TTN gene

titin

Normal Function

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

Within muscle cells, titin is an essential component of structures called sarcomeres. Sarcomeres are the basic units of muscle tensing (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.

Health Conditions Related to Genetic Changes

Centronuclear myopathy

Several variants (also known as 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 variants 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 variants prevent the production of titin protein. It is unclear how *TTN* gene variants 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.

Early-onset myopathy with fatal cardiomyopathy

Variants 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.

Familial dilated cardiomyopathy

Many *TTN* gene variants 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 variants account for approximately one-quarter of all cases of familial dilated cardiomyopathy. These variants 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.

Hereditary myopathy with early respiratory failure

Several variants 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 variants 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.

Limb-girdle muscular dystrophy

A small number of *TTN* gene variants 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 variant, known as FINmaj, causes LGMD2J when it occurs in both copies of the *TTN* gene. The FINmaj variant 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.

Tibial muscular dystrophy

Several variants 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 variant (described above) has been found to cause tibial muscular dystrophy in all affected people of Finnish descent. Other *TTN* gene variants cause tibial muscular dystrophy in non-Finnish European populations. This condition is caused by variants that occur in one copy of the *TTN* gene.

Researchers predict that the *TTN* gene variants 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 variants 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 variants in the *TTN* gene and how they affect the many versions of titin that are produced in different muscles.

Arrhythmogenic right ventricular cardiomyopathy

MedlinePlus Genetics provides information about Arrhythmogenic right ventricular cardiomyopathy

Familial hypertrophic cardiomyopathy

MedlinePlus Genetics provides information about Familial hypertrophic cardiomyopathy

Other disorders

TTN gene variants can cause muscle problems that begin before or soon after birth. Scientists suggest that early-onset forms of titin-related muscle disorders be grouped as congenital titinopathy. Often, fetuses with this condition move less than normal in the uterus. Affected babies may have low muscle tone (hypotonia) or joint deformities that limit their ability to move (contractures). Babies and children with congenital titinopathy can have muscle weakness in the neck, arms, or legs which usually worsens slowly, and they often learn to walk later than their peers. Abnormal side-to-side curvature of the spine (scoliosis) and difficulty breathing also commonly occur, and they can worsen rapidly. Some individuals with congenital titinopathy have heart problems. It is not clear how *TTN* gene variants affect the titin protein and cause congenital titinopathy. Researchers suspect that the version (isoform) of the titin protein affected by the gene variant may help determine the set of features in affected individuals.

Other Names for This Gene

- CMH9
- CMPD4

- CONNECTIN
- EOMFC
- LGMD2J
- MYLK5
- TITIN_HUMAN
- TMD

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of TTN (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=7273[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28TTN%5BTIAB%5D%29+OR+%28titin%5BTIAB%5D%29+OR+%28connectin%5BTIAB%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1080+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- TITIN; TTN (https://omim.org/entry/188840)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/7273)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=TTN[gene])

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Genomic Location

The *TTN* gene is found on chromosome 2 (https://medlineplus.gov/genetics/chromosome/2/).

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