Muscular Dystrophy

The muscular dystrophies (MD) are a group of genetic diseases characterized by progressive weakness and degeneration of the skeletal or voluntary muscles and replacement of the dead (apoptotic) muscles by fibrous or other nonfunctional tissues. This causes progressive loss of control of body movement.

The muscles of the heart and chest walls are also affected sooner or later and may be the cause of the cardio-respiratory failure which may be fatal. Other involuntary muscles or organs may get affected in some forms of muscular dystrophy, and a few forms involve other organs as well. Some forms of MD are seen in infancy or childhood, while others may not appear until middle age or later. The disorders differ in terms of the distribution and extent of muscle weakness, age of onset, rate of progression, and pattern of inheritance.

Duchenne MD is the most common form of MD and primarily affects boys. It is caused by the absence of dystrophin, a protein involved in maintaining the integrity of muscle and regeneration after apoptosis (programmed natural cell death followed by regeneration of the same number and type of cells). Most boys are unable to walk by age 12, and later need a respirator to breathe.

Symptoms

All of the muscles may be affected. Or, only specific groups of muscles may be affected, such as those around the pelvis, shoulder, or face.

Symptoms include:

- Mental retardation (only present in some types of the condition)
- Muscle weakness that slowly gets worse
- Delayed development of muscle motor skills
- Difficulty using one or more muscle groups
- Drooling
- Eyelid drooping (ptosis)
- Frequent falls
- Loss of strength in a muscle or group of muscles as an adult
- Loss in muscle size
- Problems walking (delayed walking)

TYPES OF MUSCULAR DYSTROPHY

- Becker Muscular Dystrophy
- Congenital Muscular Dystrophies
- Duchenne Muscular Dystrophy
Emery Dreifuss Muscular Dystrophy
Facioscapulohumeral Muscular Dystrophy
Limb-girdle Muscular Dystrophy
Myotonic Muscular Dystrophy
Oculopharyngeal Muscular Dystrophy

Becker muscular dystrophy (BMD)

The muscular dystrophies (MD) are a group of genetic disorders, which cause muscle weakness. The Becker type was first recognised in 1956 and is now known to be a much milder variant of the better known Duchenne type of Muscular Dystrophy. Becker Muscular Dystrophy is generally slowly progressive and affects only males.

Causes Becker Muscular Dystrophy

A fault in a particular gene (dystrophin) carried on the X chromosome leads to the formation of a faulty protein in muscle fibres. This protein, also called dystrophin, is absent or severely abnormal in Duchenne Muscular Dystrophy. In Becker Muscular Dystrophy a milder fault makes the dystrophin molecule smaller (or occasionally larger) or less abundant than normal. When dystrophin is abnormal the muscle fibres gradually break down and the muscles slowly become weaker. These dystrophin abnormalities in muscle provide a very good test for the diagnosis of Becker Muscular Dystrophy.

Signs and Symptoms

The pattern of muscle loss in BMD usually begins with the hips and pelvic area, the thighs and the shoulders. To compensate for weakening muscles, the person may walk with a waddling gait, walk on his toes or stick out the abdomen.

The rate of muscle degeneration varies a great deal from one person to another. Some men require wheelchairs by their 30s or later, while some manage for many years with minor aids, such as canes.

Pain and sensation

Because muscular dystrophy doesn’t affect nerves directly, touch and other senses remain normal, as does control over the smooth, or involuntary, muscles of the bladder and bowel, and sexual functions.

Muscle deterioration in BMD usually isn’t painful in itself. Some people report MUSCLE CRAMPS at times; these usually can be treated with over-the-counter pain relievers.
The heart

Like muscles in the limbs, heart muscles also can be weakened by lack of dystrophin. People with BMD often develop *cardiomyopathy* — heart muscle weakness — because of a deficiency of dystrophin. The muscle layer (*myocardium*) of the heart deteriorates, just as the skeletal muscles do.

Damage done by BMD to the heart can become life-threatening as early as the teen years, and some people with BMD have mild skeletal muscle involvement but severe cardiac problems. For these reasons, everyone with BMD should be monitored by a cardiologist. See the Medical Management section for more information on managing heart problems in BMD.

To view a presentation by cardiologist Elizabeth McNally about the heart in BMD, see the August 2012 video Cardiac Complications and Management in BMD.

Breathing and coughing

Respiratory muscles often stay strong in BMD for many years, but eventually, they may become weaker than is optimal for breathing and coughing (to clear secretions from the respiratory tract).

Learning

Doctors believe that dystrophin abnormalities in the brain may cause subtle cognitive and behavioral deficits. The learning problems seen in some people with BMD seem to occur in three general areas: attention focusing, verbal learning and memory, and emotional interaction. For more on coping with intellectual effects, see Medical Management.

Becker Muscular Dystrophy is inherited

The disorder is inherited as an X-linked recessive trait, which means that it affects only males but may be transmitted by unaffected female carriers of the gene to their sons. The sons of carriers each have a 50:50 chance of being affected. The daughters of carriers each have a 50:50 chance of being carriers. The mothers and sisters of affected males may be carriers and may need to be tested. **The sons of affected males do not carry the gene and will not be affected or transmit the gene. However, all the daughters of affected males are carriers of the gene and may transmit the disorder to the following generation.**
Becker Muscular Dystrophy can be diagnosed in childhood

Once Becker dystrophy is known to affect one male in a family it is possible by simple blood tests to identify it or rule it out in any other boys at risk from birth onwards. In most families, but not in all, prenatal diagnosis is also possible, but this is more difficult and if at all possible the situation needs to be fully assessed before a pregnancy is embarked upon.

Congenital Muscular Dystrophies

The congenital muscular dystrophies are a group of muscle conditions which usually show symptoms at a very early age. These include ullrich congenital Muscular Dystrophy, MDC1A (Muscular Dystrophy congenital, merosin negative) and rigid spine syndrome. Congenital means ‘from birth’ and in the great majority of cases of congenital muscular dystrophy the initial symptoms are present at birth or in the first few months.

Babies with Congenital Muscular Dystrophy often have hypotonia (low muscle tone or floppiness), and may have reduced movements. Other common signs are contractures (tightness) in the ankles, hips, knees and elbows. The contractures can sometimes be severe and affect several joints (known as arthrogryposis). They happen because the baby has not had the muscle strength to move freely enough in the womb. Some of these babies may also have respiratory problems because of weakness of breathing muscles. In some children who do not have contractures the first problems are only noted after a few months because of difficulties in holding the head or delay in learning how to sit unaided, stand or walk.

Types of Congenital Muscular Dystrophy

Congenital Muscular Dystrophy is a very heterogeneous group of conditions. These are generally grouped under two main types:

- Children who only have muscle weakness involving all muscles but have normal intelligence
- Children who have muscle weakness and learning difficulties, with or without seizures. Learning difficulties may be subtle, moderate or severe.
Types of Congenital MD

At least 30 different types of CMD are now recognized. At first glance, the various types of CMD seem to have little in common other than their early onset. But on the molecular level, the types can be grouped how their faulty protein affects cells.

A very small group of CMDs are linked to proteins that affect what happens inside muscle fibers, affecting how the fibers process signals from the nervous system, for example, or how they handle calcium.

But the vast majority of CMD types are related to proteins that make up or interact with the extracellular matrix that surrounds muscle fibers.

Several types of CMD that arise from gene mutations that initially seemed unrelated now appear to be related to defects in proteins that "sugar-coat" (glycosylate) a matrix protein, allowing it to connect with other proteins.

