

Myofibrillar Myopathy

Last updated February 2011

What is myofibrillar myopathy?

Myofibrillar myopathy is part of a group of disorders called muscular dystrophies that affect muscle function and cause weakness. Myofibrillar myopathy primarily affects skeletal muscles, which are muscles that the body uses for movement. In some cases, the heart (cardiac) muscle is also affected.

The signs and symptoms of myofibrillar myopathy vary widely among affected individuals, typically depending on the condition's genetic cause. Most people with this disorder begin to develop muscle weakness (myopathy) in mid-adulthood. However, features of this condition can appear anytime between infancy and late adulthood. Muscle weakness most often begins in the hands and feet (distal muscles), but some people first experience weakness in the muscles near the centre of the body (proximal muscles). Other affected individuals develop muscle weakness throughout their body. Facial muscle weakness can cause swallowing and speech difficulties. Muscle weakness worsens over time.

Other signs and symptoms of myofibrillar myopathy can include a weakened heart muscle (cardiomyopathy), muscle pain (myalgia), loss of sensation and weakness in the limbs (peripheral neuropathy), and respiratory failure. Individuals with this condition may have skeletal problems including joint stiffness (contractures) and abnormal side-to-side curvature of the spine (scoliosis). Rarely, people with this condition develop clouding of the front surface of the eyes (cataracts).

How common is myofibrillar myopathy?

The prevalence of myofibrillar myopathy is unknown.

What genes are related to myofibrillar myopathy?

Mutations in several genes can cause myofibrillar myopathy. These genes provide instructions for making proteins that play important roles in muscle fibres. Within muscle fibres, these proteins are involved in the assembly of structures called sarcomeres. Sarcomeres are necessary for muscles to tense (contract). The proteins associated with myofibrillar myopathy are normally active

on rod-like structures within the sarcomere called Z-discs. Z-discs link neighbouring sarcomeres together to form myofibrils, the basic unit of muscle fibres. The linking of sarcomeres and formation of myofibrils provide strength for muscle fibres during repeated muscle contraction and relaxation.

Gene mutations that cause myofibrillar myopathy disrupt the function of skeletal and cardiac muscle. Various muscle proteins form clumps (aggregates) in the muscle fibres of affected individuals. The aggregates prevent these proteins from functioning normally, which reduces linking between neighbouring sarcomeres. As a result, muscle fibre strength is diminished.

At least six genes have been associated with myofibrillar myopathy. Mutations in these six genes account for approximately half of all cases of this condition. Mutations in the **DES**, **MYOT**, and **LDB3** genes are responsible for the majority of cases of myofibrillar myopathy when the genetic cause is known.

More Information about the Genes DES, MYOT and LDB3

What is the official name of the *DES* gene?

The official name of this gene is “desmin.”

What is the normal function of the *DES* gene?

The *DES* gene provides instructions for making a protein called desmin. Desmin is found in heart (cardiac) muscle and muscles used for movement (skeletal muscle). Within muscle fibres, desmin proteins are important to help maintain the structure of sarcomeres, which are necessary for muscles to tense (contract). The desmin proteins surround rod-like structures called Z-discs that are located within the sarcomere. Desmin connects the Z-discs to one another, linking neighbouring sarcomeres and forming myofibrils, the basic unit of muscle fibres. The connection of sarcomeres to each other to form myofibrils is essential for maintaining muscle fibre strength during repeated cycles of contraction and relaxation.

How are changes in the *DES* gene related to health conditions?

Myofibrillar myopathy can be caused by mutations in the *DES* gene

More than 40 mutations in the *DES* gene have been found to cause myofibrillar myopathy. Most of these mutations change single protein building blocks (amino acids) in desmin. Mutated desmin proteins cluster together with other muscle proteins in the sarcomere to form clumps (aggregates). The aggregates prevent these proteins from functioning normally. A dysfunctional desmin protein cannot properly interact with Z-discs, leading to abnormalities of sarcomere structure and problems with the formation of myofibrils. *DES* gene mutations that cause myofibrillar myopathy impair the function of muscle fibres, causing weakness and the other features of this condition. People with *DES* gene mutations are more likely to have a weakened heart muscle (cardiomyopathy) than people with myofibrillar myopathy caused by mutations in other genes. In some cases, cardiomyopathy is the first symptom of this condition.

