Team Titin information sheet

This letter is for families with variant(s) in the **Titin gene** (***TTN)***. Changes in a gene are called ***mutations*** or ***variants***. These changes *may* cause **muscle weakness as well as heart problems**. You will need to discuss with your medical team to see *if* and *how* your Titin variant affects your health.

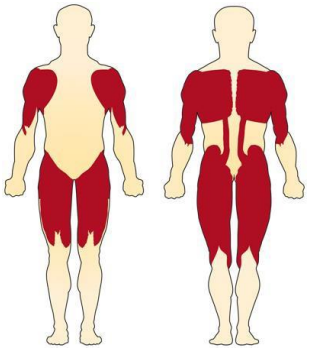
Welcome to Team Titin. You are not alone.

What is Titin?

Titin is a very large protein. It's huge! In fact, Titin is the largest protein in the human body. The Titin protein is located in muscle cells in our bodies. It is also found in the heart, which is a specialized muscle. Muscles need Titin in order to work and move. You can learn more about Titin here: **http://titinmyopathy.com**.

Titin variants often cause problems with the heart's pumping ability (dilated cardiomyopathy) and can also cause abnormalities of the heart rhythm, such as atrial fibrillation. There are many different types of titin variants, and heart disorders are usually associated with a specific subset of variants that shorten the titin protein. These are called "truncating" variants. Other types of titin variants, such as missense variants (that change a single "letter" in the titin gene) are common and are less likely to be harmful. If a person is born with two truncating titin variants, they may develop muscle weakness and heart problems from an early age. More frequently, however, people carry only a single truncating variant. It is a good idea for **everyone** who carries a titin truncating variant to have a **checkup from a heart doctor, even if they feel well.**

Titin abnormalities can cause a wide spectrum of muscle disorders called "**Titinopathy**". These disorders may be also called a "myopathy" or a "dystrophy" including limb-girdle muscular dystrophy (LGMD) and tibial muscular dystrophy. Some forms of titin-related myopathies may include centronuclear myopathy, multi-minicore myopathy, hereditary myopathy with early respiratory failure, Salih myopathy, core myopathy with heart disease, Emery-Dreifuss-like phenotype without cardiomyopathy and likely more. Muscle weakness may start in childhood or come on later as an adult. Weakness can range from mild to severe.



How to make sense of your Genetic Test Results for Titin

Some variants in a gene may lead to health problems, while others may not. Not all variants are equally problematic. Many truncating titin variants are clearly associated with a high risk of heart or muscle disease, and these are often classified as "pathogenic" or "likely-pathogenic" in the clinical genetic test report. On the other hand some variants are clearly not harmful and are classified as "benign" or "likely-benign". Often however, there is insufficient information about variants to tell if they are harmful and these are classified as "variants of uncertain significance" (VUS or VOUS). These variants need follow up by experts (see resources).

Created May 2021 by Diane Fatkin, MD, Renee Johnson, PhD , MGC and Sarah Foye, (Titin Family Advocate)

Resources

Research

For all people with Titin related muscle weakness:
[Beggs Laboratory](#)
Boston Children's Hospital
Casie Genetti, Genetic Counselor Ph: 617-919-2169
BeggsLabGC@chidlrens.harvard.edu

For help with diagnosis:
Prof Bjarne Udd, MD, PhD
Tampere Neuromuscular Center
Folkhälsan Research Institute, Helsinki
bjarne.udd@netikka.fi

Gene and heart disease research:
Prof. Diane Fatkin, MD
Victor Chang Cardiac Research Institute and St Vincent's Hospital, Australia
d.fatkin@victorchang.edu.au

Study of atypical titinopathies, including persons with skeletal or cardioskeletal symptoms and single TTN variants.
Jen Roggenbuck, MS, CGC
Ohio State University
Jennifer.Roggenbuck@osumc.edu

Some Genetic testing options:

[Free program](#) via Patient Insights Network
[Paid genetic testing](#) program through Invitae
[GeneDx](#) genetic testing

The [Lantern Project](#)

Please enroll in **The Congenital Muscle Disease International Registry!**
http://www.cmdir.org

CMDIR
congenital muscle disease international registry
leading the way to a treatment and cure

Connect with families/resources

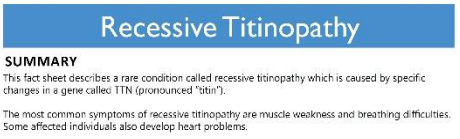
Team Titin on **Facebook**
[Private discussion group](#) for families
[Public Facebook page](#)

[ZNM - Zusammen stark! e.V.](#)
An association for centronuclear myopathies in Germany, the Netherlands and Austria.

