FDC BEAT

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Newsletter of the Familial Dilated Cardiomyopathy Project at the University of Miami

Miami, FL, USA **Volume X, Issue 1** **March 2009**

Expanding Our Family Study To Include Non-Familial IDC

Greetings from the FDC Research Project! *Since its foundation in 1993, our study keeps evolving while contributing to new knowledge about the genetics of dilated cardiomyopathy. Our progress would not have been possible without the support and enthusiasm of participants like you. In this issue, we present our plans to expand the study and explain how you can help us reach our new goals.*

Evolution of the FDC Research Project

Since the 1980s, scientists began reporting that dilated cardiomyopathy of unknown cause, called idiopathic dilated cardiomyopathy (IDC), can run in families (called FDC, familial dilated cardiomyopathy). By the time the FDC Research Project was founded in 1993, the suggested explanation for FDC was that dilated cardiomyopathy can have a genetic basis, caused by alterations (mutations) in genes that play a key role in the heart.

By studying FDC, mutations that can cause dilated cardiomyopathy have been found in more than 20 genes. Although many genes have already been discovered, a genetic cause (a positive genetic testing result) has been identified in only approximately 25% (1 out of 4) of families with FDC. This means that in 75% (3 out of 4) FDC families, yet to be discovered genes may be responsible for this heart disease. As research continues, we predict that the number of genes implicated in dilated cardiomyopathy will likely double or triple.

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Our recent data suggests that like FDC, apparently non-familial (sporadic) IDC (a known history of IDC found in only one person in a family), also has a genetic basis. However, it is still unclear why some cases are familial and others appear to be sporadic. Therefore, we propose that IDC, whether familial or sporadic, lies on a continuum of disease resulting from different degrees of genetic influence (Fg. 1, Pg. 2). We now aim to test this concept in an expanded study.

New phase of the FDC Research Project

While there is supporting evidence that apparently sporadic IDC has a genetic basis, no formal studies have been performed to test this idea. To evaluate the degree to which genetic mutations are responsible for sporadic cases, we are now expanding our program to include a large group of people who appear, at least without cardiovascular screening of all close family members, to have non-familial IDC. To accomplish our goals we need:

1. **Participation of at least 1,000 different families with apparent sporadic disease**; that is, just one person with IDC in the family. The greater the number of participants, the greater the possibility to find a statistically significant result. Studies predict that screening with echocardiogram (echo) and electrocardiogram (ECG) may find other family members who also have dilated cardiomyopathy.

2. **Participation of close family members (of all ages, with and without heart disease) of people with non-familial IDC**. Even if you are the only person with IDC in your family, you can help us tremendously by speaking with your first degree relatives (parents, siblings and children) about enrollment in our study. Spouses are also invited to enroll as controls.

Participation of your relatives is very important for us to better understand the genetics of IDC. Please tell them

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Figure 1. A Genetic Model for Familial and Sporadic IDC