CMD with adducted (drawn inward) thumbs, ophthalmoplegia (paralyzed eye muscles) and intellectual disability

Description: rare form of CMD with inward-drawn thumbs, contractures (permanent shortening) of the toe joints, weakness, lack of muscle tone, delayed walking, paralysis of eye muscles and intellectual disability

Molecular basis: unknown

Inheritance pattern: recessive (requires mutations in both copies of a gene to produce symptoms)

CMD with cerebellar atrophy (diminished size of the cerebellum, a part of the brain involved in motor control)

Description: nonprogressive form of CMD with onset by 7 months, weakness, lack of muscle tone, delayed motor milestones, lack of coordination of movements, difficulty speaking, involuntary eye movements and intellectual disability

Molecular basis: unknown

Inheritance pattern: possibly recessive (requires mutations in both copies of a gene to produce symptoms)

CMD with desmin inclusions (abnormal accumulations of the muscle protein desmin in some muscle fibers)

Description: onset of progressive weakness and low muscle tone at birth or during early infancy; small muscles; cardiac abnormalities in some; spinal curvatures at 8-14 years; joint contractures; respiratory impairment
**Molecular basis:** mutations in SEPN1 gene, causing deficiency of SEPN1 protein; protein is thought to play a role in early development or regeneration of muscle tissue

**Inheritance pattern:** recessive (requires mutations in both copies of a gene to produce symptoms)

**CMD with integrin alpha 7 mutations**

**Description:** early-onset low muscle tone, weakness; may walk at age 2-3; respiratory involvement with disease progression

**Molecular basis:** mutations in the integrin-alpha 7 gene, causing a deficiency of the integrin alpha 7 beta 1 protein; protein normally provides a link between muscle fibers and the surrounding matrix

**Inheritance pattern:** recessive (requires mutations in both copies of a gene to produce symptoms)

**CMD with joint hyperlaxity (abnormally flexible joints)**

**Description:** weakness, poor muscle tone and contractures from birth; slowly progressive; walking at 1-3 years; wheelchair later, between teens and 30s; reduced respiratory capacity that does not progress; contractures in some joints and abnormal flexibility in others; spinal curvature possible; normal intelligence

**Molecular basis:** thought to be due to mutations in the integrin alpha 9 gene, causing a deficiency of the integrin alpha 9 protein; protein normally plays a role in how cells stick to each other and to their surroundings

**Inheritance pattern:** recessive (requires mutations in both copies of a gene to produce symptoms)

**CMD with familial junctional epidermolysis bullosa**

**Description:** onset of weakness or poor muscle tone, with skin blistering, at birth; skin blisters with injury and heat; slowly progressive; many need wheelchair by age 10; elbow contractures; respiratory impairment; cardiomyopathy; diminished brain size; treatment with 3,4-diaminopyridine, which increases signal transmission from nerve to muscle, may be helpful

**Molecular basis:** mutations in the gene for the plectin protein, causing a deficiency of this protein; protein is thought to provide mechanical strength to cells and tissues

**Inheritance pattern:** recessive (requires mutations in both copies of a gene to produce symptoms)
CMD with muscle hypertrophy (enlargement of muscles); also called MDC1C

Description: low muscle tone and weakness starting in first weeks of life; may sit unassisted but walking not achieved; some muscles enlarged, especially calf muscles; other muscles small, especially in shoulder area; joint contractures in some; cognitive function usually normal; mild intellectual disability or speech problems can occur

Molecular basis: mutations in gene for fukutin-related protein (FKRP), leading to FKRP deficiency; protein normally helps glycosylate (sugar-coat) a protein called alpha-dystroglycan

Inheritance pattern: recessive (requires mutations in both copies of a gene to produce symptoms)

CMD with muscle hypertrophy and respiratory failure; also called MDC1B

Description: early-onset weakness with involvement of the diaphragm and respiratory failure; walking at 1.5 to 2.5 years; weakness does not appear to progress; generalized muscle enlargement; contractures in ankles; spinal rigidity in about 50 percent; normal intelligence

Molecular basis: mutations in unknown gene on chromosome 1

Inheritance pattern: recessive (requires mutations in both copies of a gene to produce symptoms)

CMD with muscle hypertrophy and severe intellectual disability; also called MDC1D

Description: onset around 5 months, with low muscle tone and weakness; some muscles enlarged; global developmental delay; profound intellectual disability; contractures of ankles and elbows

Molecular basis: mutations in LARGE gene, leading to deficiency of LARGE protein; protein thought to play a role in sugar-coating (glycosylation) of alpha-dystroglycan protein

Inheritance pattern: recessive (requires mutations in both copies of a gene to produce symptoms)

CMD with myasthenic syndrome

Description: rare form of CMD with onset by time of birth; weakness, lack of muscle tone, small muscles; slowly progressive; respiratory involvement possible; most survivors able to walk as children and adults; normal intelligence
**Molecular basis:** DOK7 gene mutation leading to deficiency of DOK7 protein; protein normally plays a role in forming the connections between nerves and muscles

**Inheritance pattern:** recessive (requires mutations in both copies of a gene to produce symptoms)

**CMD with (early) spinal rigidity**

**Description:** onset birth to 1 year or during first decade of life; early-onset poor muscle tone, weakness; respiratory capacity often reduced; small muscles; early improvement, followed by stabilization or slow decline; spinal rigidity beginning ages 3-7, with limited ability to flex the neck and spine; spinal curvature beginning ages 4-12 and progressing; joint contractures; minor cardiac abnormalities, if any; normal intelligence

**Molecular basis:** mutations in SEPN1 gene, causing deficiency of SEPN1 protein; protein is thought to play a role in early development or regeneration of muscle tissue

**Inheritance pattern:** recessive (requires mutations in both copies of a gene to produce symptoms)

**CMD with spinal rigidity and lamin A/C abnormality**

**Description:** weakness within first year; respiratory involvement; rigid spine, curved spine, curved feet; cardiac rhythm abnormalities in some; premature aging in some; abnormalities of fatty tissue in some

**Molecular basis:** mutation in lamin A/C gene, causing an abnormality in the lamin A or C proteins; these normally form part of a membrane that surrounds the cell nucleus

**Inheritance pattern:** dominant (requiring a mutation in only one copy of a gene to produce symptoms)

**CMD with spinal rigidity and selenoprotein deficiency**

**Description:** early-onset weakness; developmental delay; reduced respiratory capacity; fatigue; skin abnormalities; hearing loss; straight, rigid spine

**Molecular basis:** mutations in SBP2 gene, causing deficiency of SBP2 protein; protein normally involved in the production of selenoproteins

**Inheritance pattern:** recessive (requires mutations in both copies of a gene to produce symptoms)
**CMD with structural abnormalities of mitochondria (energy-producing subunits of cells)**

**Description:** poor muscle tone, weakness from birth, with late walking; loss of muscle tissue; cardiomyopathy; intellectual disability; mitochondria (seen in muscle biopsy samples) are enlarged and have an abnormal structure

**Molecular basis:** mutations in choline kinase beta gene, which leads to deficiency of choline kinase beta protein; protein normally helps make a key substance in muscle and brain

**Inheritance pattern:** recessive (requires mutations in both copies of a gene to produce symptoms)

**Fukuyama CMD; also called MDDGA4**

**Description:** common in Japan; rare in Western countries; spectrum of severity; weakness and low muscle tone within first year; some achieve walking; joint contractures; spinal curvatures; seizures in 50 percent; intellectual disability; eye involvement

**Molecular basis:** mutations in fukutin gene, causing a deficiency of fukutin protein; protein normally helps sugar-coat (glycosylate) the alpha-dystroglycan protein in muscle and brain tissue

**Inheritance pattern:** recessive (requires mutations in both copies of a gene to produce symptoms)

**Merosin-deficient CMD; also called MDC1A**

**Description:** early-onset weakness and low muscle tone; spectrum of severity; some learn to walk at age 2-3 years; spinal curvature; contractures; respiratory impairment; intelligence often normal; seizures in about 20 percent

**Molecular basis:** mutations in laminin alpha 2 gene, leading to deficiency of laminin alpha 2 protein; leads to deficiency of laminin 211 protein, also known as merosin; protein normally helps connect muscle fiber with surrounding matrix

**Inheritance pattern:** recessive (requires mutations in both copies of a gene to produce symptoms)

**Merosin-positive CMD; this is an old term referring to a variety of CMD types in which merosin is normal**

**Description:** examples are CMD with early spinal rigidity; CMD with muscle hypertrophy; CMD with muscle hypertrophy and respiratory failure; CMD with myasthenic syndrome; and Ullrich CMD; see individual listings for different types

**Molecular basis:** variety of gene mutations, causing variety of protein defects that do not affect merosin protein
**Inheritance pattern:** recessive (requires mutations in both copies of a gene to produce symptoms)

### Santavuori muscle-eye-brain disease

**Description:** low muscle tone at birth; slow development; intellectual disability; eye abnormalities

**Molecular basis:** Mutations in POMGnT1 gene, causing deficiency of POMGnT1 protein; protein normally helps sugar-coat (glycosylate) the alpha-dystroglycan protein