Sarah Foye,
Titin Family Advocate
FoyeSarah@gmail.com
973-797-9305

Titin Information **Website** [link](#)

Recessive [titinopathy fact sheet](#) for families.



Care

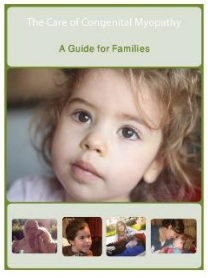
Heart health information
DCM Foundation
https://dcmfoundation.org/

DCM Foundation
Hope for People with Dilated Cardiomyopathy

Children's Cardiomyopathy Foundation

[Children's Cardiomyopathy Foundation](#)

The Care of Congenital Myopathy: A guide for families [link](#).



Summary of Evidence-based Guideline for patients and their families Limb-Girdle and distal muscular dystrophies [link.](#)

Recessive Titinopathy

SUMMARY

This fact sheet describes a rare condition called recessive titinopathy which is caused by specific changes in a gene called TTN (pronounced "titin").

The most common symptoms of recessive titinopathy are muscle weakness and breathing difficulties. Some affected individuals also develop heart problems.

WHAT IS RECESSIVE TITINOPATHY?

Recessive titinopathy is a muscle condition that can affect many parts of the body. The muscle weakness caused by this disorder often becomes apparent during pregnancy (e.g. reduced in utero movements), at birth, or during the first few months of life. However, sometimes the weakness develops a little bit later on (during until childhood or adolescence).

Some affected individuals develop relatively mild symptoms. Others develop much more severe symptoms. The reasons for these differences are not yet well understood.

The most common symptoms of recessive titinopathy are:

- **Muscle weakness** which results in difficulty moving the arms, legs, truck, head and/or neck. Sometimes there is also weakness of the muscles of the face which can make it harder to make normal facial expressions, or make the eyelids appear slightly "droopy" (eyelid ptosis).
- **Bone and joint changes** such as:
  - » Joint tightness that can make it harder to bend certain joints, for example the hips, knees, elbows, wrists, fingers and/or feet.
  - » Spinal changes such as spinal stiffness which makes bending forward more difficult, or a fixed curvature of the spine (scoliosis).
  - » Chest wall changes caused by weakness of the chest wall muscles may cause the breast bone and ribs to protrude outwards or compress inwards.
- **Feeding difficulties**: Weakness of the muscles used when eating may result in difficulties chewing and swallowing.
- **Breathing difficulties**: Weakness of the chest muscles and the main internal breathing muscle that sits just under our lungs (diaphragm) sometimes results in difficulties coughing and/or breathing. Breathing difficulties are often much more pronounced during sleep when muscles are generally more relaxed. Coughing and breathing difficulties can be present from birth or develop over time.
- **Heart problems**: The heart may not quite develop in the normal way or become unusually large and less efficient at pumping blood around the body (dilated cardiomyopathy). In some affected individuals, an irregular heartbeat may develop (arrhythmia). These heart changes may be present from birth or develop over time.

WHAT CAUSES RECESSIVE TITINOPATHY?

Recessive titinopathy is caused by specific changes in a gene called TTN ("titin").

The TTN gene is located on chromosome number 2 and it provides the instructions to make a very large protein called titin.

The titin protein is important for muscles in the body to function properly. Together with other proteins the body makes, titin is needed by different muscles of the body to contract and relax in the correct way.

In individuals with recessive titinopathy, both copies of the TTN gene are faulty due to the presence of a spelling mistake within the gene. These spelling mistakes are sometimes referred to as mutations, or pathogenic (disease-causing) variants. Without a properly working copy of the TTN gene, the body is no able to produce enough normal titin protein. This, in turn, impacts muscle function and results in the development of recessive titinopathy symptoms.

Our body is made up of millions of cells, and in each cell there are instructions, called genes, that make all the necessary structural components and chemicals for the body to function. These genes are packaged onto little long strands known as chromosomes.

We all have 46 chromosomes arranged into 23 pairs. One copy of each pair is inherited from our mother and the other from our father. The first 22 chromosome pairs are numbered and are known as autosomal chromosomes. The 23rd pair is made up of the sex chromosomes called X and Y. Males have an X and a Y chromosome and females have two copies of the X chromosome.

Since all our chromosomes come in pairs, all our genes also come in pairs. Sometimes, a genes may have a variation in the instruction that causes the gene to no longer function properly. This variation is called a mutation or pathogenic variant, and means that the product produced by the gene, called a protein, is impaired or even absent.

