FDC BEAT

Newsletter of the Familial Dilated Cardiomyopathy Project at Oregon Health & Science University
Portland, Oregon, USA Volume IV, Issue 2 September 2003

The Genetics of Familial Dilated Cardiomyopathy

Hello from the Familial Dilated Cardiomyopathy (FDC) Research Project at Oregon Health and Science University! The main goal of our study is to learn about the genes involved in the development of FDC. Identifying these genes will help in understanding the cause(s) of dilated cardiomyopathy and heart failure, hopefully leading to improved management and treatment. Knowing the FDC gene in a family may also improve early intervention and prevention strategies for at-risk family members. While there is still much to be learned about the genetics of FDC, there have been a number of reports in the medical literature about genes and FDC. This issue of our newsletter focuses on what is currently known about the genes associated with this condition.

WHAT IS A GENE?

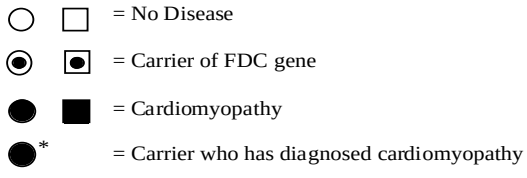
Before getting to the details of FDC genes, we thought a quick review of genetics and inheritance might be helpful. A **gene** is defined as a unit of heredity. A gene is like a recipe, a set of instructions to create a final product. In the case of genes, the final product is usually some kind of protein produced by the body for a specific function. Gene proteins play a role in all aspects of our growth and development; physical characteristics such as eye color, hair color, height; and of course in the functioning of organs and muscles, such as the heart.

Genes themselves are made up of biochemical molecules called **DNA** (deoxyribonucleic acid). There are 4 distinct types of DNA molecules, known as A, T, C, and G. These 4 molecules make up the **"DNA code".** Much like letters of the alphabet combine to form specific words, DNA code molecules arranged in a specific order and number create a unique set of instructions for each gene. Should any of a gene's normal DNA code be missing, rearranged, or changed in any way, the protein the gene makes may be affected and not perform it's proper function. Think about what a different outcome you have if you change only one letter in a word, such as the "A" in SOAP to a "U"- SOUP. Such is the case for changes in a gene's DNA code. Such changes can have a profound effect on a person's health; changes such as these are known as gene **mutations**. A mutation in a gene can cause someone to develop a health condition such as FDC.

HOW ARE GENES INHERITED?

From the time we are a single cell created at fertilization, we have all of the 30,000 genes that humans are currently thought to have. These genes reside in the center (**nucleus**) of our body's cells. We have two copies of every gene-one from our mother, the other from our father (the exception to this are genes involved in X-linked inheritance, which is discussed later). With some genetic diseases, both copies of the gene must have a mutation for someone to have the disease. With others, having one mutated copy is enough to cause disease, even though a normal copy of the gene is also present. In FDC, both types of **inheritance patterns** can be seen. Understanding inheritance patterns can provide important information as to whom in the family may be at risk of developing cardiomyopathy. **It is important to note that sometimes it is not possible to determine which type of inheritance is involved in a particular family, as the inheritance patterns are not always obvious or can look like one another merely by chance. The pedigrees below are meant to be examples and may not apply to your family.**

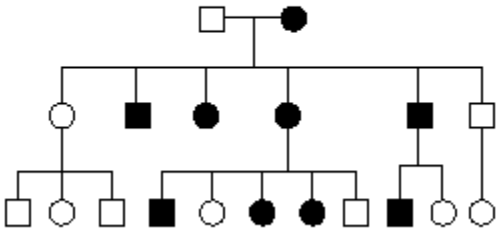
Pedigree Key



Autosomal Dominant (AD) Inheritance

With AD inheritance, having one mutated gene copy is enough to cause FDC, even though a normal copy of the gene is also present. In FDC families with an AD FDC gene, only one of the parents usually carries a mutated copy of the gene. Dilated cardiomyopathy is usually seen in multiple generations and can affect both males and females. Each child of a parent carrying a mutated FDC gene has a 50% chance of also carrying that mutation, putting them at risk for developing cardiomyopathy. Most FDC families follow this type of genetic pattern. The known FDC AD genes are cardiac actin, desmin, lamin A/C, delta-sarcoglycan, beta-myosin heavy chain, cardiac-troponin T, alpha-tropomyosin, titin, metavinculin, phospolamban, muscle LIM protein/MLP, and myosin binding protein C.

