

# *Genetic Basis of Cardiomyopathy*

## A GUIDE FOR PATIENTS AND FAMILIES



**LABORATORY FOR MOLECULAR MEDICINE**



CENTER FOR PERSONALIZED  
GENETIC MEDICINE



**This booklet has been prepared for patients, families and healthcare professionals who are interested in finding out more information on the genetics of cardiomyopathy.**

## **ABOUT THE LABORATORY**

The Laboratory for Molecular Medicine (LMM) is a not for-profit CLIA-certified clinical diagnostic laboratory in the Partners HealthCare Center for Personalized Genetic Medicine, a teaching affiliate of Harvard Medical School. The LMM's close connection to the research community and cutting-edge technology ensures rapid translation of research discoveries into clinical tests that are offered by the laboratory. The LMM is dedicated to ensuring the privacy and confidentiality for all individuals who decide to pursue genetic testing.

*This booklet was created by the following staff at the Laboratory for Molecular Medicine and Partners HealthCare Center for Personalized Genetic Medicine.*

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**We would like to thank the many other people who gave helpful comments and suggestions on the numerous drafts of this booklet.**

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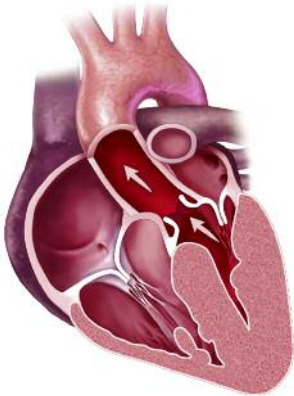
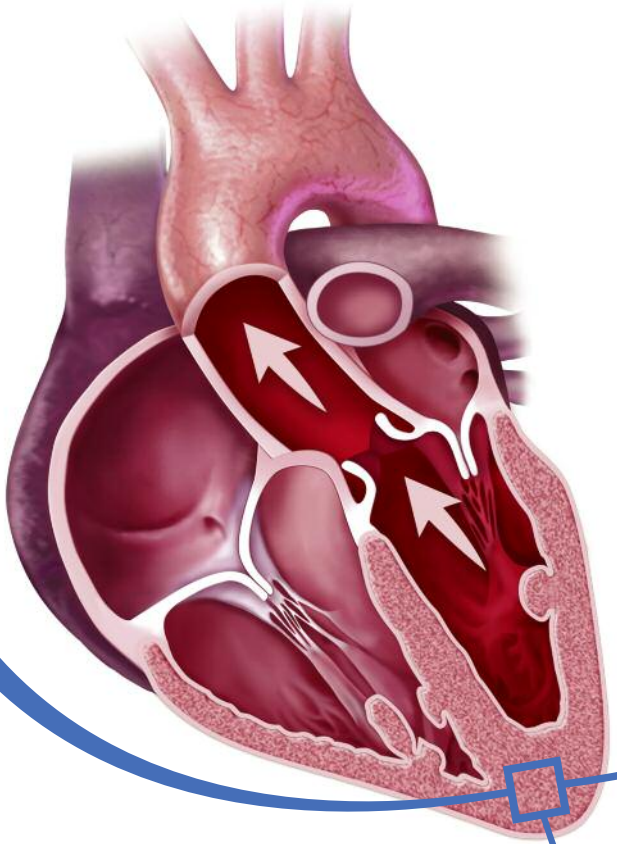
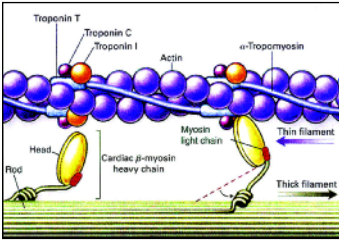
# WHAT IS CARDIOMYOPATHY?

**Cardiomyopathy is a disease that affects the muscles of the heart. There are different types, including hypertrophic, dilated, restrictive and arrhythmogenic right ventricular cardiomyopathy. These diseases affect the function of the heart and lead to serious illness in the patient. Many forms of cardiomyopathy have a genetic basis. As a result, family members of a patient with cardiomyopathy are often at risk to develop disease.**

# TYPES OF CARDIOMYOPATHY

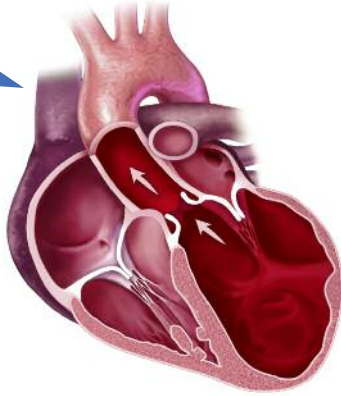
## Sarcomere

The sarcomere plays a major role in the structure, contraction and relaxation of the cardiac muscles.