Gene mutations may be inherited from a parent, or occur for the first time in an individual. Once you have a gene mutation however, it may be passed on to future generations. This is referred to as genetic inheritance.

Some people (for example many parents of individuals with recessive titinopathy) have one copy of the TTN gene that has a variation that makes it faulty. The other copy of their TTN gene is still functioning normally. Because these people have at least one working copy of the TTN gene, their muscle fibres usually produce produce enough of the titin protein for the muscles of the body to function normally, and are known as recessive titinopathy carriers.

Recessive titinopathy carriers will not develop the symptoms of recessive titinopathy but because they produce less titin protein, they do have an increased risk of developing heart problems such as cardiomyopathy or an irregular heartbeat. However, not all carriers develop heart problems during their lifetime, and the heart problems that do develop in recessive titinopathy carriers usually don't develop until carriers reach adulthood.

Sometimes genetic testing finds a variant in TTN that doctors have not seen before, and it is not clear whether it causes disease. This is called a "Variant of Unknown Significance" or VOUS or VUS.

HOW IS RECESSIVE TITINOPATHY INHERITED?

Recessive titinopathy is a genetic condition that follows a pattern of autosomal recessive inheritance.

Autosomal means that the TTN gene is located on an autosomal chromosome (chromosome 2), which is one of the numbered chromosomes that both males and females have. Because of this, recessive titinopathy affects both sexes equally.

Recessive means that, in order to develop signs and symptoms of the condition both copies of the TTN gene must be faulty. If a couple are both genetic carriers for recessive titinopathy (Figure 1), in every pregnancy there is a:

- 1 chance in 4 (25% chance) that they will have a child who inherits both copies of the recessive TTN gene mutation from them. In this case, no working gene product will be produced and the child will be affected by recessive titinopathy.
- 1 chance in 4 (25% chance) that their child will inherit both copies of the working gene and will not be affected by recessive titinopathy. In this case the child also won't be a genetic carrier.
- 1 chance in 2 (2 chances in 4 or 50% chance) that their child will inherit the recessive TTN gene mutation from one parent and the working copy of the gene from the other. This means the child will be an unaffected genetic carrier for recessive titinopathy, just like the parents.