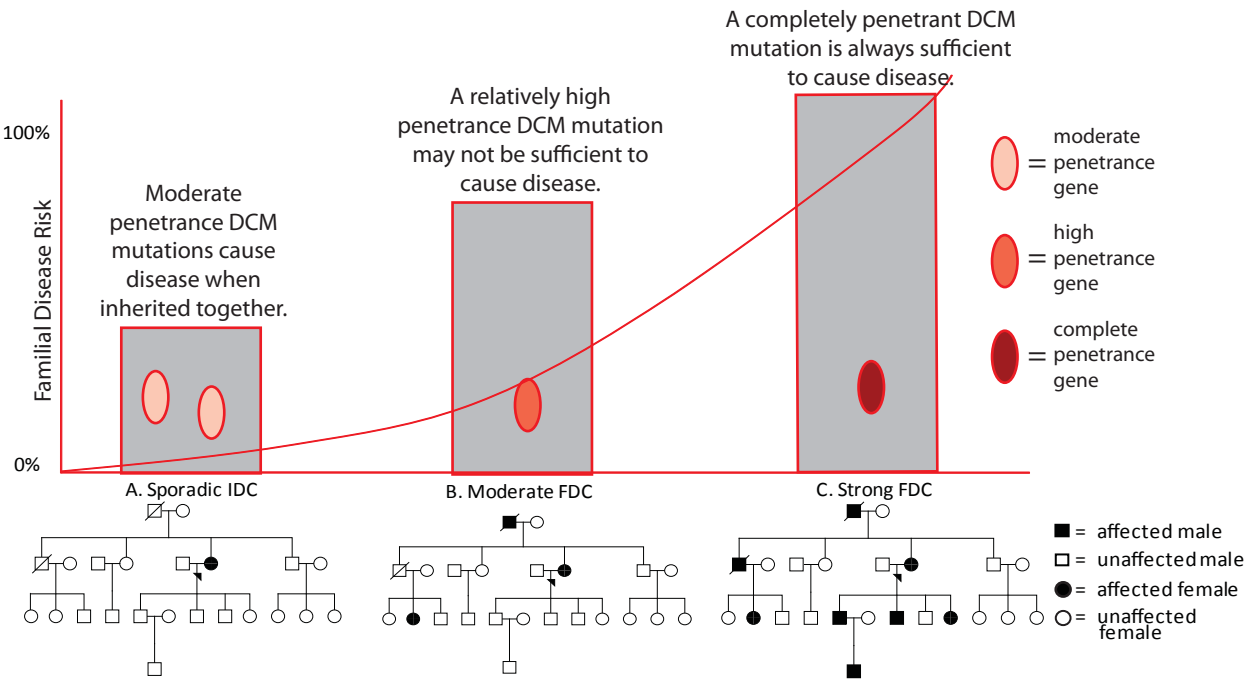

Figure 1. A Genetic Model for Familial and Sporadic IDC. Not everyone with DCM has a positive family history. This figure shows our view about how different gene changes can have a stronger or lesser effect (are more or less penetrant) and how this could lead to sporadic IDC (Pedigree A). In sporadic IDC cases, it is possible that multiple moderate penetrance genes contribute to risk for IDC. These genes could be inherited from varying sides of the family, and only result in IDC if they are inherited in certain combinations. Environmental (for example, diet or alcohol intake) and/or additional genetic influences on DCM mutations can modify the gene's penetrance (contribute to or protect against disease). For simplicity, these environmental influences are not shown.

Expanding Our Study... Continued from page 1

about the study and have them contact us, or get their permission for us to call them. We need two things from relatives who participate in the study:

1. **A blood sample.** This is how we obtain a sample of DNA, or genetic material, to study.

2. **Cardiovascular screening results.** Cardiovascular screening for our study includes:
   - Echocardiogram (echo)
   - Electrocardiogram (ECG)
   - Physical exam by a doctor or nurse

Cardiovascular screening will help identify family members who, despite having no symptoms, already have signs of an enlarged heart or abnormal results on one of their heart screenings. Screening of first degree relatives not only serves a research purpose, but can also result in direct clinical benefits. If a person is identified early in the disease process and started on drug therapy, the eventual quality of life and life expectancy is likely to improve. If the heart is found to be enlarged and/or its function found to be abnormal after receiving an ECG and echo, then early disease may be identified and treatment initiated. If these tests are normal, it is reassuring, but a normal test does not eliminate the possibility that disease could develop later. Therefore, repeat screening is recommended every 3-5 years, or sooner if symptoms are present.

Both a blood sample and cardiovascular screening from relatives will enable us to draw stronger conclusions about our results. Each of us has a unique combination of changes in our DNA. Sometimes, but not always, these changes can cause disease. If we detect a change, we need to determine if the change is disease-causing or benign. Participation of family members is key in this process. Some examples showing how family members can help our research are presented in Box 1 on Page 3.

The value of the FDC Research Project to you and your family members

The cause of IDC is still unknown in a number of cases. If our proposal that IDC has a genetic basis that can be inherited is proven true, this knowledge will improve the diagnosis and management of dilated cardiomyopathy.

Moreover, we may discover the cause of dilated cardiomyopathy in your family. If we do, we will notify you so that you can have the research results confirmed and integrated into your health care. Also, if we identify a genetic cause of dilated cardiomyopathy in you, then your relatives can have genetic testing to determine if they are at high risk for dilated cardiomyopathy. Those at high risk can be managed more effectively. If you have relatives who already have IDC, they may also benefit from confirming that a genetic predisposition played a significant role in the development of their heart disease.

Please Contact Us! We'd Like to Hear from You.

Big or small, sporadic or familial, staying in touch with our families is important to us. As the FDC Research Project continues to grow, it becomes more important that we keep our records up-to-date so that we can remain in contact with you as our research progress. Please let us know about:

1. **Contact information changes**. Updated contact information will not only allow you to continue receiving this newsletter; it will also allow us to reach you if we ever have significant genetic results that could affect your health.

