpoint (i.e., change from baseline in the 6-minute walk test), though there was benefit for some secondary endpoints [McDonald et al 2017].

Myostatin inactivation. The protein myostatin has an inhibitory effect on muscle growth; without it, mice that would otherwise express the DMD phenotype have increased muscle mass compared with those with a wild type myostatin gene [Wagner et al 2002]. Animals treated with antibodies to myostatin have increased muscle mass and strength, lower serum creatine kinase, and less histologic evidence of muscle damage [Bogdanovich et al 2002], suggesting a potential therapeutic target to increase muscle bulk and strength in humans with DMD [McNally 2004].

Wagner et al [2008] conducted a double-blind placebo-controlled multinational randomized study of 116 subjects to test the safety of a neutralizing antibody to myostatin, MYO-029. Campbell et al [2017] found that ACE-031, a fusion protein that binds myostatin and related ligands, noted a trend toward maintenance of the

six-minute walk test compared with a decline in the placebo group (not statistically significant), as well as a trend toward increased lean body mass and bone mineral density and reduced fat mass; however, the study was stopped due to non-muscle-related adverse effects.

Cell therapy. Skeletal muscle progenitors continue to be investigated in the treatment of DMD. A promising technique in mice isolates and transplants muscle satellite cells, a natural source of cells for muscle regeneration [Blau 2008, Cerletti et al 2008].

Idebenone. A randomized controlled trial of the antioxidant idebenone showed significantly reduced decline in respiratory function as measured by peak expiratory flow and other pulmonary function tests [Buyse et al 2015]. Nearly all of the 64 individuals with DMD (age 10-18 years) were nonambulatory at baseline. Further study is needed to determine if idebenone treatment improves outcomes such as the time to assisted ventilation or to death.

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://eudract.ema.europa.eu/) in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

The dystrophinopathies are inherited in an X-linked manner.

Risk to Family Members

Parents of a proband

- The father of an affected male will not have the disorder nor will he be hemizygous for the *DMD* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote.
- If a woman has more than one affected child and no other affected relatives and if the *DMD* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism. The likelihood of germline mosaicism for a *DMD* pathogenic variant in this instance is 15%-20% (empiric risk). Consequently, each of her offspring is at increased risk of inheriting the *DMD* pathogenic variant [van Essen et al 1992, van Essen et al 2003, Wang et al 2017].
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote or the affected male may have a *de novo* *DMD* pathogenic variant, in which case the mother is not a heterozygote. Approximately two thirds of mothers of males with Duchenne muscular dystrophy (DMD) and no family history of DMD are heterozygotes.
- Recommendations for the mother of a proband include molecular genetic testing; heterozygous females need to be identified for the purpose of cardiac surveillance (see Surveillance).
- Molecular genetic testing can be used to determine the point of origin of a *de novo* pathogenic variant. This information is important for determining which branches of the family are at risk for the dystrophinopathies.

- Rarely, a female may be the only affected family member. A female proband may have inherited the *DMD* pathogenic variant from either her mother or her father or the pathogenic variant may be *de novo*. Molecular genetic testing of the mother (and possibly – or subsequently – the father) is recommended.

Sibs of a proband

- The risk to sibs of a male proband depends on the genetic status of the mother; if the proband is female, the risk to sibs depends the genetic status of the mother and the father.
- If the mother of a proband is heterozygous for a *DMD* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygotes and may have a range of clinical manifestations (see Clinical Description).
- If the *DMD* pathogenic variant identified in a male proband is not detectable in maternal leukocyte DNA, it is possible that the proband has a *de novo* pathogenic variant. However, because the likelihood of maternal germline mosaicism in this instance is 15%-20%, the sibs of a proband are at increased risk of inheriting the family-specific *DMD* pathogenic variant.
- If the mother has concomitant somatic and germline mosaicism, the risk to sibs of inheriting the family-specific *DMD* pathogenic variant may be higher than if the mother has germline mosaicism only [van Essen et al 2003].
- If the father of an affected female has a *DMD* pathogenic variant, he will transmit it to all of his daughters and none of his sons.