## Hypertrophic Cardiomyopathy

HCM is a very common genetic heart disorder, affecting about one in every 500 people. The most notable feature is left ventricular hypertrophy (LVH), or thickening of the walls surrounding the left ventricle. HCM is primarily caused by changes, or mutations, in the genes that code for proteins in the sarcomere.

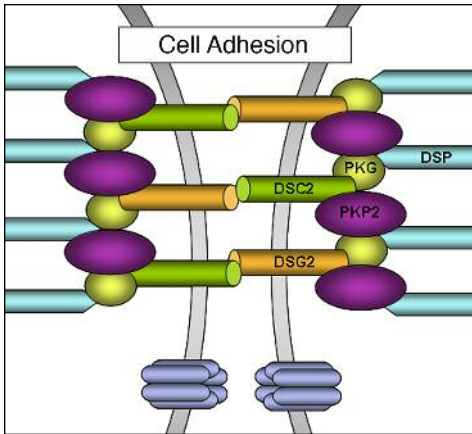


## Dilated Cardiomyopathy

DCM is seen in about one in every 2500 individuals. DCM is characterized by left ventricle enlargement (LVE), or dilation, and reduced pumping function. The enlargement is a result of a weakened heart muscle. Studies have shown that 20-35% of primary DCM is caused by inherited genetic changes. Some of these genes are the same sarcomere genes associated with HCM. The other genes associated with DCM affect additional systems of the body and changes in these genes can cause DCM as well as other clinical disease.

## Desmosome

Desmosomes play an important role in connecting cells to each other.



## Arrhythmogenic Right Ventricular Cardiomyopathy

ARVC is estimated to affect approximately 1/5000 people. In this disease the heart muscle is gradually replaced by fat tissue. This mostly occurs in the right ventricle but over time may also involve the left. About half of cases of ARVC are caused by genetic mutations in genes which are involved in the formation and function of desmosomes.

## Syndromes involving cardiomyopathy

There are other genetic diseases in which cardiomyopathy is one part of a more complex disease. These diseases typically present with features in various systems of the body and are not specifically a disease of the heart. However, in some patients cardiomyopathy may be the first, or only feature of disease. One example is Fabry disease. Males with classic Fabry disease often have severe heart and neurological disease but females, who typically have milder symptoms, may only have hypertrophic cardiomyopathy. If a physician suspects more symptoms than just cardiomyopathy, genetic testing can be used to assist in making a diagnosis.

