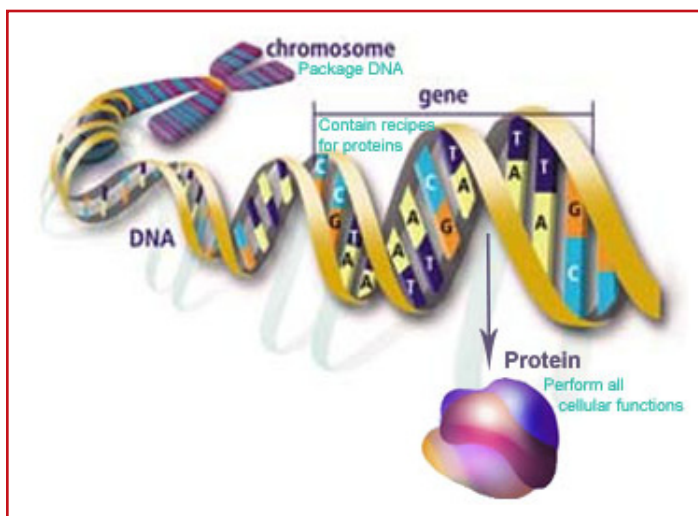




*Genetics is playing an increasingly important role in the early detection, monitoring and treatment of certain inherited cardiovascular disorders, including hypertrophic cardiomyopathy (HCM), the most common of these conditions. Building on knowledge obtained through leading research into the genetic basis of HCM, the Brigham and Women's Hospital Cardiovascular Genetics Center is enhancing the care of patients with this heart ailment and providing a means of early recognition for family members who are at risk. This brochure was developed to help patients with HCM and their families understand the basic genetics of this disease and what they can learn through genetic testing.*

## What are genes?

In recent years, there has been an explosion in scientific understanding of our genes—the basic units of heredity. Handed down to us through generations, our genes are essentially a road map into who we are. Our genes influence what we look like, inspire our so called “natural” talents and, influence our overall health and risk for disease. For instance, some of us are at a higher risk for certain diseases because certain genes we inherit may contain an error, called a mutation. Everyone carries some types of genetic variations and mutations. Whether or not a particular mutation leads to disease depends on a variety of factors. To understand what it means when you carry a gene mutation for a particular illness, such as HCM, it's best to step back and look at the bigger picture, starting with DNA—the genetic fabric that links us to past and future generations.



## What is DNA and how does it work?

DNA (deoxyribonucleic acid) is a chemical strand contained in every single one of our cells. Genes are the basic units of DNA, and they are made up of a series of nucleotides (sometimes called bases) abbreviated A, C, G, and T, that are strung together in specific arrangements side by side. These strings of letters spell out genes that describe important instructions enabling each cell to do its job.

DNA in humans is arranged into 23 pairs of distinct chromosomes (Figure 1), one set from each parent, for a total of 46 chromosomes. Chromosome pairs 1-22 are called autosomes and are common to both males and females. The final pair of chromosomes are the sex chromosomes, referred to as X and Y, because they determine a person's gender. Typically, women have two X chromosomes (XX) and men have an X and a Y (XY) chromosome. The chromosome provides structure for DNA and each chromosome contains many genes. Each gene spells out the code for cells to make specific proteins. It's the proteins that do the actual work, performing a variety of important functions in our body. Since we have two sets of chromosomes we have two copies of our genes.

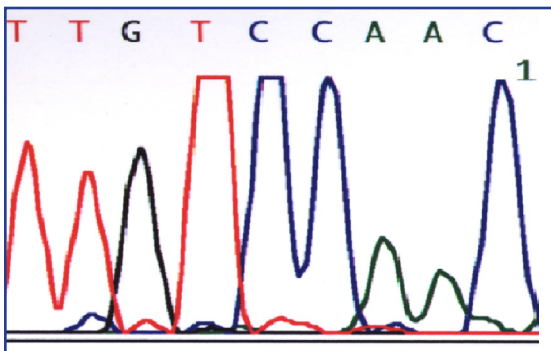
**Figure 1.** Illustration of a chromosome, gene, and a protein

Source: U.S. Department of Energy Human Genome Program <http://www.ornl.gov/hgmis>