**Inheritance pattern:** recessive (requires mutations in both copies of a gene to produce symptoms)

### Ullrich CMD

**Description:** early-onset weakness, poor muscle tone; severity varies; some joints have contractures; some joints have hyperlaxity (excessive flexibility); spinal rigidity, curvature; respiratory impairment; soft skin; normal cardiac function; normal intelligence

**Molecular basis:** mutations in COLGA1, COL6A2 or COL6A3 genes, causing deficiency of or abnormalities in collagen 6 protein; protein normally has an anchoring function in many tissues, including the matrix surrounding muscle fibers

**Inheritance pattern:** dominant (requiring a mutation in only one copy of a gene to produce symptoms) or recessive (requires mutations in both copies of a gene to produce symptoms)

### Walker-Warburg syndrome: MDDGA type

**Description:** early-onset weakness with brain and eye abnormalities; intellectual disability

**Molecular basis:** mutations in B3GNT1 gene, causing deficiency of the B3GNT1 protein; protein normally helps sugar-coat (glycosylate) alpha-dystroglycan

**Inheritance pattern:** recessive (requires mutations in both copies of a gene to produce symptoms)

### Walker-Warburg syndrome: MDDGA1 type

**Description:** early-onset weakness with brain and eye abnormalities; intellectual disability

**Molecular basis:** mutations in POMT1 gene, causing deficiency of POMT1 protein; protein normally helps sugar-coat (glycosylate) alpha-dystroglycan

**Inheritance pattern:** recessive (requires mutations in both copies of a gene to produce symptoms)
Walker-Warburg syndrome: MDDGA2 type

Description: early-onset weakness with brain and eye abnormalities; intellectual disability

Molecular basis: mutations in POMT2 gene, causing deficiency of POMT2 protein; protein normally helps sugar-coat (glycosylate) alpha-dystroglycan

Inheritance pattern: recessive (requires mutations in both copies of a gene to produce symptoms)

- Walker-Warburg syndrome: MDDGA3 type; same as Santavuori muscle-eye-brain disease
- Walker-Warburg syndrome: MDDGA4 type; same as Fukuyama CMD
- Walker-Warburg syndrome: MDDGB5 type; same as CMD with muscle hypertrophy (MDC1C)
- Walker-Warburg syndrome: MDDGA6 type; same as CMD with muscle hypertrophy and severe intellectual disability (MDC1D)

Walker-Warburg syndrome: MDDGA7 type

Description: early-onset weakness with brain and eye abnormalities; intellectual disability

Molecular basis: mutations in ISPD gene, causing deficiency of the ISPD protein; protein normally helps sugar-coat (glycosylate) alpha-dystroglycan

Inheritance pattern: recessive (requires mutations in both copies of a gene to produce symptoms)

Walker-Warburg syndrome: MDDGA8 type

Description: early-onset weakness with brain and eye abnormalities; intellectual disability

Molecular basis: mutations in GTDC2 gene, causing deficiency of the GTDC2 protein; protein may help sugar-coat (glycosylate) alpha-dystroglycan
**Inheritance pattern:** recessive (requires mutations in both copies of a gene to produce symptoms)

**Walker-Warburg syndrome: MDDGA10 type**

**Description:** early-onset weakness with brain and eye abnormalities; intellectual disability

**Molecular basis:** mutations in TMEM5 gene, causing deficiency of the TMEM5 protein; protein may help sugar-coat (glycosylate) alpha-dystroglycan

**Inheritance pattern:** recessive (requires mutations in both copies of a gene to produce symptoms)

**Walker-Warburg syndrome: MDDGA11 type**

**Description:** early-onset weakness with brain and eye abnormalities; intellectual disability

**Molecular basis:** mutations in B3GALNT2 gene, causing deficiency of the B3GALNT2 protein; protein normally helps sugar-coat (glycosylate) alpha-dystroglycan

**Inheritance pattern:** recessive (requires mutations in both copies of a gene to produce symptoms)

**Walker-Warburg syndrome: MDDGA12 type**

**Description:** early-onset weakness with brain and eye abnormalities; intellectual disability

**Molecular basis:** Mutations in SGK196 gene, causing deficiency of SGK196 protein; protein normally may help sugar-coat (glycosylate) alpha-dystroglycan

**Inheritance pattern:** recessive (requires mutations in both copies of a gene to produce symptoms)

**The extracellular matrix and CMD**

The extracellular — outside the cell — matrix is the substance that surrounds the cells of a tissue, such as muscle, providing physical and biochemical support.

An important role of the matrix around muscle fibers is force transmission. For a muscle to pull against bones, it needs to have contact with something that transmits force from the muscle fibers onto the tendons and bones.

When all is going well, the matrix transmits that force, as well as chemical signals that muscles need to stay healthy.

The matrix is a key supporting structure for the survival and regeneration of muscle. When cells lose touch with their surrounding matrix — as happens in most types of CMD — trouble follows.
Muscle fibers are surrounded by the membrane that separates the inside of the fiber from material outside the fiber – The extra cellular matrix

Most of the molecular defects that cause congenital muscular dystrophies affect proteins in the extracellular matrix, such as laminin 211, intergin, collagen or 6 alpha – distroglycan. The protein known as fukutin, fukutin related proteins, POMT 1, POMT2, POMgnT12, large and other all participate in special “sugar coating” (glycoslation) of alpha- dystroglycan. The sugar coating is shown as blue. Various other proteins shown — such as the sarcoglycans and dystrophin — can, when flawed or missing, cause muscular dystrophies other than CMD.
**Signs and Symptoms**

The term congenital muscular dystrophy (CMD) is actually the name for a group of muscular dystrophies united by the fact that muscle weakness begins in infancy or very early childhood (typically before age 2). Congenital diseases are those in which the symptoms are present at or soon after birth.

Most children with CMD exhibit some progressive muscle weakness, although they can have different symptoms, degrees of severity and rates of progression.

This weakness, usually first identified as hypotonia, or lack of muscle tone, can make an infant seem “floppy.” Later, infants and toddlers may be slow to meet motor milestones such as rolling over, sitting up or walking, or may not meet some milestones at all.

Some of the rarer forms of CMD are also accompanied by significant learning disabilities, or mental retardation. For more on the specific symptoms of different types of CMD.

**How is congenital muscular dystrophy diagnosed?**

A baby with Congenital Muscular Dystrophy is usually first diagnosed as a ‘floppy baby’. Doctors can see the symptoms described above, but as these could be due to a number of different conditions, they have to conduct a series of tests to try to make an accurate diagnosis.

Firstly a **blood test** is taken and the level of a muscle enzyme assessed (the creatine kinase or CK level). In approximately 40% of cases of congenital muscular dystrophy this level is 5-20 times higher than normal.

**Muscle ultrasound** may also help to detect abnormalities of the muscle. The technique is very simple, similar to the ultrasound studies carried out in pregnancy and may provide further evidence of the involvement of the muscle.

An **electromyography (EMG)** test may also be done. A small needle is inserted into muscle and the electric activity recorded. This test may provide evidence of an abnormal pattern of electric activity in the muscle.

At this stage however even in the cases with high CK levels, abnormal muscle ultrasound and EMG, an additional test which is required in almost every case is a muscle biopsy.

**Muscle biopsy** can help to identify the subtype of congenital muscular dystrophy to provide a precise diagnosis in several ways:
When the muscle is studied under the microscope, it will show variation in the size of muscle fibres and that some of these fibres are replaced by fat and fibrous tissue. In addition, the production of individual components of the muscle fibre can be studied in detail with specialised tests. This greatly helps to narrow down the diagnostic possibilities.

In the forms of congenital muscular dystrophy in which the gene defect has been identified, genetic tests will provide the ultimate diagnosis.

Prenatal diagnosis is possible in several types of congenital muscular dystrophy. It is based on the ability to detect the genetic abnormality in the developing foetus. This however can only be used in the forms of congenital muscular dystrophy associated with a recognised gene defect or a specific protein deficiency.

Duchenne muscular dystrophy

Duchenne muscular dystrophy is an inherited disorder that involves muscle weakness, which quickly gets worse.

It is one of more than 20 types of muscular dystrophy. All the muscular dystrophies are caused by faults in genes (the units of inheritance that parents pass on to their children) and they cause progressive muscle weakness because muscle cells break down and are gradually lost. The Duchenne type affects only boys (with extremely rare exceptions) and a problem in this gene is known to result in a defect in a single important protein in muscle fibres called dystrophin. It is named after Dr Duchenne de Boulogne who worked in Paris in the mid-19th century who was one of the first people to study the muscular dystrophies.