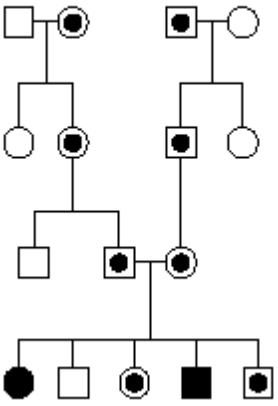
Autosomal Dominant Inheritance



Autosomal Recessive (AR) Inheritance

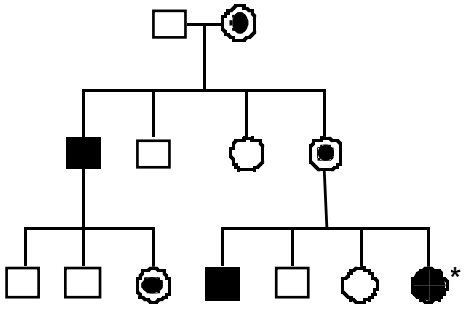
With AR inheritance, both copies of the gene must have a mutation for someone to have the disease. In families with AR FDC both unaffected parents carry an FDC gene and have a 25% chance of each child inheriting both copies of the mutated gene. Cardiomyopathy is usually diagnosed in only one generation amongst brothers and/or sisters. This type of inheritance may be more common among certain ethnic groups and if parents are related to each other. AR inheritance is thought to be uncommon in FDC. AD inheritance can look like AR, as a younger generation can develop and be diagnosed with FDC prior to a parent, giving the misperception that cardiomyopathy is not seen in multiple generations. This is why current recommendations for screening with echocardiogram and EKG include all first-degree relatives (children, siblings, and parents) of a family member diagnosed with unexplained dilated cardiomyopathy. There are no particular genes yet identified with AR FDC.

Autosomal recessive inheritance



X-Linked (XL) Inheritance

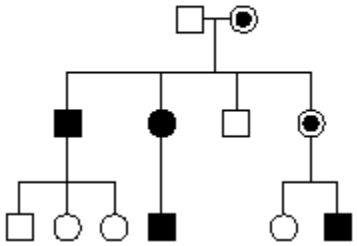
XL inheritance is thought to occur in about 10% of FDC families. In these families males are affected and the gene is inherited from the mother who carries the FDC gene. If FDC is XL, than the condition cannot be passed from father to son (which differentiates it from AD inheritance). For women with the FDC gene, each child has a 50% chance of inheriting the FDC gene. All daughters of males with FDC will carry the FDC gene mutation. Females carrying the FDC gene may develop cardiomyopathy, but it is usually less severe than that of males in the family. The known XL FDC genes are Dystrophin and Tafazzin/G4.5.



Mitochodrial Inheritance

Mitochondria are particles found inside cells, commonly known as the "power houses" that supply energy to the cells. Mitochondria have their own DNA, separate from the DNA described above. Since we inherit our mitochondria from our mothers, mutations in mitochondrial DNA causing FDC will only be passed from a female to sons and/or daughters. Multiple generations can be affected. It can be difficult to distin-

Mitochondrial inheritance



guish this type of inheritance from the others, however the frequency of this type of inheritance in FDC is thought to be rare. The known Mitochondrial DNA FDC genes are tRNA(leu), tRNA(ile), and tRNA(his).

It is important to remember that we all carry altered genes that may put ourselves and our children at risk for any one of many different kinds of health problems, such as diabetes, cancer, and heart disease. No one's genes are "perfect".

FDC GENES

To date 17 FDC genes have been reported in the medical literature. This is evidence that FDC is **heterogeneous**, meaning one gene can cause FDC in one family while a different gene is the culprit in another family. Most of these genes are associated with AD FDC and each have only been reported in one or two families, meaning each particular gene may be an uncommon cause for FDC (except for the Lamin A/C gene -- see below). Most of these genes code for proteins that are important components of heart and other muscle, which would make sense that mutations in these genes could cause cardiomyopathy.

