DCM BEAT

www.fdc.to
Newsletter of the Dilated Cardiomyopathy Project at The Ohio State University
Columbus, OH, USA **Volume XIV, Issue 2** **July 2013**

Titin Gene Mutations: Updated Testing for DCM

Early this year, we reported that gene changes (mutations) in a gene called titin (gene symbol TTN) were found and reported as the cause of DCM in seven of our participant families. The report, published in Circulation Cardiovascular Genetics (April 2013, volume 6, number 2), presents these findings as well as the unique challenges related to fully understanding the role of titin in DCM. In this issue of FDC Beat, we highlight these findings and what they mean for you.

What is titin?

Titin is the name of a gene that codes instructions to make the largest known protein in the human body. The protein, also known as titin, is important for the normal process of tightening and relaxing of heart muscle and the muscles involved in body movement (skeletal muscle). A recent report by another research group identified a specific category of mutations (known as truncating mutations) in approximately 20% (20 of every 100) of individuals with DCM.

Titin truncating mutations

A mutation is a change in a gene's code. You can think of a mutation as a spelling error in a sentence. Just like there are different types of spelling errors, there are different types of mutations. The majority of mutations that cause DCM are known as **missense mutations**. If we think of missense mutations as spelling errors, they would be similar to a sentence in which the error changes one word (for example, "*The day is h**a**t.*" instead of "*The day is h**o**t.*").

Following the spelling error example, a **truncating mutation** (the type involved in titin-DCM), would be a spelling error in which a sentence ends prematurely. An example of a truncating mutation, using the spelling error example, would be "*The day is.*" instead of "*The day is hot.*" Therefore, titin truncating mutations are those in which the gene code error leads to a shorter version of the titin protein. Shorter forms of titin are thought to cause instability in the heart muscle, leading to DCM.

Our titin report

For our paper, we first selected 17 large families with multiple relatives with DCM in which research testing had been negative. Next, we did exome sequencing, a form of genetic testing in which all genes are read in one single test. Only genes that were thought to be relevant to DCM were analyzed. In seven of the seventeen families, a truncating mutation in titin was identified that explained the family condition.

Another two families were found to have truncating titin mutations in only one affected family member. Other affected family members did not carry the same mutation, indicating that the titin mutation is not causing DCM in those families. In a few families, titin truncating mutations were present along with other known DCM-causing mutations, again suggesting that titin may not be the DCM family gene.

In several other families, titin missense (as opposed to truncating) mutations were also identified in titin. We do not think that titin missense mutations cause DCM in those families. This is because missense mutations in titin have been identified in healthy adult individuals without DCM or a family history of DCM. In fact, it is estimated that healthy individuals carry an average of 23 missense mutations in titin!

Continued in page 2...

Titin testing... Continued from page 1

Another problem we identified was that, similar to missense mutations, truncating mutations in titin are also found in healthy people without DCM or a family history of DCM. Although truncating mutations in titin are found less frequently in healthy individuals (compared to missense mutations in healthy individuals), the fact that they can be found in healthy individuals is problematic when deciding which mutations are disease-causing and which are not.

We concluded that, while titin truncating mutations contribute to the cause of DCM, providers and researchers will continue to face challenges when determining the true meaning of a positive genetic testing result in titin.

Implications for people with DCM

Soon after the recent reports linking titin to DCM, clinical genetic testing laboratories updated their genetic testing menus to include this gene. The implications for people with DCM are below. The implications for family members depend on genetic testing findings in the person with DCM in the family.

1. **People with DCM who have not undergone genetic testing.** A person with DCM who has not undergone clinical genetic testing may benefit from genetic testing, as the test's ability to detect mutations has increased (with the addition of titin) from 20% to 40%.

2. **People with DCM with negative or uninformative genetic testing results.** A person with DCM who underwent clinical genetic testing and received negative or inconclusive results may want to consider repeating their genetic testing to evaluate titin.