Causes

Duchenne muscular dystrophy is a form of muscular dystrophy. It worsens quickly. Other muscular dystrophies (including Becker's muscular dystrophy) get worse much more slowly.

Duchenne muscular dystrophy is caused by a defective gene for dystrophin (a protein in the muscles). However, it often occurs in people without a known family history of the condition.

Because of the way the disease is inherited, it usually affects boys. The sons of females who are carriers of the disease (women with a defective gene, but no symptoms themselves) each have a 50% chance of having the disease. The daughters each have a 50% chance of being carriers. Very rarely, a girl can be affected by the disease.

Duchenne muscular dystrophy occurs in about 1 out of every 3,600 male infants. Because this is an inherited disorder, risks include a family history of Duchenne muscular dystrophy.
**Symptoms**

Symptoms usually appear before age 6 and may appear as early as infancy.

They may include:

- **Fatigue**
- Learning difficulties (the IQ can be below 75)
- Intellectual disability (possible, but does not get worse over time)

**Muscle weakness:**

- Begins in the legs and pelvis, but also occurs less severely in the arms, neck, and other areas of the body
- Problems with motor skills (running, hopping, jumping)
- Frequent falls
- Trouble getting up from a lying position or climbing stairs
- Weakness quickly gets worse

Progressive difficulty walking:

- Ability to walk may be lost by age 12, and the child will have to use a wheelchair
- Breathing difficulties and heart disease usually start by age 20

**Exams and Tests**

A complete nervous system (neurological), heart, lung, and muscle exam may show:

- Abnormal heart muscle (**cardiomyopathy**)
- **Congestive heart failure** or irregular heart rhythm (**arrhythmia**)
- Deformities of the chest and back (**scoliosis**)
- Enlarged muscles of the calves, buttocks, and shoulders (around age 4 or 5). These muscles are eventually replaced by fat and connective tissue (**pseudohypertrophy**).
- Loss of muscle mass (**wasting**)
- **Muscle contractures** in the heels, legs
- Muscle deformities
- Respiratory disorders, including **pneumonia** and swallowing with food or fluid passing into the lungs (in late stages of the disease)

**Tests may include:**

- Electromyography (**EMG**)
- Genetic tests
Muscle biopsy
Serum CPK

**Possible Complications**

- Cardiomyopathy (can also occur in female carriers, who should also be screened)
- Congestive heart failure (rare)
- Deformities
- Heart arrhythmias (rare)
- Mental impairment (varies, usually minimal)
- Permanent, progressive disability, including decreased mobility and decreased ability to care for self
- Pneumonia or other respiratory infections
- Respiratory failure

**Prevention**

People with a family history of the disorder may want to seek genetic counseling. Genetic studies done during pregnancy are very accurate in detecting Duchenne muscular dystrophy.

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**Emery-Dreifuss muscular dystrophy**

This form of muscular dystrophy was named after Professor Emery in the UK and Professor Dreifuss in the United States, who together first described the disorder nearly 40 years ago. Emery-Dreifuss muscular dystrophy affects the arms, legs, spine, face, neck, and heart. This disease is characterized by **contractures** of the elbows and the Achilles tendons at an early age, slowly progressive muscle **wasting** and **weakness**, and life potentially life-threatening heart muscle disease.

Like other muscular dystrophies it is a wasting disease of muscle. It usually begins in childhood or adolescence. The features, which make it unique and different from other muscular dystrophies, are the early development of muscle contractures, the distribution of muscle weakness, and the fact that the heart may be affected in a particular way.

In this condition they limit elbow straightening so that the arms are often held in a semi-flexed way, they result in a tendency to walk on the toes, and they limit forward bending of the neck.

In the upper limbs weakness affects mainly the shoulders and upper arms. In the lower limbs, unlike most other dystrophies, weakness affects the lower legs first. This distribution of muscle
weakness is sometimes referred to as ‘scapulo-humero-peroneal’.

At first there is difficulty in raising the arms above the head and lifting heavy objects, and a tendency to trip over carpets. Later on the hip and thigh muscles also become affected so that climbing stairs becomes increasingly difficult, as does rising from a chair without assistance.

**Signs and Symptoms**

The symptoms of Emery-Dreifuss muscular dystrophy (EDMD) usually become apparent by 10 years of age. Early signs include “toe-walking” because of stiff Achilles’ tendons in the heels, and difficulty bending the elbows. Other early symptoms include weakness and wasting of shoulder, upper arm and calf muscles.

The contractures (joint stiffening) that occur early in EDMD may make arm, neck, heel and spine movements difficult. However, progression of muscle weakness seems to occur very slowly in EDMD and may not become a source of difficulty until later in **life**.

Fainting due to heart abnormalities also can be an early sign of EDMD. Usually, cardiac problems are detectable by age 20, but they can occur at earlier stages in the disease as well. Some **women** who are genetic carriers for X-linked EDMD also may be at risk for cardiac problems, and this risk may increase with age. (X-linked EDMD carriers don’t tend to have muscle weakness or contractures.)

Intellect isn’t affected.

In general the condition is less severe than many other forms of muscular dystrophy and though life expectancy may be shortened, many affected individuals can expect to reach middle age or later. However, it is essential that affected individuals be checked at frequent intervals, say every 12 months, to ensure that the heart is not affected. There is evidence that a more severe recessive form also exists. Here weakness is present and progresses rapidly from early childhood, however this is very rare.

**Medical Care**

No specific treatment for EDMD exists, but aggressive supportive care is essential to preserve muscle activity, to provide for maximal functional ability, and to prolong life expectancy.

The primary concern is preventing sudden cardiac death.

- **Pacemakers** should be inserted in patients with bradycardia.
- Intra-atrial thrombus, cerebral embolization, and cardiomyopathy may still occur even in patients treated with pacemaker.
- Cardiac transplantation should be considered in patients with progressive untreatable cardiomyopathy.
- Ventricular arrhythmias may occur late in the disease and for this reason a cardioverter-
defibrillator may be preferable to a simple pacemaker.

The other main concern is prevention and correction of skeletal abnormalities (contractures) and to maintain ambulation.
- Achilles tenotomy may help stabilize ankle contractures.
- Neck and spine contractures may benefit from surgical intervention (internal fixation with rods), but the benefit must be weighed against the risk of loss of ambulation. Aggressive use of passive stretching, bracing, and orthopedic procedures allows the patient to remain independent for as long as possible.
As in other hereditary myopathies, a team approach including a neurologist, pulmonologist, cardiologist, orthopedic surgeon, physiatrist, physical therapist, orthotist, and counselors ensures the best possible therapy.

Surgical Care
The goal is to keep the patient as mobile as possible for as long as possible.
Orthopedic surgery (eg, tendon release) may be needed to correct or prevent contractures and to increase range of motion.

Consultations
Cardiologist: Early referral and evaluation by a cardiologist is mandatory for persons with EDMD, immediately after diagnosis. Not only is cardiac disease always present, it may manifest unexpectedly as syncope or sudden death. Typically, ECG, 24 hour Holter-monitoring, and echocardiography should be performed yearly. Treatment with a pacemaker if the patient is symptomatic or if the ECG shows significant bradycardia or rhythm disturbances can be lifesaving. However, sudden cardiac death has been reported in patients with a pacemaker, and the insertion of a defibrillator has been recommended. As many as 20% of female carriers may have significant cardiac disease and should be monitored with annual ECGs.
Pulmonologist
Orthopedic surgeon
Physical medicine specialist and a physical therapist
Orthotist

**Facioscapulohumeral Muscular Dystrophy, FSHD**

IFSHD; if not detected and treated early it can interfere with learning and cognitive development What is Facioscapulohumeral Muscular Dystrophy, FSHD or FSH Disease?

Facioscapulohumeral muscular dystrophy or FSHD is the most prevalent of the nine primary types of muscular dystrophy affecting adults and children. Muscular dystrophy in general connotes a genetic, hereditary muscle disease that causes progressive muscle weakness. FSHD
is also broadly characterized as a neuromuscular disease (NMD), as muscular dystrophy is a subset of NMD. Muscular dystrophies are alike in that they cause progressive skeletal muscle weakness, defects in the biochemical, physical and structural components of muscle, and the death of muscle cells and tissue. However, researchers believe that the causes of each of the muscular dystrophies are not necessarily the same.