What is the official name of the *MYOT* gene?

The official name of this gene is "myotilin."

What is the normal function of the *MYOT* gene?

The *MYOT* gene provides instructions for making a protein called myotilin. Myotilin is found in heart (cardiac) muscle and muscles used for movement (skeletal muscle). Within muscle fibres, myotilin proteins are found in structures called sarcomeres, which are necessary for muscles to tense (contract). Myotilin attaches, (binds) to other proteins, to help form sarcomeres. Myotilin is also involved in linking neighbouring sarcomeres to each another to form myofibrils, the basic unit of muscle fibres. The connection of sarcomeres to each other and the formation of myofibrils are essential for maintaining muscle fibre strength during repeated cycles of contraction and relaxation.

How are changes in the *MYOT* gene related to health conditions?

Myofibrillar myopathy can be caused by mutations in the *MYOT* gene

At least five mutations in the *MYOT* gene have been found to cause myofibrillar myopathy. Most of these mutations are located in an area of the gene known as exon 2. *MYOT* gene mutations that cause myofibrillar myopathy change single protein building blocks (amino acids) in myotilin. Mutated myotilin proteins cluster together with

other muscle proteins in the sarcomere to form clumps (aggregates). The aggregates prevent these proteins from functioning normally. A dysfunctional myotilin protein cannot properly bind with other proteins, preventing the formation of sarcomeres and myofibrils. *MYOT* gene mutations that cause myofibrillar myopathy impair the function of muscle fibres, causing weakness and the other features of this condition.

What is the official name of the *LDB3* gene?

The official name of this gene is "LIM domain binding 3."

What is the normal function of the *LDB3* gene?

The *LDB3* gene provides instructions for making a protein called LIM domain binding 3 (LDB3). The LDB3 protein is found in heart (cardiac) muscle and muscles used for movement (skeletal muscle). Within muscle fibres, LDB3 proteins are found in structures called sarcomeres, which are necessary for muscles to tense (contract). This protein attaches (binds) to other proteins and is involved in maintaining the stability of rod-like structures within sarcomeres called Z-discs. Z-discs link neighbouring sarcomeres together to form myofibrils, the basic unit of muscle fibres. The linking of sarcomeres and formation of myofibrils provide strength for muscle fibres during repeated cycles of muscle contraction and relaxation.

Several different versions (isoforms) of the LDB3 protein are produced from the *LDB3* gene.

How are changes in the *LDB3* gene related to health conditions?

Myofibrillar myopathy can be caused by mutations in the *LDB3* gene

At least three mutations in the *LDB3* gene have been found to cause myofibrillar myopathy. These mutations change single protein building blocks (amino acids) in the LDB3 protein. Mutated LDB3 proteins cluster together with other muscle proteins in the sarcomere to form clumps (aggregates). The aggregates prevent these proteins from functioning normally. A dysfunctional desmin protein cannot properly interact with Z-discs, leading to abnormalities of sarcomere structure and problems with the formation of myofibrils. *LDB3* gene mutations that cause myofibrillar myopathy impair the function of muscle fibres, causing weakness and the other features of this condition.

How do people inherit myofibrillar myopathy?

This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder.

In some cases, an affected person inherits the mutation from one affected parent. Other cases result from new mutations in the gene and occur in people with no history of the disorder in their family.

Congenital Muscular Dystrophies Support group and Web Links

Even when all the different types of Congenital Muscular Dystrophies are considered together, the number of individuals affected is much smaller than for the more common types of neuromuscular disease like DMD and SMA. For this reason, there aren't very many organizations that deal exclusively with Congenital Muscular Dystrophies. There are many more organizations that cover all neuromuscular diseases, and these ones of course also support individuals with Congenital Muscular Dystrophies and their families.

Muscular Dystrophy Association of New Zealand supports people with nearly sixty different neuromuscular conditions including Congenital Muscular Dystrophies and Myofibrillar Myopathy.

Web: www.mda.org.nz/home.html