Offspring of a proband

- Males with *DMD* usually die before reproductive age or are too debilitated to reproduce. If they were to reproduce, all male offspring would be unaffected and all female offspring would be heterozygotes and could have a range of clinical manifestations (see Clinical Description).
- Males with Becker muscular dystrophy (BMD) and *DMD*-associated dilated cardiomyopathy (DCM) may reproduce. All of the daughters will be heterozygotes. None of the sons will inherit their father's *DMD* pathogenic variant.
- Women with a *DMD* pathogenic variant have a 50% chance of transmitting the pathogenic variant to each child.

Other family members. The proband's maternal grandmother, maternal aunts, and their offspring may be at risk of being heterozygotes or being affected (depending on their sex, family relationship, and the carrier status of the proband's mother).

Heterozygote Detection

Carrier testing is possible for at-risk females. See Management, Evaluation of Relatives at Risk.

Females who are identified as heterozygous for a *DMD* pathogenic variant need to be informed of their risk for *DMD*-associated cardiomyopathy, as well as the recommended surveillance.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

BMD and *DMD*-associated DCM are sometimes observed in the same family [Palmucci et al 2000]. Thus, the entire spectrum of possible muscle disease should be considered when obtaining a family history and providing genetic counseling.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *DMD* pathogenic variant has been identified in an affected family member, prenatal testing and preimplantation genetic testing are possible.

Fetal muscle biopsy. In utero fetal muscle biopsy has been used in the prenatal diagnosis of DMD in families with DMD in which the *DMD* pathogenic variant is not known [Ladwig et al 2002].

The history of molecular diagnostic testing in DMD and the impact of new techniques including chromosome microarray (CMA) analysis and noninvasive prenatal diagnosis methods are reviewed in various publications [Raymond et al 2010, Xu et al 2015, Parks et al 2016].

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).

- **CureDuchenne**
Phone: 949-872-2552
Email: info@cureduchenne.org
www.cureduchenne.org
- **Medical Home Portal**
[Duchenne and Becker Muscular Dystrophy](#)
- **MedlinePlus**
[Duchenne and Becker muscular dystrophy](#)
- **NCBI Genes and Disease**
[Duchenne muscular dystrophy](#)
- **Parent Project Muscular Dystrophy**
Phone: 800-714-5437; 201-944-9985
Email: info@parentprojectmd.org
www.parentprojectmd.org
- **American Heart Association**
[Dilated Cardiomyopathy \(DCM\)](#)

- **Children's Cardiomyopathy Foundation**

Phone: 866-808-2873 (toll-free)

Fax: 201-227-7016

Email: info@childrenscardiomyopathy.org

www.childrenscardiomyopathy.org

- **European Neuromuscular Centre (ENMC)**

Netherlands

Phone: 31 35 5480481

Email: enmc@enmc.org

www.enmc.org

- **Muscular Dystrophy Association (MDA) - USA**

Phone: 833-275-6321

www.mda.org

- **Muscular Dystrophy Canada**

Canada

Phone: 800-567-2873

Email: info@muscle.ca

www.muscle.ca

- **Muscular Dystrophy UK**

United Kingdom

Phone: 0800 652 6352

www.musculardystrophyuk.org

- **Duchenne Registry**

Parent Project Muscular Dystrophy fights to end Duchenne. We accelerate research, raise our voices to impact policy, demand optimal care for every single family, and strive to ensure access to approved therapies.

Parent Project for Muscular Dystrophy Research

Phone: 888-520-8675

Email: coordinator@duchenregistry.org

www.duchenregistry.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Dystrophinopathies: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
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Table A. continued from previous page.

DMD	Xp21.2-p21.1	Dystrophin	DMD homepage - Leiden Muscular Dystrophy pages	DMD	DMD
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Data are compiled from the following standard references: gene from [HGNC](#); chromosome locus from [OMIM](#); protein from [UniProt](#). For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click [here](#).