The major symptom of FSHD is the progressive weakening and loss of skeletal muscles. The usual location of these weaknesses at onset is the origin of the name: face (facio), shoulder girdle (scapulo) and upper arms (humeral). Early weaknesses of the muscles of the eye (open and close) and mouth (smile, pucker, whistle) are distinctive for FSHD. These symptoms, in combination with weaknesses in the muscles that stabilize the scapulae (shoulder blades), are often the basis of the physician’s diagnosis of FSHD.

In most cases, FSHD muscle involvement starts in the face and slowly progresses to the shoulder and upper arm muscles and then down to the abdominal and foot extensor muscles. Foot drop and foot weakness are early manifestations. Initial signs of FSHD include difficulty reaching above the shoulder level, foot drop, scapular winging and facial weakness. Weakness in the abdominal muscles can cause a protuberant abdomen and lumbar lordosis. The lower abdominal muscles are usually weaker than the upper abdominal muscles. This distribution of weakness is not seen in many other diseases and, therefore, is very specific to FSHD.

Although the progression of FSHD is quite variable, it is usually relatively slow. With FSHD, most affected people develop unbalanced (side-to-side) weaknesses. The reason for this asymmetry is unknown.

In more than half of FSHD cases, there are other symptoms including high-frequency hearing loss and/or abnormalities of blood vessels in the back of the eye. The vascular abnormalities in the back of the eye lead to vision problems in only about 1% of the cases. Since these abnormalities are not exclusive to FSHD, one must bear in mind that their presence alone, in an FSHD at-risk individual, is insufficient for a diagnosis of FSHD.

Although not typical, some patients with FSHD have respiratory insufficiency, especially those with severe FSHD.

FSHD generally presents outward signs in 95% of affected individuals by the second decade of life for men and the third decade of life for women. The disease is said to have a penetrance of 95% in men by the second decade and in women by the third decade.

FSHD is worldwide in distribution, affects both sexes equally and has no particular racial, geographic or ethnic distribution. Therefore, FSHD can appear in any family and happen at any time.
Types of FSHD

FSHD has been classified into two types: FSHD1A and FSHD1B. The symptoms are the same; the difference between the types is in their genetic locus.

Facioscapulohumeral muscular dystrophy 1A (FSHD1A), also known as chromosome 4 linked facioscapulohumeral muscular dystrophy, is by far the most common. FSHD1A is associated by genetic testing with the deletion of 3.3-kb repeats from a chromosomal tandem repeat called D4Z4 located near the end of chromosome 4 at the 4q35-qter location. The D4Z4 region is a polymorphic variable number tandem repeat (VNTR) array consisting of 3.3 kb units. Unaffected individuals have a chromosome 4 D4Z4 array that has a span of 11 to 150 contiguous units. In individuals with FSHD1A, the chromosome 4 D4Z4 repeat array is contracted to a range between 1 to 10 contiguous units. There is a rough and inverse relationship between clinical severity and the number of repeats; patients with the fewest repeats typically have the most severe symptoms.

Facioscapulohumeral muscular dystrophy 1B (FSHD1B), also known as non-chromosome 4 linked facioscapulohumeral muscular dystrophy, is much less prevalent than FSHD1A. It may be caused by different genes from FSHD1A, located on the same (despite its title) or different chromosomes.

Infantile FSHD or IFSHD is a more severe form of FSHD1A and FSHD1B that has recently been categorized as a subtype of FSHD1A and FSHD1B. What makes the disease more severe has not yet been determined. Hearing loss (high frequency bilateral sensorineural), vision problems (Coats’ Disease and retinal telangiectasias), and seizures have been documented in IFSHD. Hearing loss is often more severe in

Causes of Facioscapulohumeral muscular dystrophy

It is a genetic condition, present from when or soon after egg and sperm come together at conception. Normally, at a particular site on the gene map, each of us has many copies of a particular sequence of genetic instruction (DNA), arranged like a train of identical carriages. FSH muscular dystrophy is caused when the number of copies is reduced below a certain level, like a train having too few carriages. In some way this seems to influence the production or assembly of several of the protein components of the affected muscles.

In facioscapulohumeral muscular dystrophy (FSHD), a small section of the DNA on chromosome 4 that’s shorter than usual is inherited in an autosomal dominant pattern, meaning it only takes one such mutation (from one parent) to cause the disorder. This altered piece of DNA also can occur spontaneously in a child as he or she develops in the womb.
FSHD can affect either males or females. In a small number of people with FSHD, the usual chromosome 4 mutation can’t be identified. In most affected people, it can be, with genetic testing. (For more on this, see Diagnosis.)

FSHD is one of many genetic disorders in which germ line mosaicism is believed to occur. Germ line refers to egg or sperm cells. In this phenomenon, some sperm or egg cells in a parent carry a particular mutation.

In families with more than one child with FSHD but no previous family history, it’s likely that one parent has germ line mosaicism and that affected children were conceived with egg or sperm cells carrying the FSHD mutation. In these situations, the parents have no symptoms, and, if their blood cells are tested, they don’t show the mutation.

For more about genetics of FSHD and other neuromuscular diseases, see Facts About Genetics and Neuromuscular Diseases.

For help in understanding your family’s specific situation and planning for future children, it’s best to meet with a genetic counselor. You can obtain a referral to a counselor through your MDA clinic.

## Limb-girdle Muscular Dystrophy

**Myotonic Muscular Dystrophy**

**Oculopharyngeal Muscular Dystrophy**

Limb-girdle muscular dystrophy (LIMB-GIRDLE MUSCULAR DYSTROPHY) can be a complicated subject since there are many different types. Not all of the information on this page will be relevant to everybody with the diagnosis.

Muscular dystrophy is the name given to a group of inherited conditions where there is a progressive wasting and weakening of muscle. There are many different types of muscular dystrophy. One of the ways in which the different types of muscular dystrophy are distinguished is by noting the groups of muscle that are involved first. The limb-girdle group of muscular dystrophies is so called because generally they cause weakness in the shoulder and pelvic girdle for example the big muscles around the top (proximal) part of arms and legs (hip, thigh and shoulder muscles). Usually weakness of the legs is noticed before that of the arms and usually the muscle of the face are unaffected.

### Causes

There are at least 19 forms of LGMD, and they’re classified by the genetic flaws that appear to cause them. Some 15 specific genes that lead to production of muscle proteins have been implicated as definite causes of LGMD when they’re flawed. MDA research was behind much of
the work that identified these LGMD genes.

Genes, located on chromosomes in each cell in the body, are the codes, or recipes, for production of the body’s various proteins. The genes associated with LGMD normally make proteins necessary for muscle function.

When protein problems arise because one of these genes is faulty, fibers in the muscles don’t work properly. Gradually, the muscles become weak enough that people experience the symptoms of limb-girdle muscular dystrophy. Because LGMD is progressive, the muscles continue to get weaker throughout the person’s lifetime.

Six of the genes that, when flawed, cause LGMD lead to production of proteins that are normally located in the muscle cell membrane, a thin sheath that surrounds each muscle cell, helping to protect it from injury during muscle contraction. If any of these proteins is missing, the membrane probably loses some of its “shock absorber” qualities and has a harder time protecting the muscle cell from injury during normal contraction and relaxation cycles.

In LGMD, the muscle membrane also may be “leaky,” letting substances in or out that are supposed to stay on one side of the membrane or the other. Membrane proteins, when they’re made correctly and are in their normal positions, may also perform other essential functions in the cell; these functions may be defective when one or more of the proteins are absent.

Not all of the muscle proteins associated with LGMD are in the membrane, however. For instance, calpain-3 is probably located in the main part of the muscle cell, and myotilin and telethonin are located in the part of the muscle cell that allows it to contract and relax.

The types of LGMD are generally classified by letters and numbers that indicate which gene is known or suspected to be involved and whether the disorder is inherited as a dominant or recessive condition, meaning whether one or two flawed genes are needed to cause it.

Some physicians classify LGMD according to which protein is missing or deficient, if this is known. For example, one form may be called alpha-sarcoglycan deficiency, and another is known as beta-sarcoglycan deficiency. In the future, the term limb-girdle muscular dystrophy may become obsolete and be replaced by more specific terms.

**How is LGMD inherited?**

Bewildered patients often ask, “But it doesn’t run in the family, so how could it be genetic?”

LGMD can run in a family, even if only one person in the biological family has it. This is because of the ways in which genetic diseases are inherited.