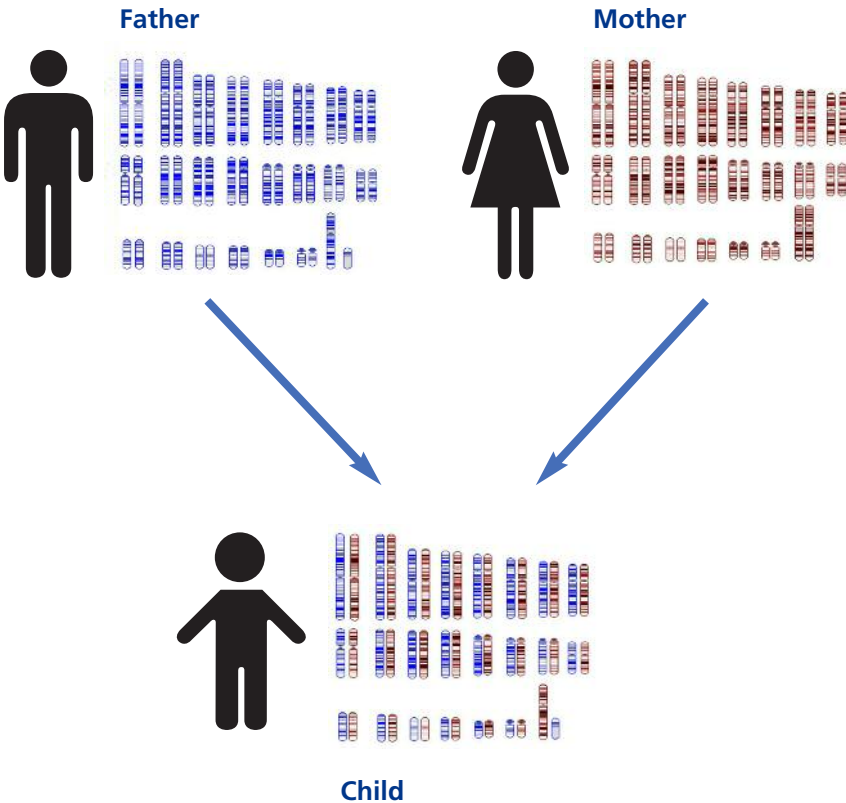
## Restrictive Cardiomyopathy

RCM is a rare form of cardiomyopathy. It is characterized by a stiffening of the ventricular walls. Little information is available about the genetic causes of this disease.

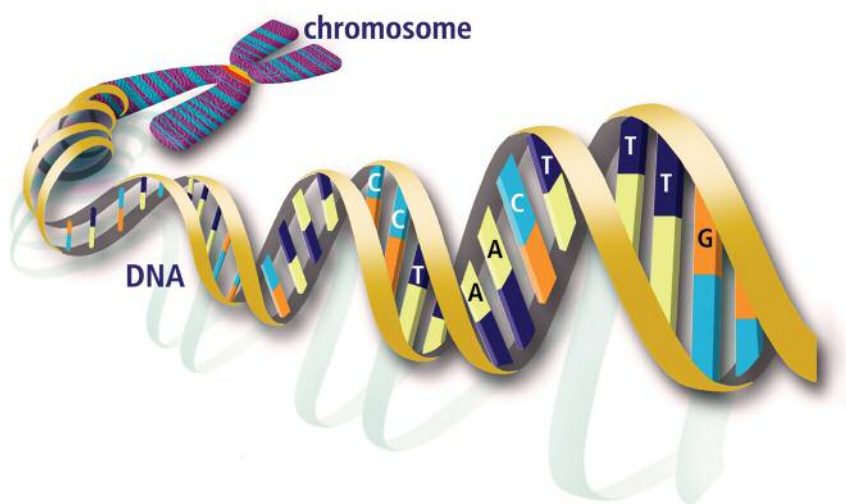
# GENETICS

Most forms of cardiomyopathy are caused by abnormal gene sequences. These genes are passed down through a family, carried on structures called **chromosomes**.

People have 23 pairs of chromosomes, including a pair of sex chromosomes. Each pair consists of one chromosome that is inherited from the mother and one that is inherited from the father. The first 22 pairs are numbered 1-22 based on their size. The 23rd pair (X and Y) are the sex chromosomes that determine the gender of a person. Girls inherit two X chromosomes, whereas boys receive one X chromosome and one Y chromosome. The following figure demonstrates how chromosomes are passed down from a mother and father to a child.



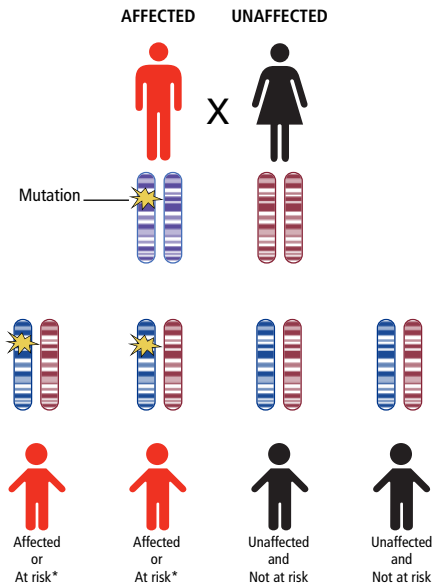
The role of these chromosomes is to carry segments of information known as **genes**. Along these chromosomes are about 25,000 different genes which provide the directions for how our bodies will develop and function. All of the genes in our bodies are made of a chemical called deoxyribonucleic acid or **DNA**. DNA contains four building blocks, or bases: adenine (A), cytosine (C), guanine (G), and thymidine (T). These bases can be strung together in many different combinations to create segments of unique DNA sequences. Some of these segments code for genes, which contain the instructions for life.



Because people have two copies of every chromosome, they also have two copies of every gene. The DNA sequences of these genes are more or less the same in everyone. However, sometimes there is a DNA change, or variant, in one person's gene that is not present in most people. This DNA change is called a **mutation**. Some mutations do not interfere with the health of an individual; these are often referred to as benign variants or **polymorphisms**. Other mutations disrupt the gene enough so it does not function correctly. These are the types of mutation that cause cardiomyopathy.

