FDC BEAT

Newsletter of the Familial Dilated Cardiomyopathy Project at Oregon Health & Science University
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$$ FDC Project Receives NIH Refunding! $$

We are pleased to announce that the FDC Research Project has been refunded by the National Institutes of Health (NIH). The NIH, an agency within the Department of Health and Human Services, is a major federal funding source for scientific and medical research. Originally the NIH funded the FDC Project in 1998 for 3 years. The currently awarded funding will allow us to continue our work studying familial dilated cardiomyopathy for the next 4 years! Less than one third of the grants approved for funding receive high enough priority to actually meet pay lines. Thus, receiving this funding is a reflection of the progress made since the project was started, and validates the overall scientific significance of continuing the study of dilated cardiomyopathy.

Now that we have secured funding, we have reviewed our goals and priorities for the coming months and years. This issue of our newsletter outlines our activities and introduces you to our expanding staff. We hope that this will give you a sense of what we do and the essential role you play as part of the FDC effort. As always, thank you for your participation and support!

THE FDC PROJECT: WHAT ARE WE DOING?

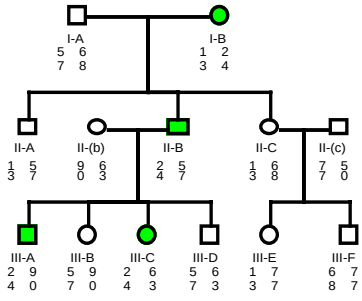
Our objectives can be divided into two major categories: 1) **Gene identification** and 2) **FDC characterization**. The activities involved in these major tasks are detailed below.

GENE LINKAGE AND IDENTIFICATION

(see GENETICS 101 page 4 for background)

Of course the ultimate goal is still the same - to identify genes that cause FDC. The basic scientific approaches known as **genotyping** and **linkage analysis** help in accomplishing this goal. These techniques look for a specific pattern of DNA that is present in family members diagnosed with cardiomyopathy that is different from the DNA pattern of family members that do not have cardiomyopathy. This requires searching through all the DNA of each individual family member's blood sample. This is done using **markers**, portions of DNA at known locations throughout the human genome (like mileposts on a very long highway). The specific pattern of DNA at marker sites varies from individual to individual, so the first step is to determine each person's DNA pattern at each marker site. This is called genotyping. Linkage analysis then seeks to locate a genotype that is associated with cardiomyopathy, that is, which marker is "linked" to the cardiomyopathy in a family (see illustration).

To illustrate this more clearly, let's use eye color as our "marker". Say we know that the eye color gene is located on chromosome B. In Family E, all those with blue eyes have cardiomyopathy, but everyone with brown eyes does not. This tells us that the gene for eye color and cardiomyopathy are close to one another, as blue eye color is "linked" with cardiomyopathy. Since we know that the gene for eye color is on chromosome B, now we can look at chromosome B in more detail to find the cardiomyopathy gene. Now this is just an example; there is no association with eye color and cardiomyopathy!



Each column of numbers represents an individual's genotype at 2 DNA markers (ex. Ind. I-B has genotype 1,3 & 2,4).

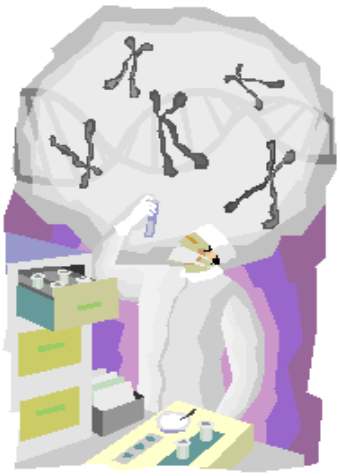
Green symbol indicates individuals with FDC. The genotype 2,4 appears to be linked to cardiomyopathy in this family - only affected family members have this genotype.

continued on page 2, WHAT ARE WE DOING?

WHAT ARE WE DOING? continued...

There are about 250 markers that must be initially analyzed in each individual taking into account their genotype, relation to other relatives, and cardiomyopathy status. Because marker patterns are unique to each family, linkage analysis needs to be performed for every marker on every individual in every family. Even with computers and automated programs to help, it can take almost a full 24 hours to obtain data on just a couple dozen markers!