LGMD can be inherited in one of two basic ways, known as the **autosomal dominant pattern** and the **autosomal recessive pattern**. The word autosomal means that the genes involved aren’t on the X or Y chromosome and, therefore, don’t have a preference for either men or women.

In diseases with dominant inheritance patterns, a person who inherits a flawed gene from one
parent will have disease symptoms. That parent would also have the disease. In diseases with recessive inheritance, a person must inherit two flawed genes — one from each parent — to have disease symptoms. The parents don’t have symptoms.

A recessive form of LGMD can show up in one person when there’s no family history. Other family members may have been carriers, having no disease symptoms. Carriers have the genetic flaw (mutation) on a chromosome and can have a child with the disease, but only if the child’s other parent is also a carrier. So it isn’t unusual for carriers of a rare recessive disease not to know they’re carriers until someone in the family develops the disease.

Just to make things a little more complicated, a person with LGMD may have a brand new genetic mutation (after all, they have to start somewhere), so there may really be no family history or even carriers of the disorder in the family. However, once someone develops a genetic disease, even if the mutation is spontaneous (new) with that person, he or she can then pass on the mutation to any offspring, thereby introducing the gene for the disease into the family.

The details of inheritance risks for any particular form of LGMD depend on many circumstances, including exactly which type of LGMD has been diagnosed. A good way to find out more is to talk to your MDA clinic physician or ask to see the genetic counselor at the MDA clinic. More information can be found in MDA’s booklet Facts About Genetics and Neuromuscular Diseases.

TYPES OF LIMB GIRDLE MUSCULAR DYSTROPHY

Background

(LIMB GIRDLE MUSCULAR DYSTROPHY) LGMD classification has been made based on clinical and molecular characteristics. It divides cases into autosomal dominant ((LIMB GIRDLE MUSCULAR DYSTROPHY-LGMD1) and autosomal recessive ((LIMB GIRDLE MUSCULAR DYSTROPHY-LGMD2) syndromes. Dominant means inherited from one parent and recessive means inherited from both the parents. This list continues to expand, and, as of this writing, specific mutations are known for 3 autosomal dominant (LIMB GIRDLE MUSCULAR DYSTROPHY-LGMDs and 14 autosomal recessive (LIMB GIRDLE MUSCULAR DYSTROPHY)LGMDs.

Age

The age of onset varies among the different mutations. Age of onset can vary among families with the same mutation. Reported age of onset of (LIMB GIRDLE MUSCULAR DYSTROPHY) LGMDs is between 1 and 50 years,

Types of (LIMB GIRDLE MUSCULAR DYSTROPHY) LGMD
Autosomal recessive limb-girdle muscular dystrophy (LGMD): All patients have a history of progressive, proximal muscle weakness. Described below are the major distinguishing characteristics.

**LGMD2A (calpainopathy)**

(LIMB GIRDLE MUSCULAR DYSTROPHY-LGMD2A is likely the most common autosomal recessive LGMD, accounting for up to 30% of all cases. The most typical presentation is of weakness due to scapular-humeral-pelvic weakness that may be similar to the presentation of facioscapulohumeral dystrophy, but without facial weakness. Hip-girdle weakness is most prominent in the gluteus maximus and hip adductors. Along with abdominal weakness, this leads to a wide-based, lordotic gait. The combination of scapular winging, severe weakness of hip adductors and elbow flexors, normal respiratory function, and contractures has specificity for LGMD2A. Atrophy is often prominent. Progression tends to be slow, and wheelchair use begins 11-28 years after the onset of symptoms. The clinical course varies widely among and within families. Facial and cardiac involvements have not been reported.

**LGMD2B (dysferlinopathy)**

(LIMB GIRDLE MUSCULAR DYSTROPHY-LGMD2B is also a common cause of autosomal recessive LGMD. In the limb-girdle presentation, pelvic and femoral muscles are affected first, with the proximal portions of the arms becoming weak later. With Miyoshi myopathy, the presentation includes gastrocnemius weakness and difficulty with toe walking. The forearm muscles are weak and atrophic, with sparing of intrinsic hand muscles. As the disease progresses, the 2 modes of presentation usually become indistinguishable. The most common phenotype (25-35% of patients) have a mixed picture with both proximal and distal weakness. The patient's gait is unique, with a waddling component combined with inability to raise his or her heels off the ground. The disease slowly progresses, and patients are usually confined to a wheelchair 10-30 years after the onset of weakness. Rare cases present with distal leg pain or swelling with or without weakness or with asymptomatic hyperCKemia. Misdiagnosis as polymyositis can occur since inflammation can be present on muscle biopsy.
LIMB GIRDLE MUSCULAR DYSTROPHY (LGMD2C-2F) (Sarcoglycanopathies)

Onset is usually at ages 6-8 years, but onset at or before 2 years and as late as the teens (or even adulthood) have been reported. Some delay in motor milestones is not uncommon. Weakness affects the hip and abdominal and shoulder musculature. Scapular winging is more common in (LIMB GIRDLE MUSCULAR DYSTROPHY) LGMD2C-2F than in Duchenne muscular dystrophy. Hypertrophy of the calf is common, and the tongue muscles may become enlarged. Progression tends to be more rapid than that of other (LIMB GIRDLE MUSCULAR DYSTROPHY) LGMDs, with loss of ambulation usually at 12-16 years but can be as early as 10 years. Patients with a late onset tend to have a more slowly progressive course. Intelligence is normal. Cardiomyopathy is reported in about 30% of cases and is most common with (LIMB GIRDLE MUSCULAR DYSTROPHY) LGMD2E or 2F. Progressive weakness leads to restrictive lung disease and hypoventilation and the need for ventilatory assistance.

LIMB GIRDLE MUSCULAR DYSTROPHY (LGMD2G) (telethoninopathy)

(LIMB GIRDLE MUSCULAR DYSTROPHY)LGMD2G has been reported in only a few patients, with significant phenotypic variability between and within families. The age of onset is 2-15 years. Weakness is predominantly proximal, but one half of patients may present with foot drop and anterior compartment atrophy, and nearly all eventually develop distal leg weakness. Gluteal and thigh atrophy may be prominent. Calf hypertrophy occurs in about 50%. Wheelchair confinement occurs in the third to fourth decade. Cardiomyopathy occurs in about 50%.

LIMB GIRDLE MUSCULAR DYSTROPHY (LGMD2H) (tripartite motif–containing gene 32 [TRIM32]–related dystrophy)

(LIMB GIRDLE MUSCULAR DYSTROPHY)LGMD2H has been observed mostly in the Hutterite people of Manitoba. A few non-Hutterites also have been shown to have (LIMB GIRDLE MUSCULAR DYSTROPHY) LGMD2H and have a more variable phenotype. This disease is allelic with sarcotubular myopathy (see Congenital Myopathies). Most Hutterite patients have a mild phenotype, with limb-girdle weakness and a waddling gait at presentation. The proximal arm muscles and the distal leg muscles are involved late. The age
of onset is 8-27 years, but some patients are asymptomatic in their third decade. Back pain and fatigue are common. Progression is slow, with continued ambulation until around 50 years of age or later. In non-Hutterites, scapular winging is common. Other features can include facial weakness, respiratory insufficiency, ankle contractures, and cramps. Presentation can be in the late first decade into young adulthood, and one patient had asymptomatic hyperCKemia noted at age 64.