## What is a mutation?

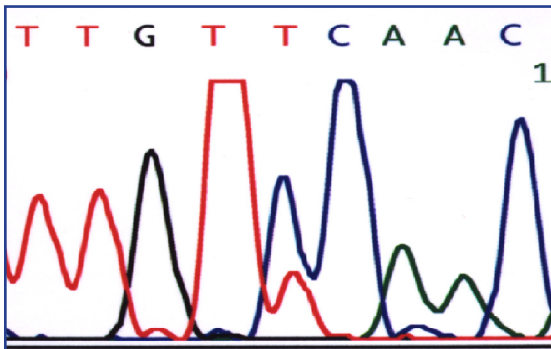
If there is a change or “misspelling” in the nucleotide letter sequence of a gene, the protein may not be made or may not work properly. This misspelling of a gene is what we call a mutation (Figure 2). The entire collection of DNA in each cell is called the genome. Scientists believe that humans have approximately 20,000-25,000 genes in their genome. Although the same set of genes is contained in most of the cells of our body, not all genes are important or are even turned on in every part of the body. For example, a particular gene may only play a role in the heart but not in the muscles in the arms or legs; therefore, a mutation in this gene would directly impact heart and not other parts of the body.

**Figure 2.** DNA Sequence Mutation



Normal DNA Sequence :

TCC is spelled at a specific location in the gene



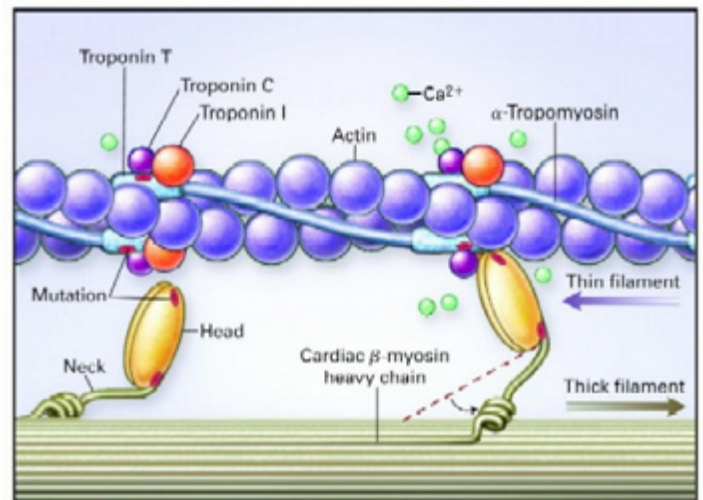
HCM Patient :

A DNA Mutation results in the substitution of T for C on one copy of DNA, inherited from the parent with HCM. The other copy was inherited from the unaffected parent and has the normal spelling with C in the middle position.

## What genes are involved with HCM?

DNA is passed on from generation to generation, so when a condition like HCM runs in families, this points to a genetic cause. Research has taught us that HCM is caused by mutations in a group of related genes that make up what is known as the cardiac sarcomere (Figure 3). The sarcomere is a network of proteins that make up the molecular motor of the heart and coordinate the contraction and relaxation of the heart muscle. A mutation in any one of at least 11 genes can lead to HCM, a condition characterized by a thickening of the heart muscle (left ventricular hypertrophy). To date, more than 600 mutations have been identified in these genes.

We also know that there are other genes, including genes that are important in maintaining the heart’s energy supply from stored sugar (glycogen), that can cause a condition that mimics HCM, causing a similar-appearing thickening of the heart muscle.

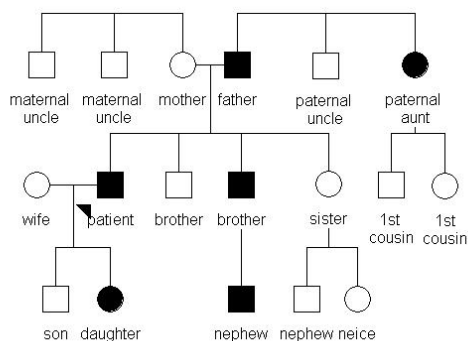


**Figure 3.** Illustration of the sarcomere.

Some components of the thick and thin filaments slide past each other to either generate or transmit the force of contraction; other sarcomere components direct this activity. (Adapted from Kamisago, M. et al. N Engl J Med. 2000;343:1688-96. Copyright © 2000 Massachusetts Medical Society. All rights reserved.)

## How is HCM inherited?

HCM is an autosomal dominant condition. The term autosomal tells us that the responsible gene(s) is located on chromosomes 1-22, affecting males and females equally. The term dominant means that although we have two copies of each gene, a mutation in just one copy is enough to cause HCM, even though there is still one copy of the gene without a mutation. A person that carries a mutation has a 50% chance of passing the mutation on to his/her children, regardless of whether he/she has an obvious diagnosis. If a person does not carry a mutation, it is not possible to pass it on to the next generation. As such, in families with HCM, approximately half of the members will be affected. (See Figure 4.)