If a marker that links to cardiomyopathy is found, this gives information about the location of a potential cardiomyopathy gene. This narrows the region in which to focus further linkage efforts to isolate the gene. Once the gene itself is identified, one can look for the specific change (mutation) within the gene that is causing the cardiomyopathy.



Linkage analysis requires very large families, with blood samples and clinical evaluations of at least 20 living family members, and DNA from 8-10 affected people, spanning at least 3 generations. Large families must be analyzed first, to avoid false linkage results that can occur using only families with a few members. The information gained from the larger families can then be applied to smaller families. However, FDC is hetero-geneous, meaning one gene may cause FDC in one family while a completely different gene may be responsible in a different family. Thus an initial linkage analysis result may identify the causative gene in some families and not others, necessitating repeating the whole process of genotyping and linkage analysis for each participating large family.

Currently we have several large families participating (and are always looking for more!). The lab is continuing to analyze their DNA, searching for the markers associated with FDC. As you will see on page 3, our laboratory staff is growing to accommodate the growing number of samples and participating families in the study.

The lab's efforts are helped tremendously by having accurate information with regards to each person's health, knowing who in the family has been diagnosed with cardiomyopathy. **So, as always, if you have had any change in your health status, or have had a recent echocardiogram and/or EKG, please let us know! Call us toll free at: 1-877-800-3430.**

FDC CHARACTERIZATION

Another important aspect of our research is to further understand the presentation and progression of FDC, to look for trends in aspects such as age of onset, common symptoms, echo and EKG findings, rate of disease progression, use of medications, and need for transplants. This again stresses the importance for keeping us up to date on how you are doing.

Certainly the understanding of these aspects of FDC are intertwined with the genetic findings, as some of the variability in what FDC looks like in different families may be due to different causative genes. The combined knowledge of genetic information and disease characteristics may be important for the health care of a person with FDC. The more families we are able to enroll and the more clinical data/medical records we are able to collect, the better idea we may have about what to expect from FDC in terms of prevention, management, and treatment.

One vital way that we have committed to this aspect of our research is by purchasing a powerful computer database program called Progeny that will help us organize and track all of this clinical data more quickly and efficiently. It even draws pedigrees (family trees) with the click of a few buttons, a great help for drawing some of our larger families containing hundreds of relatives, as well as updating family history information for any size family. It is password protected so only the appropriate FDC staff will be able to access and edit any data contained in this database.

Almost 100 families, large and small, are enrolled in the study. We continue to receive new referrals from our clinic, outside physicians, and directly from families via our website (www.fdc.to); a few have even come from you - educating your health care providers about FDC. We will continue to recruit large families to participate in the study, which may include a screening trip to a city where the majority of family members are located. Individuals from any size FDC family that are able to travel to OHSU can also be screened at our clinical research center on campus.

We hope that through these objectives we will contribute to furthering the knowledge of FDC - what causes it, how best to treat it, and perhaps, someday a cure.

Introductions!!

As mentioned in our introductory article, the FDC project has expanded the laboratory staff in our continuing efforts to identify the genetic bases of FDC. Other staff changes have also taken place. Here is the update on the current FDC project team - welcome to all!

We are very excited to announce that **Duanxiang Li, M.D., M.S.** will be joining the FDC lab as a Research Assistant Professor of Medicine in Cardiology in August. Dr. Li received his doctor of medicine degree at Hengyang Medical College in China, and completed a cardiovascular research fellowship at the University of Leeds, United Kingdom. He now comes to us from Baylor College of Medicine where he has been an Instructor of Medicine and a laboratory researcher in the genetics of cardiomyopathies. He has published in the medical literature and presented at medical conferences extensively on FDC and other cardiovascular genetics research. We are extremely fortunate to have him join our team. Dr. Li will work closely with **Petra Jakobs, PhD.**, also a Research Assistant Professor (Cardiology) with us since 1998, **Mike Litt, PhD.**, Professor Emeritus of Molecular and Medical Genetics and a long time senior collaborator, and other members of our basic science group, identifying potential FDC genes.