**LIMB GIRDLE MUSCULAR DYSTROPHY (LGMD2I) (fukutin-related proteinopathy)**

(LIMB GIRDLE MUSCULAR DYSTROPHY)LGMD2I may be a fairly common cause of autosomal recessive (LIMB GIRDLE MUSCULAR DYSTROPHY) LGMD, causing 11% of all cases in Brazil and 38% of cases in Denmark. The disease is allelic with congenital muscular dystrophy 1C (MDC 1C). (See Congenital Muscular Dystrophy.) The presentation of patients with a mutation in fukutin-related protein (FKRP) gene can vary from severe congenital muscular dystrophy to mild, late-onset (LIMB GIRDLE MUSCULAR DYSTROPHY) LGMD. The (LIMB GIRDLE MUSCULAR DYSTROPHY) LGMD phenotype is variable. Patients can have a severe Duchenne-like presentation with delay in motor milestones, hypotonia, and severe proximal weakness. Progression to wheelchair by the teenage years and restrictive respiratory failure (even when patients are ambulant) is common. Like in Duchenne muscular dystrophy, treatment with corticosteroids may improve strength. The most common presentation is with a Becker-like onset with normal early motor milestones. An adult-onset form occurs at 11-40 years of age and is slowly progressive. In a large study in Denmark, 2 groups of patients could be delineated based on genotype-phenotype correlations. Of the 38 patients studied, 27 (71%) had a homozygous mutation (826A>C) while 11 (29%) had a compound heterozygous mutation.11 The patients with a homozygous mutation had a later onset (mean of 18 y) and slower progression than patients with a compound heterozygous mutation. Only 15% lost the ability to ambulate by their mid 40s. Presentation with exertional myoglobinuria, calf hypertrophy and cardiomyopathy were all more common than in patients with a compound heterozygous mutation. The patients with a compound heterozygous mutation had an earlier onset (mean of 5 y) and more rapid progression. All lost the ability to ambulate by their mid 20s. Tongue hypertrophy, more severe respiratory failure, contractures, and spine abnormalities were more common than in patients with a homozygous mutation. Cardiac involvement can occur in up to 60% of patients with (LIMB GIRDLE MUSCULAR DYSTROPHY) LGMD2I as measured by reduced left ventricular ejection fraction.12 There is no clear correlation between severity of cardiac disease and severity of muscle disease. Severely abnormal ejection fraction can occur in about 10% of patients and may cause symptomatic congestive heart failure. Rhythm abnormalities are not present.
LIMB GIRDLE MUSCULAR DYSTROPHY (LGMD2J) (titinopathy)

LGMD2J has been described only in Finnish patients. Some family members have a typical limb girdle phenotype with severe proximal weakness (LGMD2J) while other family members have distal dominant weakness (Finnish [tibial] muscular dystrophy). The onset of the LGMD syndrome is at ~10-30 years, with proximal weakness. Some patients later develop distal weakness. The disease slowly progresses, and wheelchair confinement usually occurs within 20 years, but some patients are ambulant past 60 years. No facial weakness or cardiac involvement is noted.

LIMB GIRDLE MUSCULAR DYSTROPHY (LGMD2K)

LGMD2K has been described in Turkish and Italian families. The disease is allelic with Walker-Warburg syndrome. The age of onset is 1-6 years. LGMD2K is characterized by severe proximal muscle weakness with slow progression. Contractures may be present. Results of ophthalmologic and funduscopic examinations, including electroretinography, are normal. Facial dysmorphic features and mental retardation may occur, though brains MRIs are normal.

LIMB GIRDLE MUSCULAR DYSTROPHY (LGMD2L)

LGMD2L has been described in French-Canadian families. Age of onset is between 11 and 50 years (mean 33 y). While there is intra-familial variability, all patients had quadriceps weakness and atrophy that could be asymmetric. Muscle pain is common. Facial weakness, calf hypertrophy, and contractures are uncommon. Progression is slow, but wheelchair confinement can occur after 10 years.

LIMB GIRDLE MUSCULAR DYSTROPHY (LGMD2M)

LGMD2M has been described in 3 patients in 2 families with a mutation in the fukutin gene.
The disease is allelic with Fukuyama congenital muscular dystrophy. Patients presented with hypotonia before age 1 year. Progression was moderate with proximal greater than distal weakness affecting the legs more than the arms. The affected children, now aged 7-9 years can still walk. Interestingly, these children have worsening weakness during febrile illnesses, and like boys with Duchenne muscular dystrophy, their weakness improves with steroids. All children had normal intelligence and normal brain MRIs.

**Autosomal-dominant (LIMB GIRDLE MUSCULAR DYSTROPHY) -LGMD:**

Autosomal dominant (LIMB GIRDLE MUSCULAR DYSTROPHY) LGMD is less common than autosomal recessive (LIMB GIRDLE MUSCULAR DYSTROPHY) LGMD, accounting for about 10% of all cases. In general, patients with autosomal dominant (LIMB GIRDLE MUSCULAR DYSTROPHY) LGMD have a later onset and slower course than those of autosomal recessive (LIMB GIRDLE MUSCULAR DYSTROPHY) LGMD. Creatine kinase (CK) elevations are also not as great in autosomal dominant (LIMB GIRDLE MUSCULAR DYSTROPHY) LGMD as in autosomal recessive (LIMB GIRDLE MUSCULAR DYSTROPHY) LGMD.

*(LIMB GIRDLE MUSCULAR DYSTROPHY)LGMD1A (myotilinopathy, also Myofibrillar myopathies)*

Onset varies from young adulthood to the mid 70s. Presentation is often with distal weakness causing foot drop, but can also be distal and proximal or just proximal, but progresses to clinically significant proximal and distal weakness in all patients. The progression is slow, with late loss of ambulation or, rarely, respiratory insufficiency. Dysarthria may be prominent. Cardiomyopathy or arrhythmia is noted in 50%. Neuropathy noted in more than 50% may account for distal weakness.

**(LIMB GIRDLE MUSCULAR DYSTROPHY)LGMD1B (laminopathy, allelic with autosomal dominant Emery-Dreifuss muscular dystrophy).**

Onset can be from childhood. (LIMB GIRDLE MUSCULAR DYSTROPHY)LGMD1B results in proximal weakness with slow progression. Distal limb and facial weakness may be late manifestations. Cardiac disease begins by the 30s-50s and affects two thirds of patients. Atrioventricular (AV) block progresses from first degree to complete. Dilated cardiomyopathy and ventricular arrhythmias may also be present.

**(LIMB GIRDLE MUSCULAR DYSTROPHY)LGMD1C (caveolinopathy)**

Onset is usually in the first or second decade, but it may manifest into early adulthood. Presentation is usually with proximal weakness but can also be with distal weakness.
Progression is slow to moderate and may be variable within families. Patients may present without weakness, but with myalgia, exercise-induced cramps, or rippling muscles and rhabdomyolysis has been reported. Calf hypertrophy affects some patients. Adults usually remain ambulant. Patients may also present with elevation of CK levels without weakness but with myalgia and cramps, distal weakness, hypertrophic cardiomyopathy, or rippling-muscle disease. The last condition is mechanical or activity-induced, electrically silent muscle contraction that moves laterally in wavelike fashion across the muscle. Myoedema, or mounding of the muscle after percussion, may be observed. Patients may also have proximal weakness, muscle hypertrophy, or myalgias.

**Limb Girdle Muscular Dystrophy**

**LGMD1D** (Online Mendelian Inheritance in Man [OMIM] %603511)
Two families have been described.
Onset is in adulthood, with proximal weakness. Progression is slow. Dysarthria may be present.

**LGMD1E** (Dilated cardiomyopathy with conduction defect and muscular dystrophy, OMIM %602067)
One large family has been described. Onset is in early adulthood, with proximal weakness. Progression is slow. Cardiac arrhythmia and cardiomyopathy are noted in all patients beginning 1-2 decades after weakness and may lead to sudden death.

**LGMD1F**
One large family has been described. Onset is from the first year of life to the mid 50s. **LGMD1F** causes early proximal weakness with progression to distal weakness in most patients. Patients with a young onset may have rapid progression and require use of a wheelchair by their 20s-30s. They may also have facial and respiratory weakness and/or spinal deformity.

**LGMD1G**
One family has been described. Onset is in the 30s-40s. Presentation is with proximal weakness and progression is slow.
Myotonic Muscular Dystrophy

People with myotonic dystrophy, like those with other dystrophies, experience muscle weakness and wasting which is usually progressive. There are many differences, though, in the type of problem that people with myotonic dystrophy may have. These may include the following:

Types of muscles involved are usually in the face, jaw and neck area; the large, weight-bearing muscles of the legs and thighs are much less affected.

Rate of deterioration is commonly slow, with little change over a long period; some people never have significant muscle disability. Muscle stiffness or 'myotonia' is characteristic, especially affecting the hands. Involvement of other body systems is frequent; associated problems may include cataracts, disturbance of heart rhythm, hormonal problems and, in children, learning difficulties.

Age at onset is very variable. Symptoms may appear at any time from birth to old age.

Causes

The changes in muscle and other body systems in myotonic dystrophy are now known to result from a specific genetic change (mutation) which in most cases involves a gene on chromosome number 19. The same change occurs in patients world-wide, but it is variable in extent, even in a single family, because it is unstable. The length of a particular ‘triple repeat sequence’ (CTG) is expanded in patients and this may vary from a slight expansion in mildly affected individuals to a very large one in severely affected children. Until recently it has not been clear how genetic change causes the condition: the most likely mechanism is now thought to be that the expanded repeat is converted normally into the next stage (RNA - Ribonucleic acid), but then is unable to leave the cell nucleus. As a result of this trapping, a range of other types of RNA are affected, as are the protein they produce, which helps explain how a single genetic change can affect different body processes.