**Figure 4.** Example of an autosomal dominant pedigree.

The arrowhead indicates the person being evaluated. Males are represented by squares and females by circles. The darkened shapes indicate family members with HCM.

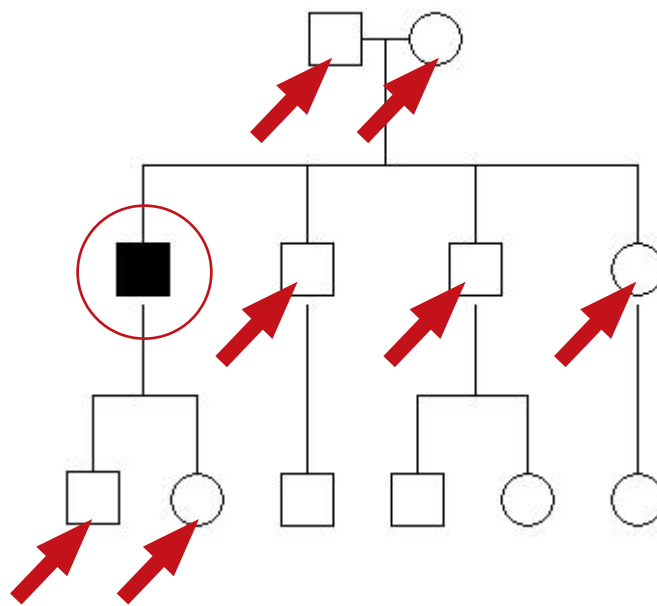
## Are there cases when HCM occurs but isn't inherited?

In some families, it seems that there is only one affected person. There may be a few reasons for this to happen. The mutation may have arisen spontaneously just in that individual during early embryologic development, rather than being inherited from an affected parent. This is referred to as a sporadic or spontaneous mutation and is typically contained in all, or most, of the cells in the body, including the sperm and egg cells (which contain the genetic information we will pass on to our children). Therefore, a person with a sporadic mutation has the same 50/50 chance of passing the mutation on to his/her children as a person with an established and recognized family history of HCM. In other cases where there is no obvious family history, it is also possible that there are family members who are so mildly affected that they do not know that they have HCM.

## Who in the family should be evaluated?

A clinical examination is appropriate for immediate family members of the patient diagnosed with HCM. This would include parents, siblings, and children—referred to as first degree relatives. (See Figure 5.) Any first degree relative may be carrying the HCM gene mutation and may unknowingly have a mild condition or be at risk for developing HCM in the future. A clinical evaluation should be performed by a cardiologist familiar with HCM and will typically include a physical examination, an electrocardiogram (a representation of the electrical activity of the heart) and an echocardiogram (an ultrasound study of the heart to look for increased wall thickening.)

Some people may have HCM without obvious symptoms, so this evaluation should be performed even if family members are feeling well. If symptoms change or develop, always notify your doctor.



**Figure 5.** Pedigree showing first degree relatives who should seek clinical evaluation for HCM. The circled individual indicates a person that has been diagnosed with HCM.

The arrows point to the first-degree family members who should be clinically screened for HCM. If the sibling of an affected person has no evidence of HCM, their children do not necessarily need to be screened unless symptoms are present.

## Will my HCM be as mild or as severe as my family member's condition?

Like many other inherited conditions, there may be a great deal of variation in how people with HCM are affected - even within the same family. Some family members may have very few symptoms of their disease while other relatives may have progressive heart failure or sudden death. In some cases, a person may carry a disease-causing mutation, but not develop any signs or symptoms of the condition until later in life. In HCM, thickening of the heart muscle may not be detectable until adolescence, early adulthood or, in rare cases, middle adulthood or later. From studying families with HCM, we believe that although the penetrance (the likelihood of developing the condition if a gene mutation is inherited) is dependent on age, the majority of individuals who inherit the mutation will at some point develop evidence of HCM. However, we cannot accurately predict when this evidence may develop or how severe or mild it may be based on simply knowing that the gene mutation is present. Clear evidence of HCM may not become noticeable until later in life, so repeated evaluation of family members over time is recommended as described in Figure 6.

