This letter is for families with variant(s) in the **Titin gene**, also abbreviated as ***TTN***. Changes in the Titin protein may cause **muscle weakness as well as heart problems**. You will need to discuss with your doctor if and how your Titin variant affects your health.

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 each of the individual muscle cells in our bodies. It is also found in the heart, which is a very specialized muscle. Muscles need Titin in order to work and move. You can learn more about Titin here: **http://titinmyopathy.com**.

What is a Titin Myopathy?
In medical terms, "Myo" refers to muscle and "-opathy" at the end of a word means that the word describes a medical disease or condition. So "myopathy" is a medical illness involving muscles. Myopathies result in muscle weakness and muscle fatigue. "Titin Myopathy" is a specific category of myopathy where the muscle problem is caused by a change in the Titin gene and subsequently the protein.

What is a Titin-related Dystrophy?
A Titin dystrophy is a muscle disorder where muscle cells break down. Dystrophies generally result in weakness that gets worse over time.

A common heart problem caused by variants in the Titin gene is known as dilated cardiomyopathy. Sometimes other heart issues are also present in people with changes in their Titin gene. It is a good idea to have a checkup from a heart doctor if you have **even a single variant** in the Titin gene. This may also apply to family members.

Disorders due to Titin variants include:

- Dilated cardiomyopathy (heart condition)
- Limb-girdle muscular dystrophy type 2J (LGMD2J)
- Congenital centronuclear myopathy (CNM)
- Late-onset autosomal dominant Tibial Muscular Dystrophy (TMD)
- Hereditary myopathy with early respiratory failure (HMERF)
- Early-onset myopathy with fatal cardiomyopathy, EOMFC
- Multi-minicore Disease with Heart Disease (MmDHD) including clinical variations
- Early adult onset recessive distal titinopathy
- Early onset recessive generalized myopathy with ankle contractures
- Adult onset recessive proximal muscular dystrophy
- Childhood-juvenile onset Emery-Dreifuss–like phenotype without cardiomyopathy

How to make sense of your Variant of Unknown Significance Results for Titin

Changes found in a gene are sometimes called ***mutations*** or ***variants***. Some variants in a gene may lead to health problems, while others may not.

Sometimes a genetic testing laboratory will find a variant in a gene that they have not seen before, and they do not know if it causes disease or not. When a lab comes across a variant, but it has not yet been reported to cause disease, they call it a "Variant of Unknown Significance" or **VOUS** or **VUS**.

There are many great doctors, researchers and clinicians working to discover which VOUSs cause disease and which do not. This is one reason why it's really helpful for people like you to ***register in our patient registry the Congenital Muscle Disease International Registry*** www.cmdir.org and enroll in research.

Interpreting Titin genetic testing results can be tricky. One reason for this is that Titin is such a huge gene. Titin's size matters for several reasons: one is that until recently, scientists did not have the technology to tackle such a giant gene. New tools have allowed researchers to learn more about Titin, and doctors are beginning to reveal what kind of changes in Titin are disease-causing and which are not. The second reason is that because Titin is so large and has so many parts (known as exomes), there are many chances for variation.

Let's think about tires on a car for a moment. Most cars have four tires. If I went out into my garage and measured the pressure in 4 tires of my car, it's likely that all of them are properly filled. Now, imagine if I had a car that had the same number of tires as Titin has exons: 363! If I checked the tire pressure of 363 tires, it would be much more likely to find one that was low on air. The larger the sample size, the more likely I am to find some variation in tire pressure. Some cars run just fine with a tire low on air, just like some genes work just fine with some variants. However, some tires are low on air because they are functionally flawed like with a tire with nail puncture. It's the same with genes. Some variants in the gene cause it to not function properly.

VOUS, now what?

So, if you have been diagnosed with a VOUS, how do you figure out if it is the cause of your condition or not? Here are a few recommendations:

Additional testing options:

- If one or two disease causing variants were identified in the same gene, testing is recommended for other relatives who might be at risk to be affected or a carrier. People who have single variants in the Titin gene may be at risk for heart problems.
- If two disease causing variants are identified in the same gene, testing of parents may be recommended to determine whether each parent carries one of the identified variants.
- For variants of unknown significance, other kinds of testing might be necessary. These tests may provide additional information to aid in the reclassification of a VOUS and/or help support or refute the diagnosis of a specific disorder. For Titin, this might include medical tests such as:
    - Heart function tests such as EKG and echocardiogram
    - CPK blood levels
    - Neurological examination
    - Muscle ultrasound or MRI, etc.
    - Breathing tests (including a sleep study and pulmonary function test that measures breathing capacity and cough strength)

Genetic Counseling

- If you participated in the LGMD-diagnosis.org program, a 30 minute telephone session with an Emory Genetics counselor is available at no additional charge. This genetic counseling session is designed to help participants better understand what the report says and provide guidance about further testing options for themselves and family members. To schedule a telephone appointment, please contact Alonda Sims, Emory Genetics Laboratory, at 404-727-3875.

- Schedule a formal genetic counseling session near you. You can use the "find a genetic counselor" tool on the National Society of Genetic Counselors website, www.nsgc.org, to contact a genetic counselor in your area. It is ideal to find a genetic counselor that specializes in neuromuscular disorders.

Enroll in Research

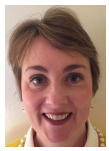
Some researchers can help answer whether a Titin VOUS is disease causing or not. Here are two researchers working on Titin that you can contact:

Beggs Laboratory
Boston Children's Hospital
Casie Genetti, Genetic Counselor
Ph: 617-919-2169
cgenetti@enders.tch.harvard.edu

National Institutes of Health
National Institute of Neurological Disorders and Stroke Neurogenetics Branch
Neuromuscular and Neurogenetic Disorders of Childhood Section
Sandra Donkervoort, MS,CGC
Genetic Counselor
Ph: 301-496-0272
donkervoorts@mail.nih.gov

Here are some places to find more information:

Sarah Foye, Titin Family Advocate
foyesarah@gmail.com
(973) 797-9305



Titin Related Muscle and Heart Disorders Community
https://www.facebook.com/TitinRelatedCentronuclearMyopathy

Titin Myopathy Website:
http://titinmyopathy.com

The Congenital Muscle Disease International Registry
www.cmdir.org