2. **Your cardiovascular health.** We'd like to know about:
   a. A change in your health status, such as a diagnosis of cardiomyopathy or other heart problem.
   b. Cardiac tests/procedures performed. If you have had a certain test multiple times, such as an annual echo or ECG, we'd like to know the results each time.

3. **Family history updates.** Family history changes over time. The more family history information we have, the better we will be able to understand the dilated cardiomyopathy in your family. See Box 2 ("Family History Tips") for the type of information we need.

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Box 1. Ways that Participation of Your Family Members Can Help the FDC Research Study

Example 1: An individual with IDC is found to have a gene change (mutation). If the same mutation is found in one or more 1st degree relatives (parents, siblings, children) who have been screened and found to have no evidence of dilated cardiomyopathy, the gene change has an unknown role in disease or possibly no role at all.

Example 2: An individual with IDC is found to have a mutation, and the mutation is also found one or more 1st degree relatives who are asymptomatic but have signs of dilated cardiomyopathy on a cardiac screening testing. In this case, there is greater evidence pointing at the identified mutation as responsible for disease in that family.

Example 3: An individual with IDC is found to have a mutation, and the mutation was not found in either parent. This means that the mutation occurred for the first time in the affected individual. When a mutation occurs for the first time in an affected individual, it is said to be a new mutation, or a "de novo" mutation. Although a person who has a new mutation did not inherit it from a parent, the mutation can be passed onto his or her children. Because neither parent has the mutation, siblings of a person with a "de novo" mutation are not expected to have the mutation.

In all of the above cases, genetic information will be compared across all families.

Box 2. Family History Tips

Please let us know if any of the following things have recently occurred in your family:

- Heart failure (sometimes referred to as congestive heart failure)
- Cardiomyopathy (heart muscle disease of any cause)
- Heart transplant
- Heart attack, especially if sudden and no history of coronary artery disease, stents or bypass surgery
- Arrhythmias (irregular heartbeat)
- Pacemakers, defibrillators (ICD)
- Fainting spells (sometimes thought to be a seizure disorder)
- Sudden or unexplained death, especially at a young age
- Stroke
- Death of a family member, especially if previously enrolled in the study

Cardiac Screening for FDC Research Participants

Cardiac evaluation of all study participants is a very important component of our research study. This includes family members who do not have any symptoms of heart disease but do have a first degree relative (parent, sibling, child) in our study with IDC. Ideally, individuals will have insurance coverage for this screening and can do so through their primary care physician's or a cardiologist's office. However, we recognize that this is not always possible for a myriad of reasons.

Therefore, we are able to offer a cardiac evaluation for research purposes through the General Clinical Research Center (GCRC) at the University of Miami. This center is staffed by trained health care professionals. If any of the tests are abnormal, we will provide you with this information so that you may seek appropriate medical follow-up. We can give you a copy of your research screening report.

For FDC Research Project participants, cardiovascular screening at the UM GCRC is free of charge. Although travel to Miami is not provided, the GCRC welcomes local and out-of-state participants.

To schedule an appointment or learn more about the GCRC, please contact us toll free at 1-877-800-3430.

In The Next FDC Beat Issue…

A Review of The New Cardiomyopathy Medical Guidelines: What Do They Mean for You?

"Genetic Evaluation of Cardiomyopathy – A Heart Failure Society of America Practice Guideline." Hershberger et.al. (2009). Journal of Cardiac Failure (15): 83 – 97.

Please Contact Us... Continued from page 3

4. **Family members interested in participating.** We are always interested in enrolling additional family members in the study. With your relatives' permission, you can give us their contact information to discuss enrollment in the study.

5. **If we have contacted you informing you about genetic findings that need further clarification by additional medical records and/or participation from additional relatives**, please contact us so that we can discuss this more. If confirmed, these results can have a significant impact on your healthcare or your relatives' health care.

6. **How we can improve the way we do our work.** Please let us know what topics you would like to read about in this newsletter or what your experience has been like as a participant in our study.

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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.

CALL US AT OUR TOLL FREE NUMBER: 877-800-3430

EMAIL US THROUGH THE "Contact Us" PAGE ON OUR WEBSITE: WWW.FDC.TO

FDC BEAT Newsletter

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