Guidelines for Clinical Screening with Physical Examination, Echocardiography and Electrocardiogram (ECG or EKG)*	
Age	Recommendation
<12 years	Optional unless: <ul style="list-style-type: none"> <li>Family history of early HCM-related death, early development of LV hypertrophy, or other adverse complications</li> <li>Competitive athlete in intense training program</li> <li>Onset of symptoms</li> <li>Other clinical suspicion of early LV hypertrophy</li> </ul>
12-18 years	Repeat evaluation every 12-18 months
>18-21 years	<ul style="list-style-type: none"> <li>Repeat evaluation approximately every 5 years, or in response to symptoms.</li> <li>Tailor evaluation if there is a family pattern of late-onset LV hypertrophy or HCM-related complications</li> </ul>

**Figure 6**

Source: Maron BJ et al. Proposal for Contemporary Screening Strategies in Families with Hypertrophic Cardiomyopathy. J Am Coll Cardiol 2004;44:2125-32.

If genetic testing information is available, screening is only necessary for family members who test positive and are found to carry the gene mutation that causes HCM in the family.

## How does genetic testing for HCM work?

Genetic testing for HCM involves taking a sample of DNA and looking at each nucleotide in the eight sarcomere genes that most commonly cause HCM to see if there is a mutation-- any change from the usual sequence. The DNA sample used for the test can be obtained from blood, saliva, or tissue. By analyzing five genes, MYH7, MYBPC3, TNNT2, TNNI3, and TPM1, a mutation can be found in 50-60% of individuals who are thought to have HCM. By looking at three additional genes: ACTC, MLC2 and MLC3, a mutation can be detected in an additional 5-10% of patients with HCM. All together, current genetic testing for HCM can detect a mutation in 55-70% of people with a suspected diagnosis of HCM (See Figure 7.). Mutations in two other genes involved in glycogen metabolism (named PRKAG2 and LAMP2) cause a condition that mimics HCM, also causing LVH. Genetic testing is available for both of these genes. It is our hope to see faster and less expensive genetic screening methods within the next decade, making genetic testing available to all individuals with HCM.

Gene Symbol	Protein Name	Detection Rate
<b>SARCOMERE GENES</b>		55-70%
MYH7	β-cardiac myosin heavy chain	
MYBPC3	Cardiac myosin-binding protein c	
TNNT2	Cardiac troponin T	
TNNI3	Cardiac troponin I	
TPM1	α-Tropomyosin	
ACTC	Cardiac actin	
MYL2	Cardiac myosin regulatory light chain	
MYL3	Cardiac myosin essential light chain	
<b>METABOLISM GENES</b>		Unknown
PRKAG2	5-AMP-activated protein kinase, gamma-2 subunit	
LAMP2	Lysosomal associated membrane protein 2	

**Figure 7. Genes that cause HCM**

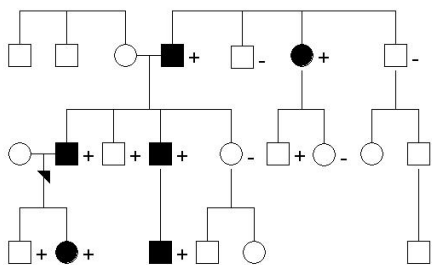
In order for your genetic test results to be accurately interpreted, they should be evaluated by a doctor familiar with genetics and HCM while factoring in your specific personal medical and family history.

## What are the benefits of HCM genetic testing?

Genetic testing is primarily used to confirm a diagnosis of HCM and to identify family members who are at risk for developing HCM because a relative is carrying an HCM related mutation. Although HCM cannot be prevented, knowing you are at risk for developing the condition prompts doctors to monitor your condition on a routine basis (as outlined in Figure 6), which may lead to early detection, a faster response to the development of symptoms, and assist in detecting risk for more serious complications related to HCM. In addition, your own knowledge of the disease may help you to recognize clinical symptoms—shortness of breath with exercise, light-headedness, fainting, and chest pain. If you experience these symptoms, contact your doctor.

## What happens after I get my test results?

Individuals found to carry the family's mutation who do not have clinical evidence of HCM (shown as white shapes with a plus sign in Figure 8) should follow the family screening guidelines detailed in Figure 6. If a person does not carry the family's known mutation, they can rest assured that they are not at risk for developing HCM. There is no need to screen his/her children because they are not at risk to inherit the mutation or HCM.



**Figure 8.** Pedigree showing genetic and clinical test results.

The plus and minus signs indicate positive and negative genetic test results. Darkened shapes represent people who are clinically affected.