3. **People with DCM with positive genetic testing results.** Because titin mutations may be present along with mutations in other DCM genes, a person with DCM who tested positive may benefit from repeat genetic testing to evaluate titin, especially if the provider suspects that more than one mutation may be at play in a family.

Implications for participants of our study

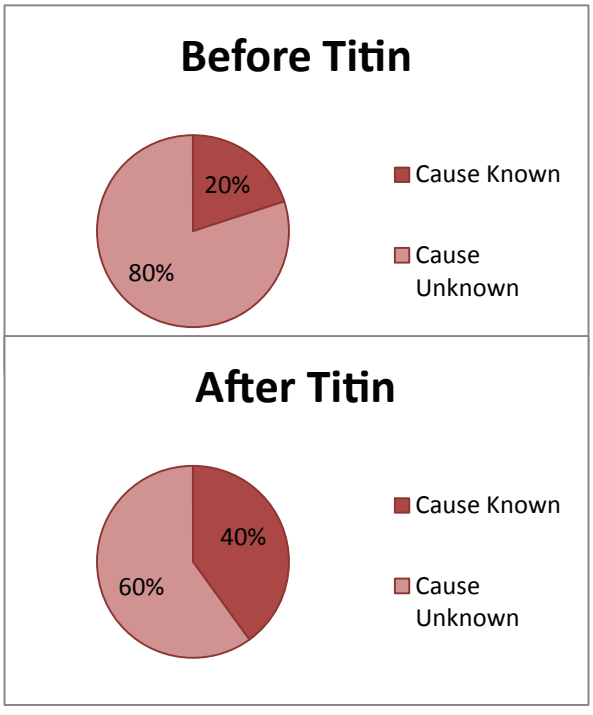
Notification letters were sent to adult participating members from the seven families that we reported. Following our established protocol, these notification letters inform participants in those families that a research result is available and that, in order to receive an official report, genetic counseling and confirmatory testing at a clinical laboratory is indicated. Our research continues in all of our families. For our research participants, general implications are below. As always, we welcome inquiries regarding the status of our research.

1. **Families who received a results notification prior to 2013.** It is possible that titin has not been evaluated. However, we are continuing our research and we will send notifications should more findings become available. In the meantime, participants who already received a results notification from us should ask their provider if clinical genetic testing including titin would be beneficial.

2. **Families who have not received a results notification from us.** We only tested 17 of our families for titin. Another few hundred families are currently being tested. If you have not received a notification letter, it is possible that a result will be reported in the future. These results can take months or years to complete. According to medical guidelines, clinical genetic testing should be considered.

The impact of titin in genetic DCM

The fraction of cases with known DCM mutations is now 40% (40 of every 100 tested):



Staff Updates: Farewell to Lizzie, Welcome Claire!

It is time to say farewell to our student research assistant **Elizabeth "Lizzie" Baack**, who has received a scholarship to attend The University of Texas Genetic Counseling Program at Houston.

By the time this newsletter goes to production, Lizzie will be getting ready for the big move. She left the following note to our participating families:

Sadly, I must announce that I am leaving the DCM Research Project at the end of July. I will be attending the Genetic Counseling Graduate Program at the University of Texas at Houston starting this fall and though I am sad to leave Ohio and Ohio State, I am excited to start the next chapter of my life. In the year that I have been with the project, I have learned so much from the wonderful people on this research team and have truly enjoyed working with them.

Also, I am grateful to you all, the participants, family and friends, for sharing your experiences with DCM with me.

My experience here has been very rewarding and the support of genetics research, by so many people like you, is both touching and inspiring. It is my hope that, in my career as a genetic counselor, I will be able to continue to contribute to important genetics research projects, like this one, and to help further our knowledge of genetics.

I wish all the best for the DCM Research Project and I look forward to seeing what other amazing things the team will discover as their research continues. Best of luck to everyone! Thank you so much!

