

This fact sheet describes a number of genetic heart diseases known as **cardiomyopathies** and includes the symptoms, causes, and any treatment or testing that is available.

In summary

- There are three main types of cardiomyopathy:
 - ◊ Hypertrophic cardiomyopathy (HCM)
 - ◊ Dilated cardiomyopathy (DCM)
 - ◊ Arrhythmogenic right ventricular cardiomyopathy (ARVC)
- Heart palpitations, dizziness and fainting, cardiac arrest and sudden cardiac death are all possible symptoms of a cardiomyopathy or another genetic heart disease
- First-degree relatives (parents, siblings and children) of an individual who has a cardiomyopathy are usually at a 50% risk of also developing the condition
- Cardiac arrest and sudden cardiac death are often the first signs of cardiomyopathy in an individual therefore it is very important that everyone with a family history be seen by a cardiologist and considers genetic testing where available.

WHAT ARE CARDIOMYOPATHIES?

Cardiomyopathies are a group of conditions that involve abnormalities of the heart muscle. Some forms involve an inherited predisposition:

1. Hypertrophic cardiomyopathy (HCM)
2. Dilated cardiomyopathy (DCM)
3. Arrhythmogenic right ventricular cardiomyopathy (ARVC)

Some common aspects across these three conditions include:

- They all affect the heart muscle, but may differ in the area they affect
- They may present with common symptoms such as palpitations, chest pain and fainting
- Each carries a small but significant risk of sudden cardiac death
- Close relatives of an individual with a cardiomyopathy are at an increased risk and should have regular cardiac screening to monitor for any changes in the heart
- Genetic testing is available in some, but not all, cases and can help to clarify who in the family is at risk
- Some individuals that inherit a predisposition to cardiomyopathy may not have any symptoms but should have ongoing screening

1. Hypertrophic cardiomyopathy (HCM)

HCM is characterised by thickening of the left ventricle, the main pumping chamber of the heart (Figure 57.1). In a normal heart the thickness of the left ventricle wall is between 7 to 10mm, however individuals with HCM have a thickness greater than 13mm. If there is no family history of HCM, thickness greater than 15mm is needed for diagnosis. The thickened muscle is less efficient and results in symptoms that range from palpitations, breathlessness and chest pain through to more severe outcomes of recurrent fainting, cardiac arrest, and sudden cardiac death (SCD).

- HCM is estimated to affect 1 in 500 people in the Australian population and may be as common as 1 in 200
- Symptoms typically present during childhood and adolescence, however some people may have symptoms from birth while others may not present until late adulthood

