

TTN Gene

Subjects: Genetics & Heredity

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Titin

Keywords: genes

1. Normal Function

The *TTN* gene provides instructions for making a very large protein called titin. This protein plays an important role in muscles the body uses for movement (skeletal muscles) and in heart (cardiac) muscle. Slightly different versions (called isoforms) of titin are made in different muscles.

Within muscle cells, titin is an essential component of structures called sarcomeres. Sarcomeres are the basic units of muscle contraction; they are made of proteins that generate the mechanical force needed for muscles to contract. Titin has several functions within sarcomeres. One of the protein's main jobs is to provide structure, flexibility, and stability to these cell structures. Titin interacts with other muscle proteins, including actin and myosin, to keep the components of sarcomeres in place as muscles contract and relax. Titin also contains a spring-like region that allows muscles to stretch. Additionally, researchers have found that titin plays a role in chemical signaling and in assembling new sarcomeres.

2. Health Conditions Related to Genetic Changes

2.1. Centronuclear myopathy

At least 12 mutations in the *TTN* gene have been found to cause centronuclear myopathy, a condition that is characterized by muscle weakness (myopathy) in the skeletal muscles. Most of these mutations alter the way the gene's instructions are used to produce titin, resulting in production of an abnormal protein with reduced or altered activity in muscle cells. Other mutations prevent the production of titin protein. It is unclear how *TTN* gene mutations cause centronuclear myopathy, but it is likely that a shortage of normal titin protein leads to dysfunction of the sarcomere. Abnormal sarcomeres prevent muscle cells from contracting and relaxing normally, resulting in the muscle weakness that is characteristic of centronuclear myopathy.

2.2. Early-onset myopathy with fatal cardiomyopathy

At least two mutations in the *TTN* gene have been identified in people with early-onset myopathy with fatal cardiomyopathy (EOMFC), an inherited disease that affects both skeletal and cardiac muscle. These genetic changes occur near the end of the *TTN* gene and lead to the production of an abnormally short version of the titin protein. The defective protein disrupts the function of sarcomeres, preventing skeletal and cardiac muscle from developing and working normally. These muscle abnormalities underlie the characteristic features of EOMFC, including skeletal muscle weakness and a form of heart disease called dilated cardiomyopathy.

2.3. Familial dilated cardiomyopathy

More than 100 mutations in the *TTN* gene have been found to cause familial dilated cardiomyopathy, a condition that weakens and enlarges the heart, preventing it from pumping blood efficiently. Signs and symptoms of familial dilated cardiomyopathy typically begin in mid-adulthood and result in heart failure. *TTN* gene mutations account for approximately one-quarter of all cases of familial dilated cardiomyopathy. These mutations result in the production of an abnormal titin protein, particularly isoforms that are found in cardiac muscle. It is unclear how the altered protein causes familial dilated cardiomyopathy, but it likely impairs sarcomere function and disrupts chemical signaling. Changes in sarcomere function reduce the heart's ability to contract, weakening cardiac muscle and leading to the signs and symptoms of familial dilated cardiomyopathy.

2.4. Hereditary myopathy with early respiratory failure

Several mutations in the *TTN* gene have been found to cause hereditary myopathy with early respiratory failure (HMERF), an inherited disease that affects muscles used for movement (skeletal muscles) and muscles that are needed for breathing (respiratory muscles). These mutations change single DNA building blocks (nucleotides) in a region of the *TTN* gene called exon 344. These changes alter a region of the titin protein called the FN3 119 domain and are thought to impair the folding of the titin protein into its normal 3-dimensional shape. Researchers are studying how abnormally folded titin contributes to the muscle damage underlying the signs and symptoms of HMERF. It is unclear why these effects are usually limited to certain skeletal muscles and respiratory muscles, and do not involve cardiac muscle.

2.5. Limb-girdle muscular dystrophy

At least two *TTN* gene mutations have been found to cause limb-girdle muscular dystrophy type 2J (LGMD2J). Limb-girdle muscular dystrophy is a group of related disorders characterized by weakness and wasting of skeletal muscles, particularly in the shoulders, hips, and limbs. LGMD2J is a type of limb-girdle muscular dystrophy that has been identified primarily in the Finnish population. The genetic change found in this population deletes several amino acids and replaces them with other amino acids at the end of the titin protein. This complex mutation, known as FINmaj, causes LGMD2J when it occurs in both copies of the *TTN* gene. The FINmaj mutation may disrupt titin's interactions with other proteins that are needed to maintain muscle fibers. Loss of muscle fibers causes muscles to weaken and waste away over time, resulting in the signs and symptoms of limb-girdle muscular dystrophy.

2.6. Tibial muscular dystrophy

Several mutations in the *TTN* gene have been identified in people with tibial muscular dystrophy, a condition that primarily affects the muscles at the front of the lower leg. The FINmaj mutation (described above) has been found to cause tibial muscular dystrophy in all affected people of Finnish descent. Other *TTN* gene mutations cause tibial muscular dystrophy in non-Finnish European populations. This condition is caused by mutations that occur in one copy of the *TTN* gene.

Researchers predict that the *TTN* gene mutations responsible for tibial muscular dystrophy, including FINmaj, alter the ability of the titin protein to interact with other proteins within sarcomeres. These alterations likely impair muscle fiber maintenance or muscle contraction, causing muscles to weaken and waste away over time. It is unclear why the resulting weakness is usually limited to muscles in the lower legs in tibial muscular dystrophy.

Researchers are working to determine why some conditions resulting from *TTN* gene mutations predominantly affect cardiac muscle, some predominantly affect skeletal muscle, and some affect both. They suspect that these differences may be related to the location of mutations in the *TTN* gene and how they affect the many versions of titin that are produced in different muscles.

2.7. Arrhythmogenic right ventricular cardiomyopathy

2.8. Familial hypertrophic cardiomyopathy

3. Other Names for This Gene

- CMH9
- CMPD4
- CONNECTIN
- EOMFC
- LGMD2J
- TITIN_HUMAN
- TMD

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