FDC BEAT

Newsletter of the Familial Dilated Cardiomyopathy Project at Oregon Health & Science University

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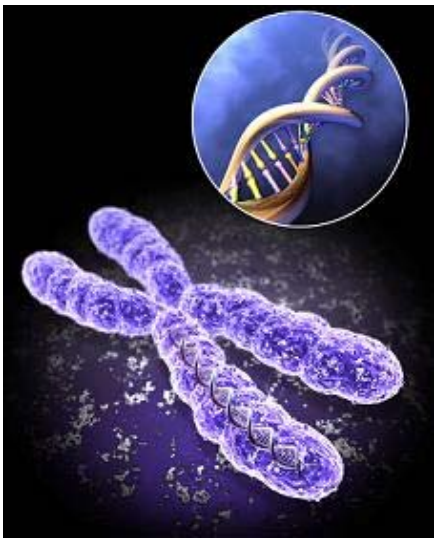
Finding the Gene in an FDC Family

The Familial Dilated Cardiomyopathy (FDC) Research Group wishes all our participants and their families a happy and healthy summer 2004. In this issue of our newsletter we discuss the ways in which our research attempts to find the gene that causes FDC in a family and how you can help us with this challenging effort.



GENES AND FDC

As you know, one of our main goals is to identify genes that cause FDC. FDC is defined as at least two close family members who have been diagnosed with idiopathic dilated cardiomyopathy (IDC), or dilated cardiomyopathy of unknown cause. When at least two close family members have IDC, this raises suspicion that there is a genetic cause for the IDC, meaning other family members may also be at risk to develop the condition.

A gene is defined as a unit of heredity. A gene is a set of instructions within DNA that tell the body how to make the proteins, the basic building blocks of our bodies, like those that make up heart muscle. We receive our genes from our mother and father; that is, genes are passed from generation to generation.

It is thought that humans have about 30,000-50,000 genes. A number of these genes are involved in heart muscle function and regulation of the heart's electrical system. When even just one of these genes is not working properly, a person may develop an enlarged and weak heart (dilated cardiomyopathy) and/or irregular heart rhythms (arrhythmias). Because so many genes play a role in heart function, each family may have a different gene causing FDC in their particular family. This makes the effort to find the culprit gene in an individual family more difficult.

WHY FIND FDC GENES?

There are number of ways that identifying an FDC gene could be of benefit to a family or person with IDC. If a simple blood test could identify an FDC gene, this would allow for more accurate diagnosis of someone's dilated cardiomyopathy and its cause, which in turn could lead to improved care and treatment. As more FDC genes are

identified and their functions in the heart understood, knowing which specific FDC gene is involved in a family might provide information as to what types of heart problems are more likely to occur, such as risk for serious arrhythmias for which implanting a cardiac defibrillator might be considered as part of preventative care.

Knowing the FDC gene in a family could also provide important information for family members. For instance, a relative without any symptoms might decide to be followed with echocardiograms and EKGs if they knew they carried an FDC gene that put them at risk for developing cardiomyopathy sometime in the future. Such information might then lead to earlier diagnosis, treatment, and maybe prevention of serious complications. On the other hand, a family member who has always assumed that they will develop heart problems, or one with very non-specific symptoms such as fatigue or palpitations, might find out they don't carry an FDC gene and can be reassured that they are not at increased risk to develop cardiomyopathy or that other causes of their symptoms should be considered.

Genetic information, however, is not a crystal ball and cannot provide all the information a person might want to know. For someone who is already diagnosed with cardiomyopathy or heart failure, their condition may be too serious for such knowledge to help with their treatment. In addition, knowing one carries an FDC gene does not predict if and when they might develop any symptoms, much less actual cardiomyopathy or how severe or mild it will be. Some FDC gene carriers may never develop any heart problems. While genetic information does have limitations, the knowledge it affords can feel empowering, perhaps taking away some of the frustration and anxiety that is commonly a part of disease - especially one like IDC/FDC that can affect many family members but in the past has offered little in explaining how and why this is happening in the family.

FINDING FDC GENES

There are two main ways to find the FDC gene in a family: **sequencing** and **linkage analysis**. Sequencing is used to look within a gene's instruction set for any alterations that would interfere with the proper working of the heart. This technique is applied to genes that have been reported in the medical journals as causes of FDC; about 16 such genes are known to date. Linkage analysis is a laboratory method that is used to find new genes that have not yet been identified but might cause FDC. Which technique is used for a specific family depends on several factors, mainly the size of the family and the number of living relatives with IDC. The larger the family and the more affected relatives, the more likely that linkage analysis can be used along with sequencing to attempt to find a family's FDC gene. Both techniques take a lot of time and effort in the lab.