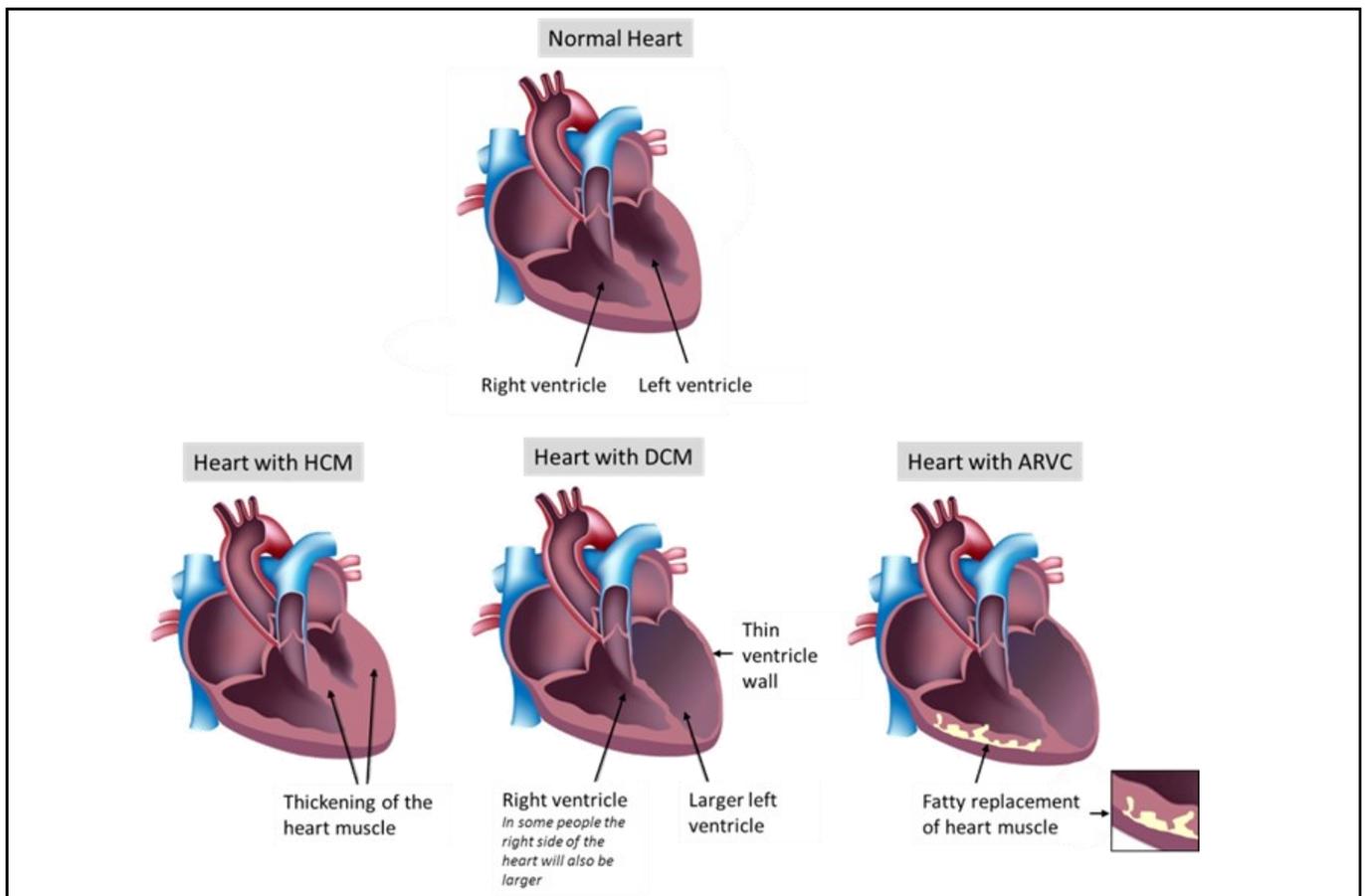


Figure 57.1: Adapted from the Australian Genetic Heart Disease Registry <http://www.heartregistry.org.au/>

2. Dilated cardiomyopathy (DCM)

In individuals with DCM the left ventricle enlarges (dilates) and the muscle wall becomes thin (see Figure 57.1). This affects the ability of the heart to effectively pump blood and can lead to symptoms such as shortness of breath, swelling of the ankles and legs, fatigue, and in rare cases SCD. There are many causes of DCM, with the inherited form accounting for 20-50% of cases overall.

3. Arrhythmogenic right ventricular cardiomyopathy (ARVC)

ARVC results in changes to the right side of the heart, where muscle cells are replaced by fat and scar tissue. In some cases the left ventricle can also be affected. (see Figure 57.1)

This results in abnormal heart rhythms and may cause the right side of the heart to become enlarged and not pump efficiently. Symptoms range from palpitations, chest pain and fainting through to SCD.

WHAT CAUSES CARDIOMYOPATHIES?

Our body is made up of millions of cells, and in each cell there are instructions, called genes, that make all the necessary structural components and chemicals for the body to function. These genes are packaged onto little long strands known as chromosomes.

We all have 46 chromosomes arranged into 23 pairs. One copy of each pair is inherited from our mother and the other from our father. The first 22 chromosome pairs are numbered and are known as autosomal chromosomes. The 23rd pair is made up of the sex chromosomes called X and Y. Males have an X and a Y chromosome and females have two copies of the X chromosome.

Since all our chromosomes come in pairs, all our genes also come in pairs. Sometimes, a gene may have a variation in the instruction that causes the gene to no longer function properly. This variation is called a **mutation** or **pathogenic variant**, and means that the product produced by the gene, called a protein, is impaired or even absent.

Gene mutations may be inherited from a parent, or occur for the first time in an individual. Once you have a gene mutation however, it may be passed on to future generations. This is referred to as genetic inheritance.

1. Hypertrophic cardiomyopathy (HCM)

HCM can be caused by a mutation in several genes, the most common of which are MYH7, MYBPC3, TNNT2 and TNNI3. These genes all play important roles in heart muscle cells by forming and supporting structures called **sarcomeres**. The role of the sarcomere is to help the heart contract so that it can pump blood around the body. Mutations in sarcomere genes may alter, reduce the amount, or remove the proteins needed for healthy heart contraction.