In addition, seven other medical journal articles have reported FDC families with "linkage" to a particular section of DNA, although the gene itself is not yet identified. It is likely that additional linkage areas and genes will be identified as FDC research continues.

There is variability between different FDC families, such as the age of onset of symptoms, presence or absence of arrhythmias, severity of the cardiomyopathy, etc. Some of this variability may be explained by the fact that different genes cause FDC in different families. Indeed, a number of the genes or linked areas of DNA have been associated with particular features of FDC. For example, families with a mutation in the **troponin** gene may have an earlier age of onset and/or more severe disease than families with another FDC gene. Genes such as **lamin A/C** and **dystrophin** may be associated with generalized muscle weakness as well as heart muscle problems. The **taffazin** XL gene, a rare cause of FDC, has only been reported in infants with severe dilated cardiomyopathy. Other reported features associated with specific FDC genes or linkage areas also include arrhythmias, mitral valve prolapse, and even hearing loss. Variability may exist even within families, which is more difficult to figure out since only one of the genes listed above would cause FDC in an individual family. It is thought that the other genes we carry (remember we have 30,000!) as well as environmental/non-genetic factors may play a role in the variability within members of the same family.

LAMIN A/C

Lamin A/C is so far the most commonly reported gene associated with FDC. Currently it is thought to be the cause of around 10% of all FDC, although its true incidence among FDC families is unknown -- further studies are needed. Lamin A/C mutations have been most commonly associated with FDC characterized by conduction system defects, such as heart block and sudden death, sometimes requiring pacemaker and/or defibrillator implants. Our group recently published two papers in the medical literature about lamin A/C and FDC:

Hershberger RE., et al. A novel lamin A/C mutation in a family with dilated cardiomyopathy, prominent conduction system disease, and need for pacemaker implantation. American Heart Journal 2002; 144 (6):1081-1086.

Jakobs PM., et al. Novel lamin A/C mutations in two families with dilated cardiomyopathy and conduction system disease. Journal of Cardiac Failure 2001; 7 (3): 249-256

Lamin A/C is interesting for a number of reasons. For one, it is the only gene so far associated with AD FDC that is not a heart muscle protein. Additionally, lamin A/C has been implicated as the genetic cause for several other familial/genetic conditions, including more generalized muscle disease (Limb-Girdle and Emery-Dreifuss muscular distrophies), nerve disease (Charcot-Marie-Tooth Neuropathy), fat distribution (Familial Partial Lipodystophy), and most recently a very rare premature aging disorder known as Progeria. The ability of lamin A/C mutations to cause so many different conditions is not well understood. So far the types of lamin A/C mutations are different within the different disorders, but there may be some overlap.

There is currently no comprehensive clinic genetic testing available for all of the FDC genes. Lamin A/C is the only AD FDC gene for which a health provider can

order genetic testing as part of a person's cardiac care. Because so many other genes are also known to cause FDC, someone tested and not found to have a lamin A/C mutation may still carry a mutation in another gene that can't yet be tested for. The hope is that with research such as ours eventually genetic testing will have fewer limitations and provide more information to more families.

As part of our research efforts we are screening all of our FDC families for mutations in lamin A/C. As a research lab we are currently unable to provide participants with individual genetic test results. However, if we do find a mutation that we think causes FDC in your family, we will inform you and every effort will be made to refer you to a CLIA-certified lab which can provide genetic testing and results for a fee. We are in the process of becoming a CLIA-certified lab for lamin A/C testing. For more inforation about CLIA vs. research genetic testing see our Nov. 2001 FDC Beat newsletter issue (contact us to request a copy if needed).

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We hope this review of FDC genetics has been helpful. More information can be found in our website www.fdc.to. Of course if you have any questions you can email us through the website or call Toll-free: 877-800-3430. A new research assistant has joined our group; **Kelly Smith** can give you information about the FDC project and can be reached at the above phone number.

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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