Because there are so many different genes that can cause FDC, sequencing must be performed for each individual family. In many families, many genes will need to be sequenced until the culprit is found, which takes even more time and effort. Often even sequencing of all the known genes will not provide an answer. This means the answer might not be found until linkage analysis in larger families helps identify new genes that can then be sequenced in hopes of finally finding the culprit gene in a smaller family.

HOW DO WE KNOW IF WE'VE FOUND THE FDC GENE IN A FAMILY?

An additional challenge in finding a family's FDC gene is knowing if what is found is indeed the real cause of dilated cardiomyopathy in the family. Generally,

when a gene's set of instructions is incomplete or altered in some way, this will ultimately affect the gene's function and lead to disease. However, sometimes changes within a gene do not affect its function and do not cause disease. For instance, think about eye color. People can have brown eyes, blue eyes, green, hazel, etc. For each eye color the gene's instructions are somewhat different, but none of these effect how the eye functions. The same can be true of changes within FDC genes – the gene's instruction set may look a little different from the "normal" set, but nevertheless does not effect the gene's role in heart function. When a gene contains a change that does not cause disease, it is known as a **polymorphism**. FDC gene changes that do cause dilated cardiomyopathy are called **mutations**.

So how do we know if we've found a harmless polymorphism versus a dilated cardiomyopathy-causing mutation in an FDC gene? One way to help determine this is to compare the gene in family members who do have and do not have dilated cardiomyopathy. If family members carry this change regardless of their heart's function, the change is more likely a polymorphism. However, if the change is only found in relatives with DCM, this provides good evidence that the change we have found is indeed responsible for the family's FDC. **This means that the more blood we have from both relatives with and without heart problems, the more confident we can be in any gene finding in our research lab.**

Blood from family members' spouses can also be helpful. Blood from "married-in" spouses can be very useful for linkage analysis. Spousal blood provides us with a large group of samples from people that usually don't have dilated cardiomyopathy themselves or in their own families, and thus is helpful to determine a polymorphism versus a mutation in an FDC gene.

WILL I BE CONTACTED IF AN FDC GENE IS FOUND IN MY FAMILY?

Yes, you will be contacted. However, as a research lab, until we receive approval, we are unable to provide participants with specific individual genetic test results. In the meantime, we can refer you to a clinical laboratory that can provide family members with genetic testing for a fee. We are currently in the process of applying for certification that will allow us to provide individual results.

WHAT CAN I DO TO HELP?

We hope the above information has helped you to see the possible benefits of our research, and more importantly, the role you can play in helping us find the answers to what causes FDC. Below are some specific things you can do to help. **Thanks for being a part of the FDC Research Team!**

*** Pass along screening recommendations to your family members.** It is currently recommended that children, siblings, and parents of a person with IDC/FDC have an echocardiogram and EKG, to look for early signs of the condition that may benefit from early treatment, and that this screening is performed about every 3-5 years if the baseline tests are normal. Any relatives with symptoms such as shortness of breath, swelling in the legs/feet, difficulty sleeping flat in bed, palpitations, dizziness/fainting, should be evaluated right away**.** Knowing what family members have and do not have any heart problems is very valuable to the study of each family.

***Discuss study participation with family members and spouses.** Blood samples and copies of heart tests results from relatives BOTH with and without heart problems, and from spouses, would help our efforts

tremendously. The more relatives that participate, the more we can learn about FDC in a family. Please have family members contact us using the information below to request blood kits. Blood can be drawn locally and sent back to us; medical release forms signed and then we request records. Costs for blood draw, shipping, and medical records are paid for by the study. All study participants receive our triannual newsletter, FDC Beat.

ANNOUNCEMENTS

Our FDC Research Associate and Genetic Counselor, **Jessica Kushner**, will be on maternity leave until the Fall, 2004. Jessica and her husband had a baby boy in late July. Congratulations to Jessica and her family!

While Jessica is gone you can contact our FDC Research Assistant, **Kelly Smith**, for blood kits and any other issues related to the study. You can reach Kelly or Jessica toll-free: 877-800-3430, ext.2, or via email: smikelly@ohsu.edu.

FDC BEAT Newsletter

FDC Beat is a triannual publication of the Familial Dilated Cardiomyopathy Project in the Division of Cardiology at Oregon Health and Science University in Portland, OR. The newsletter is not copyrighted and readers are welcome to photocopy it's content to share with family members and health care professionals.

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