Student research assistant **Claire Murphy**, who joined us in March as a volunteer, will take over Lizzie's functions. Claire talks about her experience working in the DCM Research Project:

It has been a pleasure to work with such an amazing group of people! Working here has been such a life changing experience and it continuously deepens my passion for genetics. It is rewarding to work with all of you and to know that our collaboration is for a good cause. I will be graduating from The Ohio State University in May of 2014 with a degree in Molecular Genetics and a minor in Chemistry. I also volunteer for the Alzheimer's Association and I currently serve as a Peer Advocate for the students on campus. My future endeavors include furthering my education by going to graduate school and eventually becoming a Genetic Counselor. Thank you for your participation and allowing me a chance to work with you all.

We are forever thankful for Lizzie's insights as we reactivated our project here at Ohio State and look forward to Claire formally joining our group. We welcome Claire and wish Lizzie much success!

FDC Research Project Now DCM Research Project

In April 2013, the Familial Dilated Cardiomyopathy (FDC) Research Project, our name for the last 20 years, became the Dilated Cardiomyopathy (DCM) Research Project. It's a small change with big implications.

Our initial focus, when the study was launched in 1993, was families with multiple relatives with DCM, or Familial Dilated Cardiomyopathy (FDC). The name Familial Dilated Cardiomyopathy (FDC) Research Project reflected our main study goal. While at study inception we thought that a faulty gene was being transmitted in FDC, as time went on, and we learned more about the genetics of DCM, we realized that mutations were also present in people with DCM with a negative family history.

The idea that mutations may be present in an individual with a negative family history is the reason for our name change. We want to expand our focus to prove this idea. We hope that the new name will help to better communicate that we welcome individuals with DCM with or without a family history. If proven true, this concept will revolutionize cardiovascular genetic medicine.

DCM BULLETIN BOARD

Have you had genetic testing?

We recommend that all individuals with DCM consider undergoing clinical genetic testing. This testing was not routinely available when our study began in 1993. Clinical genetic testing is done similarly to any other blood test that is ordered by your doctor and sent out to a laboratory. Your results would be provided to your doctor.

According to medical guidelines for the evaluation of cardiomyopathy, clinical genetic testing can be a complex process. Therefore, referral to centers expert in genetic evaluation should be considered. We can help you identify a clinic offering genetic counseling and testing for DCM. If you have undergone clinical genetic testing and have results, please contact us to discuss obtaining a copy of your result for our database. Regardless of your genetic test results, this information will help us in our approach to identifying the gene or genes that may be causing DCM as well as how these mutations lead to DCM. Please contact us (toll-free) at 877-800-3430 or email Ana Morales, MS, CGC at ana.morales@osumc.edu.

MEDICAL FOLLOW-UP

If anyone in your family is newly diagnosed with heart problems, please let us know. Also, if you or anyone in your family has had heart or genetic tests performed, regardless of results, we would be interested in receiving copies. Please contact us and we will send you a medical record release form. If we have sent you medical record release form(s), please send us the completed form(s) as soon as possible.

CONTACT INFORMATION UPDATES

If you have moved and/or have an email address we can contact you at, please call us at 877-800-3430 or email us through the "Contact Us" page on our website: www.fdc.to. This way we can get in touch with you for any follow-up and continue to send you the newsletter.

ADD ME TO THE MAILING LIST

If you are not currently a participant in our study, but would like to receive our newsletter, please contact us with your name and address, and we will be pleased to add you to our mailing list.

DCM BEAT Newsletter

DCM Beat (formerly FDC Beat) is a publication of the Dilated Cardiomyopathy Research Project (formerly Familial Dilated Cardiomyopathy Research Project) in the Division of Human Genetics at The Ohio State University, in Columbus, OH. The newsletter is not copyrighted and readers may photocopy its content to share with family members and health care professionals. We welcome your feedback.

DCM Research Project
The Ohio State University
Internal Medicine, Human Genetics Division
0305 Biomedical Research Tower
460 W. 12th Ave.
Columbus, OH 43210

25080 013000 12757

ADDRESS SERVICE REQUESTED

TO: