FDC BEAT

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Different Types of Cardiomyopathy in One Family: Heredity or Chance?

In our Familial Dilated Cardiomyopathy (FDC) Research Project, the majority of people with cardiomyopathy have dilated cardiomyopathy (DCM). However, we have noticed that some of our participating families have multiple types of cardiomyopathy in a single family, called 'mixed presentation.' For example, one family member may have DCM while another close relative has a different type, such as hypertrophic cardiomyopathy (HCM). Is this just coincidence or is it possible that one or several genetic alterations (mutations) can cause different clinical presentations?

Cardiomyopathy (cardio=heart; myo=muscle; pathy=disease) refers to disease of the heart muscle. There are five main types: dilated, hypertrophic, arrhythmogenic right ventricular dysplasia, left ventricular non-compaction and restrictive. These names are detailed descriptions of what happens to the shape and functioning of the heart.

The cardiomyopathies often have different causes, including exposure to toxic substances (drugs, alcohol), high blood pressure and coronary artery disease, among others. When the cause is unknown, the cardiomyopathies can have similar presentation: heart failure, arrhythmia, heart blood clots that lead to stroke, or sudden cardiac death. In these cases, genetic alterations (mutations) in genes coding for proteins that work in the heart are known to cause at least a proportion of cases.

Sometimes, even the same gene or mutation has been associated with different types of cardiomyopathy. For example, alterations in a gene called *TNNT2* cause HCM in some families and DCM in others. In this issue of FDC Beat we present a summary of the current knowledge on this topic. We describe the differences in each type of cardiomyopathy and give an overview of what is known about hereditary causes at this time.

Dilated cardiomyopathy (DCM)

DCM, the cardiomyopathy that we focus on our study, is the most common cardiomyopathy. Dilated means enlarged. When the left ventricle dilates, it means the heart chamber enlarges without thickening of the heart muscle. The heart has a right side and a left side. In DCM, the blood collecting chamber on the left side of the heart is dilated as a result of weakened heart muscle. Less frequently, enlargement of the right side of the heart may be observed. The ejection fraction (percent of blood pumped out with each heartbeat) is also reduced. Age of onset is usually in the 30-50s. More than 30 genes have been reported that, when altered, can result in DCM, accounting for ~30% of familial cases of DCM. Preliminary studies show an estimated 25-30% of cases with no family history can have mutations as well.

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Collecting Heart Tissue Samples

In the FDC Research Project, we primarily study DNA extracted from blood samples, looking to discover and better understand genetic causes of dilated cardiomyopathy (DCM). Because blood is relatively easy to obtain and from it we can extract relatively large quantities of DNA, a blood sample will remain our primary method for collecting DNA. However, there are other types of genetic information in heart tissue that cannot be obtained from a blood sample, which could lead to new discoveries about the genetics of DCM.

Our research will continue to focus on the study of inherited DNA, but we are also interested in collecting heart tissue samples for additional studies. Heart tissue contains a type of genetic material, called RNA, which is created from our bodies' DNA (the same DNA

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Hypertrophic cardiomyopathy (HCM)

HCM, less common than DCM, is thought to affect 1 in 500 people. Unlike DCM, in HCM the heart muscle on the left side of the heart grows thicker. This extra muscle growth does not help with heart function, but rather makes the heart work less efficiently. Early signs include diastolic dysfunction (a stiffness in the heart muscle that results in difficulty in filling the heart with blood before it is pumped out to the body). Heart failure can occur in some cases. HCM usually occurs in puberty and early-mid adulthood, but younger and older ages of onset have been reported. About 60-70% of the time a genetic cause is discovered in people with familial HCM, and approximately 40% of the time in sporadic cases. When genetic cause for HCM can be found, 2 genes account for 80% (8 out of 10) cases. This is different from DCM, in which no gene accounts for more than a few percent of cases. Genes that have mutations that cause HCM can also have mutations that cause DCM.

Arrhythmogenic right ventricular dysplasia (ARVD)

ARVD is thought to affect 1 in 10,000 people, but the actual number may be higher due to misdiagnosis. Although at times both the left and right side of the heart can be affected in DCM, HCM and AVRD, however, in DCM and HCM, the left side of the heart is preferentially affected while in ARVD, the right side of the heart is preferentially affected. Another feature of ARVD is that fatty tissue replaces heart muscle in some areas of the right ventricle. This fatty tissue can cause arrhythmia and sudden death. It can also cause weakening of the pumping function. Some people with ARVD can also have disease on the left side of the heart (similar to DCM) as well as heart failure. Therefore, in some cases it can be hard to differentiate ARVD from DCM. Recent reports in the medical literature have also presented people with HCM that also have fatty infiltration of the left ventricle, again supporting a possibility of a clinical overlap between ARVD and HCM. Onset is usually during adolescence or young adulthood. Mutations in eight genes have been discovered as causative of ARVD and account for almost 50% of all cases.