It is with great pleasure that we also introduce **Sharie Parks, PhD.**, who will become the newest member of our group this fall. Dr. Parks has her PhD. in Medical Genetics from the University of Alabama at Birmingham. She has much hands-on experience with DNA diagnostics and has published on the use of various techniques to diagnose genetic disease using DNA technology. With her experience working in a clinical DNA lab, she will be heading up our goal to become a CLIA-certified lab, which would allow us to provide genetic test results to individuals. She will certainly be an asset to our lab!

Susan Ludwigsen, M.A. joined the research team earlier this year as a Senior Research Associate. She received her Bachelors in Biochemical Sciences from Princeton University, NJ, and her Masters in Computer Science from Temple University in Philadelphia. Susan has extensive experience in computer programming and analysis. She worked on the Human Genome Project developing software to construct chromosome maps that are now published. Since beginning with the FDC Project, she has been at work structuring and creating computer programs that take the data received from your DNA and analyze it for determining linkage. Welcome Susan!

As some of you know, our Research Assistant, Kelly Coates, left earlier this year to pursue other professional and educational endeavors. **Gillian Moyle, B.A.**, has come on board as the new Research Assistant for the clinical team. She works closely with **Jessica Kushner, M.S., C.G.C.,** Research Associate & Genetic Counselor, enrolling families, distributing blood samples for analysis, and organizing data for entry into the new database system. Gillian received her Bachelors degree from the University of Colorado. She has experience in clinical research, previously working at a biotech company in Beaverton, Oregon conducting clinical trials for a rapid HIV detection device. She is available to help answer study participant questions through the toll free number (877-800-3430 x 2) or her direct extension 503-494-2499.

And someone you may have talked to but not know very well... **Warren Toy, B.S**., has actually been working on the FDC project since 1997. At times, some of you have spoken to Warren about enrolling in the study or being sent a blood collection kit - he is always there to help out the clinical team with such activites when needed! Warren's main responsibility is data , he keeps track of your blood collection, screening results, and contact information. Warren received his Bachelors in Environmental Health and Safety from Oregon State University. We are very thankful for all his hard work!

THE FDC PROJECT TEAM

CLINICAL GROUP:
Ray Hershberger, M.D.
Jessica Kushner, M.S., C.G.C.
Gillian Moyle, B.A.

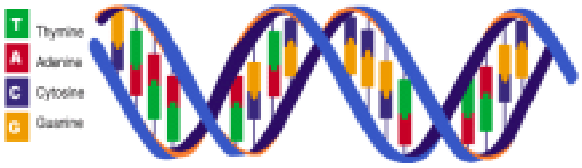
BIO-INFORMATICS GROUP
Susan Ludwigsen, B.A., M.A.
Warren Toy, B.S.

BASIC SCIENCE (LAB) GROUP:
Petra Jakobs, PhD.
Duanxiang Li, M.D., M.S.
Michael Litt, PhD.
Sharie Parks, PhD.
Sylvia Bousman, B.A.
Salam Jafari, B.A.

GENETICS 101:

A gene is defined as the unit of heredity. Genes code for proteins that perform particular functions in the body (examples: determining eye color, height, digestion, heart muscle function). A gene is like a recipe - a set of instructions that ultimately creates a final product. It is thought that humans have approximately 30,000 genes - these make up the Human Genome. We receive our genes from our mother and father, that is, genes are passed from generation to generation.

Genes are made up of DNA, which stands for the longer chemical name deoxyribonucleic acid. DNA has its own alphabet or code: A,T,C, and G (see the diagram). A gene is essentially a long string of DNA



graphic from: www.genecrc.org/lc/lc1c.htm

letters. Just as if someone mistakenly adds salt instead of sugar while following a recipe, a change in the DNA code of a gene can result in a change in the final protein product. This is commonly known as a mutation. A mutation in a gene can cause someone to develop a health condition such as FDC.

While we have 30,000 genes, we actually have much more DNA in our cells than that which codes for actual genes. The function of all this "extra" DNA is not completely clear. It is used, however, as markers in genotyping and linkage, as certain portions of this extra DNA are at known locations through out the human genome. It is very valuable to the hunt for new genes.

FDC BEAT Newsletter

FDC BEAT is a triannual publication of the Familial Dilated Cardiomyopathy Project in the Division of Cardiology at the Oregon Health & Science University in Portland, OR. The newsletter is not copyrighted and readers are welcome to photocopy its contents to share with family members and health professionals.

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