## HOW DO YOU INHERIT A GENETIC MUTATION?

The majority of mutations causing cardiomyopathy are passed through a family in a dominant pattern. For a dominant disease, there only needs to be one mutation present in a gene to cause disease. For example, if one parent passes on a gene with a dominant mutation, the child is at risk to develop cardiomyopathy even if the gene received from the other parent has the "normal sequence." In other words, the gene with the mutation, was "stronger" than the gene without the mutation. In families with this pattern of inheritance all first-degree relatives (i.e. parents, siblings and children) of an individual with a mutation are at a 50% risk for having the same mutation.



\*Individuals with a mutation and disease are considered **affected**. If they have a mutation but no disease they are considered **at risk** to develop the disease.

In a small percentage of families with cardiomyopathy, the familial mutation travels in a pattern other than dominant. For example, Fabry disease, Danon disease and Barth syndrome are all caused by genes on the X-chromosome which follows a different type of inheritance. In this case typically only males have disease. If females show symptoms they are much milder than the men in their family.



## QUESTIONS ABOUT GENETIC TESTING

### Should I have genetic testing?

The decision to have genetic testing is a personal one. The benefits and drawbacks of genetic testing must be understood by anyone considering testing so that an informed decision can be made. Genetic counselors are skilled in educating others about genetic testing and its many associated issues. You should feel free to contact a counselor or doctor if there is any information about genetic testing that is unclear, or if you would like to discuss your particular situation and the benefits of testing for you and your family.

### How does knowing my genetic status help with my care?

One of the most common reasons for having genetic testing is to confirm a clinical diagnosis. Genetic testing can provide a definitive answer, if your symptoms are not enough for a diagnosis. Testing can also determine the cause of your cardiomyopathy. It can also be useful when making decisions for clinical care. And, if the genetic cause of a person's cardiomyopathy is known, it is possible to test other family members to determine who may develop cardiomyopathy. Then only those with a mutation need to be seen by a cardiologist regularly, or alter their lifestyle. In general, how people use genetic information will vary widely depending upon their symptoms, physician's recommendations, and other factors.

### What is genetic testing?

Genetic testing is a blood test which compares the sequence of one person's gene with that of the common sequence of that gene. The comparison looks for mutations that could make the gene stop working.

There are two different forms of genetic testing that are available for cardiomyopathy, **full panel testing** and **familial mutation testing**. The **proband** is the first individual in the family to come to clinical attention. Proband testing typically involves scanning multiple genes in a panel, in search of a disease-causing mutation.

Familial mutation testing looks only for the specific mutation previously identified in another family member. It is used for determining whether or not an individual inherited that mutation, and if they are at increased risk to develop a cardiomyopathy. This type of genetic testing is much faster and cheaper than the proband testing due to the fact it is much more targeted.

**4.** Once the test is completed, the results are sent to the physician and genetic counselor who then discuss the results with the patient.



**1.** A physician and genetic counselor meet with a patient to discuss the risks and benefits of genetic testing.



## THE PROCESS OF GENETIC TESTING

**2.** The patient has their blood drawn and it is sent to a genetic testing laboratory.



**3.** The laboratory collects the DNA from the blood using a special process called "DNA extraction". They then perform the test.



## WHAT ARE THE POSSIBLE RESULTS OF MY GENETIC TESTING?

There are three possible results for your genetic testing performed at the Laboratory for Molecular Medicine

**1. Positive-** This means that the lab found what they believe is a disease-causing or “pathogenic” mutation in one of the genes tested.

**2. Inconclusive-** This means that the lab found a change in one of your genes but they are not sure if that change causes disease. The reasons for an inconclusive result are:

- The mutation has also been found in healthy people, though not in a high enough frequency to rule out a role in causing cardiomyopathy.
- Your race is one that has not been well studied and therefore common variants in your race are not yet understood.