Table B. OMIM Entries for Dystrophinopathies ([View All in OMIM](#))

300376	MUSCULAR DYSTROPHY, BECKER TYPE; BMD
300377	DYSTROPHIN; DMD
302045	CARDIOMYOPATHY, DILATED, 3B; CMD3B
310200	MUSCULAR DYSTROPHY, DUCHENNE TYPE; DMD

Gene structure. *DMD* spans 2.2 Mb of DNA and comprises 79 exons. It has at least four promoters. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. Innumerable intragenic variants have been described, many of which have been used clinically for genetic linkage analysis.

Pathogenic variants. More than 5,000 pathogenic variants have been identified in persons with DMD or BMD [Aartsma-Rus et al 2006, Flanigan et al 2009, Tuffery-Giraud et al 2009]. 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]. Duplications cluster near the 5' end of the gene, with duplication of exon 2 being the single most common duplication identified [White et al 2006].

The frequencies for types of pathogenic variants given in this section are for individuals with DMD or BMD. Data are insufficient to estimate the percentage of individuals with *DMD*-associated dilated cardiomyopathy with detectable *DMD* pathogenic variants.

Deletions of one or more exons may result in in-frame or out-of-frame transcripts and account for approximately 60%-70% of pathogenic variants in individuals with DMD and BMD [Yan et al 2004, Dent et al 2005, Prior & Bridgeman 2005, Takeshima et al 2010].

Duplications may result in in-frame or out-of-frame transcripts and account for approximately 5%-10% of pathogenic variants in males with DMD and BMD [White et al 2002, White et al 2006, Flanigan et al 2009, Takeshima et al 2010]. Duplications may be slightly more common in BMD: one small series found duplications in 14 (19%) of 75 males with BMD [Kesari et al 2008]; however, most studies, including those using newer techniques such as MLPA, have not found rates higher than 10% in BMD [Takeshima et al 2010].

Single-nucleotide variants (SNVs), small deletions or insertions, single-base changes, and splice site changes account for approximately 25%-35% of pathogenic variants in males with DMD and about 10%-20% of males with BMD [Bennett et al 2001, Mendell et al 2001, Dolinsky et al 2002, Flanigan et al 2003, Hofstra et al 2004, Takeshima et al 2010].

- Nonsense variants occur more commonly in DMD – in the range of 20%-25% of cases – as compared to fewer than 5% in BMD [Flanigan et al 2009, Takeshima et al 2010].
- Splice site variants and small insertions/deletions (indels) are a substantial proportion of sequence changes in both DMD and BMD.
- Missense variants are not a common cause of either Duchenne or Becker dystrophy.

Normal gene product. Dystrophin is a membrane-associated protein present in muscle cells and some neurons. The N-terminal domain binds to actin. A large rod domain includes 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.

Abnormal gene product. Pathogenic variants 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. In *DMD*-associated DCM, functional dystrophin is absent in the myocardium but may be normal or mildly abnormal in skeletal muscle [Ferlini et al 1999, Neri et al 2007] because *DMD*-associated DCM is associated with specific types of *DMD* pathogenic variants that have a differential response to tissue-specific transcription or alternative splicing in cardiac vs skeletal muscle.

Chapter Notes

Acknowledgments

The authors would like to thank Elizabeth DeChene, MS, CGC, and Elicia Estrella, MS, CGC, of the Program in Genomics/Harvard Neuromuscular Disease Project, Children's Hospital Boston, for their assistance in reviewing and editing the Genetic Counseling Section.

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- 20 January 2022 (aa) Revision: dystrophin restoration therapies (See Treatment of Manifestations; Table 5.)
- 26 April 2018 (ha) Comprehensive update posted live
- 26 November 2014 (me) Comprehensive update posted live
- 23 November 2011 (me) Comprehensive update posted live
- 21 March 2008 (me) Comprehensive update posted live
- 25 August 2005 (me) Comprehensive update posted live
- 1 October 2004 (cd) Revision
- 3 August 2004 (cd) Revision: Management
- 24 March 2004 (cd) Revision: Diagnosis
- 23 June 2003 (me) Comprehensive update posted live
- 5 September 2000 (me) Review posted live
- December 1999 (bk) Original submission

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