Recessive Titinopathy Inheritance Pattern

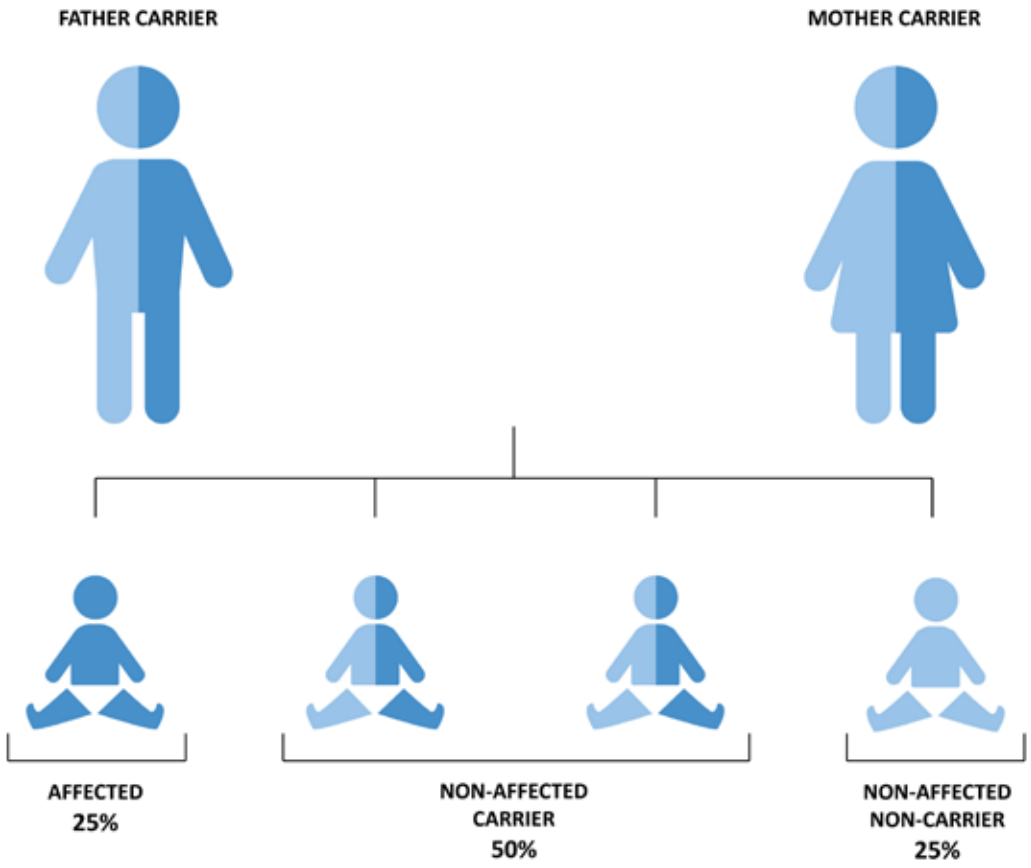


Diagram by Lucinda Lee

IS THERE ANY TESTING AVAILABLE FOR RECESSIVE TITINOPATHY?

Clinical examination and testing

The diagnosis of recessive titinopathy can be complicated and involves a comprehensive assessment of any individual who shows signs and symptoms that would be consistent with this diagnosis. Testing looks at each of the body systems potentially involved in recessive titinopathy, for example the limb, trunk, spinal neck and face muscles (which muscles are weak? how weak are they?), breathing muscles, and heart muscle. Sometimes additional testing such as a breathing (lung function or sleep study) test or heart muscle test (for example an ECG electrical trace or heart imaging) is requested to check heart and lung function. If a diagnosis of recessive titinopathy is suspected, genetic or DNA testing may help. In addition, muscle imaging studies, such as muscle ultrasound and/or muscle MRI, are sometimes used to assess which muscles are significantly impacted by the disorder. Identifying patterns of muscle involvement can help to establish the correct diagnosis.

Prenatal testing and pre-implantation genetic diagnosis (PGD)

For couples who already have one or more children with recessive titinopathy in whom the two causative faulty TTN genetic variants have been identified, genetic testing may be available during the early stages of pregnancy to determine whether or not a subsequent baby has inherited the same two TTN variants. It may also be possible to undergo pre-implantation genetic diagnosis (PGD). This involves testing an embryo created using in vitro fertilisation (IVF) for the two causative variants. Only embryos without the two causative variants are implanted into the mothers uterus to begin a pregnancy. These options are best discussed and considered before pregnancy, if at all possible possible, in order to ensure all possible risks, benefits. options and outcomes can be explored. Additional information about these testing options is available via the following links ***

Genetic Testing

Genetic testing is available which tries to identify the faulty genetic variants that cause recessive titinopathy and may be used to confirm a suspected diagnosis. If a faulty genetic variants is identified in an individual suspected of having recessive titinopathy, genetic testing can be offered to other family members to confirm if they share the same condition, or if they are recessive titinopathy carriers.

Treatment

Currently, there is no available drug treatments or cures for recessive titinopathy. Best care for someone with titinopathy involves managing the day-to-day symptoms with the support of a medical team. Changes in breathing (lung function) are common, so we recommend follow up by a breathing specialist (respiratory physician/pulmonologist). The first signs of breathing difficulties often start during sleep. Sleep studies are therefore often used to assess breathing performance. Because there is a risk of developing heart problems, it is also important to be followed regularly by a heart doctor (cardiologist). We also recommend a baseline heart check for family members who are carriers of pathogenic titin variants, and ongoing heart checks (every few years) for adult recessive titinopathy carriers.

Because of the wide variability in severity from person to person with recessive titinopathy it is difficult to predict how this condition will impact someone over their lifespan (prognosis).

RESOURCES AND REFERENCES

Resources for families:

The Care of Congenital Myopathy: A Guide for Families can be found for free online here or purchased on Amazon.

Here are some places to connect with other affected families:

- Sarah Foye, Titin Family Advocate: foyesarah@gmail.com US 1- 973-797-9305
- Titin Related Muscle and Heart Disorders Community https://www.facebook.com/TeamTitin

References:

Peter Hackman, Bjarne Udd, Carsten G. Bönnemann, Ana Ferreiro, Titinopathy Database Consortium, 219th ENMC International Workshop: Titinopathies – international database of titin mutations and phenotypes, Neuromuscular Disorders (2017), https://doi.org/10.1016/j.nmd.2017.01.009.

Oates EC, Jones KJ, Donkervoort S, Charlton A, Brammah S, Smith JE 3rd, et al. Titinopathy: Comprehensive characterization and pathogenic insights. Ann Neurol. 2018;83(6):1105–24. https://www.ncbi.nlm.nih.gov/pubmed/29691892

Genetics Home Reference: https://ghr.nlm.nih.gov/gene/TTN

OMIM: https://www.omim.org/entry/188840?search=188840%29&highlight=188840

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