*If you are found to have an inconclusive test result your doctor or genetic counselor may suggest having other members of your family tested. If everyone with disease in your family is found to have the mutation, then the lab may decide the mutation is causative for cardiomyopathy. If there are not enough affected family members to test, you may need to wait for further studies to determine if your mutation is disease-causing.*

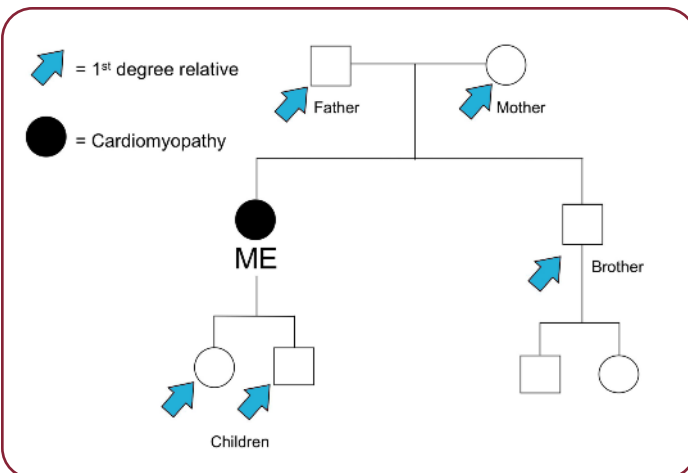
**3. Negative-** This means that the lab did not find any changes or mutations of possible clinical significance in any of the genes they sequenced. This result does not rule out that there is an underlying genetic cause for your cardiomyopathy. It is possible you carry a mutation located in a gene for which testing is not currently available.

*If you are negative, testing other family members is not usually helpful.*



### Who in my family should I share my results with?

Once you have your genetic test results your doctor or genetic counselor may discuss with you what this means for other members of your family. Since most cases of cardiomyopathy are caused by dominant mutations, all of your first degree relatives are at risk for having inherited the same mutation as you did (see figure below). It is important for these individuals to know about their risk and to discuss their options for clinical and genetic testing with a doctor. It is also important to discuss with other family members if there is any family history of heart problems, and/or sudden death. This can help determine if there are any other extended family members who should also have screening.



## How do I know if I have a family history of cardiomyopathy?

### Has anyone in your family ever...

- Had a diagnosis of cardiomyopathy or heart disease?
- Seen a cardiologist or had any tests done on their heart? (e.g. MRI, ECG)
- Been told they have an enlarged or “big” heart?
- Had heart failure or a heart attack?
- Died suddenly or had an unexplained death or accident (e.g. drowning, car accident?)
- Died at a young age or “prematurely”?
- Fainted?
- Had problems with the rhythm of their heart? (e.g. offbeat or “racing heart”)
- Had a pacemaker?
- Taken medication for their heart?

If you answer “yes” to any of the questions above it is possible that other members of your family also have cardiomyopathy and should consult a their doctor or cardiologist.

### Why are some people more severely affected in my family than others?

A large area of interest is the variable presentation of cardiomyopathy. It is not uncommon to see family members have the same type of cardiomyopathy (e.g. HCM) but may have different symptoms or ages of onset. For example, a father could develop symptoms of HCM in his late 30s but his son, who inherited the affected gene, might not develop symptoms until his 60s. Other times parents learn they have a mutation, but no symptoms, only after their child was diagnosed and genetic testing was performed.

### Could I be the first person in my family to have a mutation?

Yes. There are cases in which a genetic mutation is seen for the first time in a person whose parents do not carry the mutation. This type of mutation is called a spontaneous or “de novo” mutation, which usually developed in one of the parent’s sperm or egg. When this occurs, cardiomyopathy can suddenly begin within a family when ancestors were not affected. In this case it would have not been possible to predict that the child would be affected, but the chance of future generations having cardiomyopathy can be determined.

# RESOURCES

## **Laboratory for Molecular Medicine**

Partners HealthCare Center for Personalized Genetic Medicine

(617)768-8500

<http://pcpgm.partners.org/LMM>

## **American Heart Association**

1-800-242-8721

[www.americanheart.org](http://www.americanheart.org)

## **ARVD/C Information Website**

<http://www.arvd-arvc-info.com>

## **Brigham and Women's Cardiovascular Genetics Center**

(617)732-7921

[www.brighamandwomens.org/Departments\\_and\\_Services/medicine/services/cvcenter/genetics/](http://www.brighamandwomens.org/Departments_and_Services/medicine/services/cvcenter/genetics/)

## **Cardiomyopathy Association**

+44(0)1923 249 977

[www.cardiomyopathy.org](http://www.cardiomyopathy.org)

## **Hypertrophic Cardiomyopathy Association**

[www.4hcm.org](http://www.4hcm.org)

## **National Society of Genetic Counselors**

[www.nsgc.org](http://www.nsgc.org)

**Information on clinically available  
genetic testing for cardiomyopathy.**

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