## What are the limitations of genetic testing for HCM?

It is important to consider the limitations of genetic testing when deciding whether or not to move forward with it. First off, the test will not find a mutation in all DNA samples from people with HCM. About 30-40% of the time, the HCM genetic test does not identify a mutation in a person

with HCM. However, this does not necessarily mean that the person does not have HCM or that there is not a genetic cause for their condition, particularly if other people in the family are thought to have HCM. One reason for this margin of error is that the test looks at only the 8 genes known to cause HCM, and not all genes known to cause the condition. Furthermore, we do not yet know of every gene that may cause HCM or similar conditions. This is an area of active research.

Results from genetic testing may not be as simple as positive or negative. If a person with HCM is found to have a mutation in a sarcomere gene, it is *almost* certain that the mutation caused the disease. We can't always be entirely certain because there are subtle differences in the genetic code from person to person in the general population. These variations in the spelling of genes are sometimes harmless but sometimes cause important disease. So when the genetic testing laboratory finds a mutation, lab scientists will try to determine whether or not the mutation truly caused HCM in that person. They do this by collecting information from various sources, including previous experiences and published medical literature. Sometimes the lab will find a new mutation that has never been seen before. In the case of these novel mutations, it is helpful to have other family members submit DNA samples and medical information to better understand the mutation. In some cases, scientists may not be able to say for sure that the mutation they found caused the HCM. In this situation, it may not be possible to know if healthy relatives who inherited the mutation are at risk for developing HCM. However, standard clinical follow up to look for features of HCM over time is appropriate (see Figure 6).

If a mutation is identified in a relative with HCM, family members can be tested only for the mutation found in that relative to determine whether or not they inherited that specific mutation. If the lab is unable to find a mutation in the DNA sample of an affected family member, it is not feasible to test other family members to more definitively determine their risk of developing HCM. Another limitation of HCM genetic testing is that the results usually do not provide information about when symptoms may develop, how severe they may be, or the prognosis for the future.

## Should my child be tested?

Parents may struggle with the decision about whether or not to test their children and, if so, when. There is no universal answer to these questions. Parents must consider whether they think the uncertainty of not knowing whether the child has inherited the mutation is more difficult to live with than knowing for sure that a child has a mutation. In families with a history of early onset and/or premature death, there may be a greater benefit from more definitive early genetic diagnosis to help remove the anxiety associated with an otherwise uncertain risk for developing disease. Typically, symptoms do not arise until adolescence or adulthood.

## What are the psychological consequences of genetic testing?

The decision to pursue genetic testing should be made after careful consideration of the information you can learn and the potential psychological consequences of that information. Individuals undergoing genetic testing may experience a wide range of emotions upon receiving results, including relief and comfort, but also anger, denial, guilt, fear, and grief, among others. A person's reaction to a positive result may vary based on many things such as: age; previous thoughts about his/her health; perceived risk of developing the condition; personal experience with the condition; and the presence of children. Some family members who do not carry the gene mutation may experience unexpected guilt or isolation when they are negative and other family members are positive. Some people may feel a sense of relief with a positive result because the uncertainty of whether or not they inherited the mutation has been removed. Identifying a mutation in the family can also provide a sense of hope and optimism that the information may in some way help future generations. Finally, having definitive genetic information can empower some people to make informed decisions about their life and health.

## Are there any treatments available to prevent HCM in individuals who carry the genetic mutation?

There are no known treatments that can delay or prevent the development of HCM or the onset of symptoms, although developing new strategies for early treatment to slow, and ultimately to prevent or reverse, disease development is an active area of research. A heart-healthy diet and regular exercise is always recommended for good cardiovascular health.

## What do we hope to learn in the future through research?

In the coming years, research will continue to focus on gaining a better understanding of the underlying cellular and molecular processes that lead to HCM. By better understanding the sequence of events involved from inheriting a mutation to developing clinical signs of HCM, it may be possible to identify ways to prevent or slow further progression of HCM. Our current medical therapies focus on treating symptoms of HCM once the condition has fully developed. What we would like to do in the future is design treatments to prevent HCM from developing or reverse changes once they have occurred. To this end, we are pioneering clinical trials now that focus on treating family members who have inherited a gene mutation before HCM develops, to see if treatment can help slow the onset of HCM. It is only through genetic testing that we are able to identify such individuals. We have a lot of work left to do, but we are making progress thanks to the generous participation of families with HCM in research studies and ongoing work in the research laboratory. Together we will continue to explore new ideas about how to more effectively treat this important condition.

For more information about available HCM clinical trials please visit [www.clinicaltrials.gov](http://www.clinicaltrials.gov).