Left ventricular non compaction (LVNC)

Several weeks after conception of an embryo, the internal layer of the heart wall, which at this stage resembles a loose mesh, becomes closely packed in a process known as compaction. In LVNC, compaction fails to occur, leading to a spongy, non-dense heart muscle. This can also lead to cardiomyopathy, reduced pumping function of the heart, and eventual heart failure. Onset usually occurs during puberty but can occur in infancy or in adults. Research into LVNC is relatively new. For example, it is not well known how many people are affected by LVNC. LVNC may be sporadic, or, in 9-25% of cases, familial. LVNC has also been observed in families with DCM, HCM and ARVD. Mutations in five genes have been reported. Mutations in 3 genes that can also cause DCM or HCM were recently reported in 17% of cases.

Restrictive cardiomyopathy (RCM)

RCM is thought to be very rare, but no good figures are available. In RCM, the heart muscle becomes stiff and cannot stretch and relax properly. This finding may also be present in DCM, HCM, or LVNC, although to a lesser

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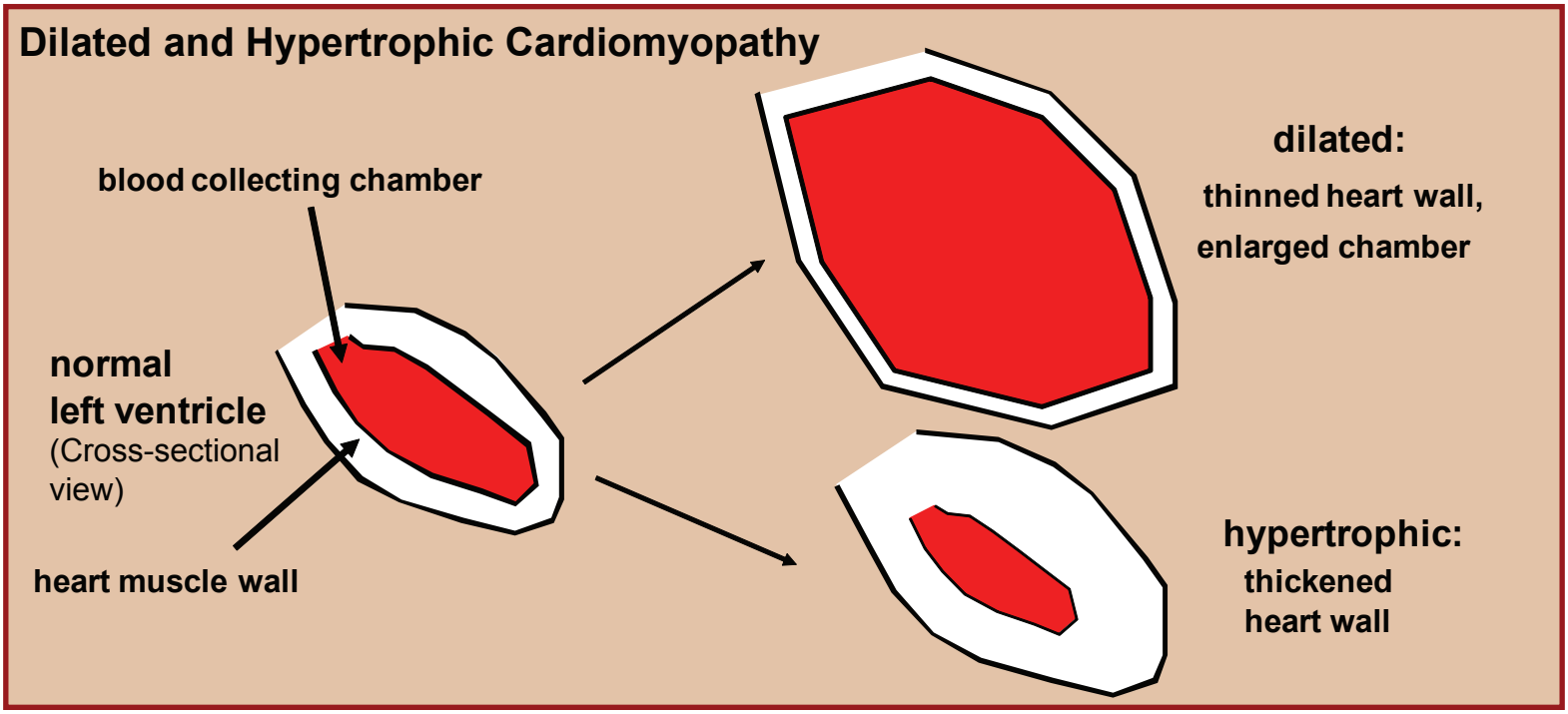