Signs and Symptoms

Myotonic dystrophy is more than just a muscle disease. Both MMD1 and MMD2 affect several aspects of physical and mental functioning, to varying degrees and with variable scope.
The following sections discuss different problems that can occur, although many people with the disease have only some of them. Most of these symptoms can be lessened with treatment. See Medical Management for information on current therapies.

**Effects on the brain**

Research suggests that, in MMD1, there may be abnormalities in the parts of the brain that determine the rhythm of sleeping and waking, making excessive daytime sleepiness a barrier to full participation in work, school or social life for many adults with the disorder. In some people, there is a kind of overall "apathy" that may be due to changes in the brain related to MMD1.

Although not as much is known about the effects of MMD2 on personality, cognition and sleepiness in MMD2 as in MMD1, it appears that people with MMD2 can have some of the same difficulties in these areas as people with MMD1, but to a lesser degree.

To learn more, read *The Brain in MMD* (cognitive and emotional aspects of MMD1) and *Excessive Daytime Sleepiness Can Be 'Debilitating' in MMD1 and MMD2* (complex effects of MMD on the brain’s sleep-wake cycles and respiratory muscles).

**Breathing and swallowing muscle weakness**

Respiratory muscle weakness does not appear to be a common feature of MMD2.

However, in MMD1, respiratory muscles weakness can affect lung function and deprive the body of needed oxygen. Weakness of the diaphragm and other breathing muscles can lead to problems getting enough oxygen when a person is asleep, even if they don’t have any symptoms of breathing difficulty while awake.

Respiratory problems in MMD1 are further aggravated, many experts believe, by an abnormality in the brain’s breathing control center. This abnormality can lead to a condition known as *sleep apnea*, in which people stop breathing for several seconds or longer many times a night while asleep.

Swallowing muscles, if weakened, can lead to *choking* or “swallowing the wrong way,” (called *aspiration*) with food or liquid going down the trachea (windpipe) to the lungs instead of down the esophagus to the stomach. Swallowing is partly voluntary and partly involuntary, and both sets of muscles can be affected.

To learn more, read *Excessive Daytime Sleepiness Can Be 'Debilitating' in MMD1 and MMD2* (complex effects of MMD on the brain’s sleep-wake cycles and respiratory muscles).

**Cataracts**
Cataracts — cloudy areas of the lens of the eye that eventually can interfere with vision — are extremely common in both MMD1 and MMD2. They generally occur earlier than the common, age-associated cataracts seen in people without MMD.

Cataracts are caused by a chemical change in the lens, which gradually goes from clear to cloudy the way the clear part of an egg changes to white when cooked. Exactly why cataracts occur in MMD isn’t known.

The person with a cataract may notice that things start to look blurry, hazy or dim, and that this worsens gradually over time. It often happens in both eyes, but not necessarily at the same time or at the same rate.

Read Keeping Your Focus: Eye Care, particularly the section called Other vision problems: Not common, sometimes treatable, for additional information about eye care in neuromuscular disorders.

### Head, neck and face muscle weakness

The muscles of the neck, jaw and parts of the head and face may weaken, especially in MMD1. Facial weakness is less common in MMD2.

Weakness and loss of bulk in these muscles leads to a characteristic appearance doctors and experienced family members recognize as MMD.

In men, early balding in the front part of the scalp is very common, adding to the distinct appearance of MMD.

Eyelids may droop (called ptosis; the “p” is silent). The chewing muscles can be affected, which makes the temples appear hollow and the face look thin.

Weak neck muscles, common in both types of MMD, can make it hard to sit up quickly or lift one’s head straight up off a bed or couch. The stronger trunk muscles have to be used for these actions.

### Heart difficulties

The heart can be affected in MMD1 or MMD2. Oddly, since MMD is mostly a muscle disease, it isn’t the muscle part of the heart (which pumps blood) that’s most affected, but rather the part that sets the rate and rhythm of the heartbeat — the heart’s conduction system.

It’s common in MMD1, especially after many years, to develop a conduction block, which is a block in the electricity-like signal that keeps the heart beating at a safe rate. This appears to occur in MMD2 as well, although there aren’t as many studies in this form of the disease.

Fainting, near fainting or dizzy spells are the usual symptoms of conduction block, and these should never be ignored. Such problems can be fatal.

In both forms of MMD, cardiac muscle impairment also can occur, although it isn’t as common as conduction abnormalities.

To learn more, read Cardiac Care in MMD: Lack of Symptoms May Mask Deadly Problems and Revising Cardiac Care in Muscular Dystrophies (covers different types of heart
problems that occur in these disorders and how to monitor and treat them).

**Insulin resistance**

Fortunately, most people with MMD1 and MMD2 don’t have diabetes, but they may develop a diabetes-like condition that is sometimes referred to as *insulin resistance*. This means the body makes insulin (a hormone needed for the cells to take up and use sugars), but for some reason, it takes more insulin to do the job because the muscle tissues don’t respond normally to the usual amounts. High blood sugar may result from insulin resistance.

**Effects on internal organs**

Most of the internal organs in the body are hollow tubes (such as the intestines) or sacs (such as the stomach). The walls of these tubes and sacs contain involuntary muscles that squeeze the organs and move things (food, liquids, a baby during childbirth and so forth) through them.

In MMD1, many of the involuntary muscles that surround the hollow organs can weaken. These include the muscles of the digestive tract, uterus and blood vessels. Such problems appear to be absent or mild in MMD2.

Abnormal action of the upper digestive tract can impair swallowing. Once food is swallowed, the involuntary muscles of the esophagus should take over and move food into the stomach. However, in MMD1, these muscles can have spasms and weakness, causing a feeling of food getting stuck and sometimes leading to inhaling food into the lungs.

The lower digestive tract — large intestine (colon), rectum and anus — also can be affected by weakness and spasm in MMD1. Crampy pain, constipation and diarrhea can occur.

The gallbladder — a sac under the liver that squeezes bile into the intestines after meals — can weaken in MMD1. People with MMD probably are more likely than the general population to develop gallstones. Symptoms are difficulty digesting fatty foods and pain in the upper right part of the abdomen. Fortunately, most people do not experience incontinence or urination problems in MMD.

Because of weakness and uncoordinated action of the muscle wall of the uterus, women with MMD1 may experience difficulties in childbirth that can be serious for both mother and baby. These may involve excessive bleeding or ineffective labor. Sometimes a Caesarean operation (C-section) is advised, but surgery also can be a problem in MMD (see *Medical Management*).

Blood pressure in MMD1 tends to be low. This is probably due to low tone of the smooth muscles in the blood vessels. It usually poses no problem and may even be one beneficial effect of MMD1.

**Limb and hand muscle weakness**
Weakness of the voluntary muscles usually is the most noticeable symptom for people with adult-onset MMD.

The distal muscles (those farthest from the center of the body) usually are the first — and sometimes the only — limb muscles affected in MMD1. Areas of the limbs affected may include the forearms, hands, lower legs and feet. Over time, these muscles get smaller, so the lower legs and arms may appear thinner than the upper legs and arms.

In MMD2, proximal muscles — those closer to the center of the body — tend to show more weakness than in MMD1. Weakness in the upper part of the leg (thigh) occurs early in MMD2. In MMD1, thigh weakness, if it occurs at all, comes later in the disease.

People with both types of MMD often notice that their grip is weak and that they have trouble using their wrist or hand muscles. The muscles that pick up the foot when walking may weaken, allowing the foot to flop down and cause tripping and falling (foot drop).

**Myotonia and muscle pain**

Myotonia of voluntary muscles can make it hard for someone with MMD1 or MMD2 to relax their grip, especially in cold temperatures. Door handles, cups, handwriting and using hand tools may pose a problem, although some people never notice it. Myotonia also can affect the muscles of the tongue and jaw, causing difficulty with speech and chewing.

Myotonia can be uncomfortable and even cause pain, although people with MMD1 and MMD2 also can have muscle pain that isn’t connected to the myotonia.

- Juvenile-Onset MMD1
- Congenital MMD1

**IMAGES MUSCULAR DISTROPHY**