extent. The heart is usually normal in size but some thickening of the heart walls (like in HCM) may be observed. This causes the body and lungs to retain fluid, resulting in eventual heart failure. In families with RCM, other relatives may present with HCM. RCM can present in childhood and may be associated with disease of skeletal muscle (muscles of the arms and legs). While some cases of familial RCM have been reported, no large studies have been conducted. Although the genetics of RCM are poorly understood, mutations in four genes have been reported. The mutations reported in RCM can also cause DCM or HCM.

Comparison of Types of Cardiomyopathy

Disease	Number of affected people	Heart findings	Proportion of familial cases	Number of genes reported	% of cases attributed to a known gene
DCM	most common	Enlarged left side, thinned heart muscle	20-50%	30	25%
HCM	1 in 500	Thickened heart muscle	90%	20	40-80%
ARVD	1 in 10,000 or higher	Enlarged right side, fatty tissue	50%	8	50%
LVNC	unknown	Ridge-like texture of the heart muscle	25%	5	unknown
RCM	rare	Stiff heart muscle	unknown	4	unknown

Regardless of the type of cardiomyopathy, all can be associated with a genetic cause. In the US, clinical genetic testing is available for DCM, HCM and ARVD. LVNC and RCM share some of the causative genes with DCM and HCM. Therefore, testing for DCM and HCM genes may be reasonable in LVNC and RCM cases. In addition to considering genetic testing, other important activities that are recommended as part of a cardiomyopathy genetic evaluation include a 3 generation family history, screening of first degree relatives of affected individuals, and genetic counseling.
We have always asked you to inform us if a family member is ever diagnosed cardiovascular disease, especially if the diagnosis is DCM. As we learn more about DCM and its relationship with other cardiomyopathies, we would like to emphasize that *we would like to know if a family member is ever diagnosed with any other type of cardiomyopathy*. Family history information provides valuable information for our research. The more we learn, the more we can improve disease management, treatments and therapies in the future.

Collecting Heart Tissue...

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that can be obtained from your blood). RNA can help to determine if certain genes are expressed in the heart, tell us more about a gene's function in the heart, and tell us if certain alterations, or mutations, in our DNA/RNA are playing a role in the development of DCM. Heart tissue can be collected from a sample of an explanted ('old') heart in a person who is undergoing a heart transplant. After transplant, pieces of the old heart are normally used for routine pathology studies and the rest is discarded. In this situation, the sample that would otherwise be discarded can be collected in the operating room for research, and needs to be planned ahead of time. (There is no pain or risk involved in removing tissue from a heart once it has been removed from your body at heart transplant.) We have developed a protocol for obtaining heart tissue from individuals who are on a heart transplant waiting list, and we will mail you and your transplant team the materials you need to have small portions of your heart muscle saved for research. The protocol will require a joint effort by yourself and your transplant team. We have successfully implemented this protocol at several US heart transplant centers.

Another source of heart tissue that would be very helpful to our research is that obtained after a person undergoes a ventricular assist device (VAD) implant. During usual placement of a VAD, a small core is removed from the tip of the left ventricle of the heart that is useful for research. At times people may undergo a heart biopsy, where just a tiny sample of heart tissue is collected. If you are having a heart biopsy, procurement of a small amount of tissue for research would add little risk to heart biopsy procedure.

If you have advance notice that you will be undergoing a heart transplant, VAD placement, or heart biopsy and would like to give a sample of heart tissue to the FDC Research Project, please notify us. We will coordinate obtaining a sample of your heart tissue for our study. By volunteering to donate some of your heart tissue, you could be of tremendous help with our effort to identify the gene(s) that cause IDC.

FDC BULLETIN BOARD

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

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 tests performed, either for follow-up or for the first time, 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.

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

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.

CONTACT INFORMATION UPDATES

If you have moved and/or have an email address we can contact you at, please call or email us so we can get in touch with you for any follow-up and continue to send you our newsletter.

FDC BEAT Newsletter

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