2. Dilated Cardiomyopathy (DCM)

Over 30 genes are implicated in DCM, and similar to HCM, are involved with sarcomeres and the contraction of heart muscle.

3. Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

Genetic causes of ARVC include at least eight genes which are involved once again in heart muscle cells. Different to HCM and DCM though, mutations in ARVC genes affect **desmosomes** which are structures that allow one heart muscle cell to communicate with the cell next to it.

When desmosomes don't work properly cells disconnect and die off, being replaced by scar tissue and fat. This stiffens the heart wall, particularly in the right ventricle, and may interrupt electrical signals that control regular heart rhythm.

Sometimes high level competitive endurance athletes are found to have heart disease similar to ARVC.

HOW ARE CARDIOMYOPATHIES INHERITED?

Most cardiomyopathies are inherited in an autosomal dominant pattern, meaning that a mutation in only one copy of a gene is sufficient to cause disease despite the other copy working properly (Figure 57.2). For every pregnancy in this situation there is a:

- 50% chance that a child, either male or female, will inherit both working copies of a gene from their parents and be healthy
- 50% chance that they will inherit one copy of the faulty gene, and one working copy and be predisposed to developing a cardiomyopathy.

A mother or a father can pass on an autosomal dominant condition and both male and female children may be affected.

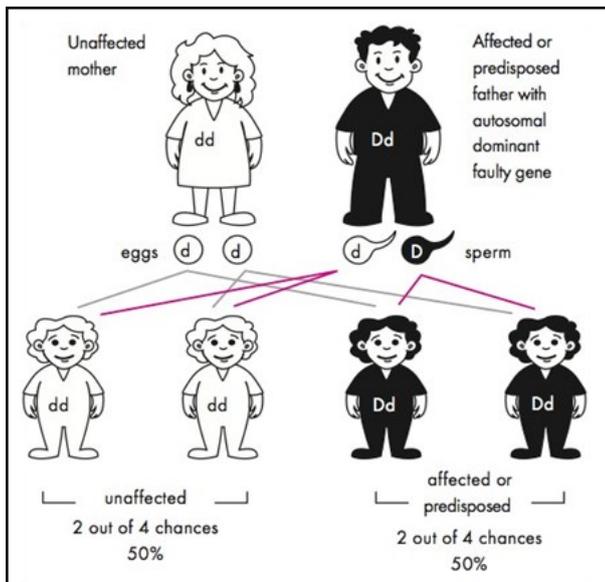


Figure 57.2: Autosomal dominant inheritance when one parent carries the autosomal dominant faulty gene copy. The autosomal dominant faulty gene copy is represented by 'D'; the working copy of the gene by 'd'.

Some Exceptions

HCM, DCM and ARVC can all be inherited in the autosomal dominant pattern explained above, however DCM and ARVC can sometimes be inherited differently. Each family should have their health history and circumstances assessed by a genetic counsellor or specialist for the most accurate information regarding the way in which a cardiomyopathy may be inherited or passed on in their family.

IS THERE ANY TESTING AND TREATMENT AVAILABLE FOR CARDIOMYOPATHIES?

Clinical Testing for Cardiomyopathy

Most cardiomyopathies are diagnosed through clinical tests which may include an ultrasound of the heart (echocardiogram) and looking at the heart rhythm (electrocardiogram). These involve examination by a cardiologist and are sufficient for diagnosis in most cases.

Because most cardiomyopathies are inherited in an autosomal dominant pattern, first degree relatives including parents, siblings and children are at a 50% risk of also having the condition. Therefore it is recommended that these at-risk relatives undergo regular cardiac screening to check for any signs of disease.

Genetic Testing for Cardiomyopathy

Genetic testing to identify the causative mutation in a family may be available, however it is very complex. The first step is a **mutation search** in an affected family member to try and identify the faulty gene. If this is identified, genetic testing can be offered to other family members who are at-risk. This is called **predictive testing**. If a mutation cannot be found though, no further genetic testing can be offered in the family and all first-degree relatives should see a cardiologist for regular cardiac review.

The benefit of genetic testing is to conclusively identify family members that are predisposed to developing a cardiomyopathy so that they can receive the appropriate cardiac care. While those that can be shown to not carry the familial mutation can be released from regular cardiac screening and are not at any increased risk for a cardiomyopathy.

There are significant limitations to genetic testing technologies currently so regular review of genetic information is recommended as new technologies arise and may be able to detect changes not previously seen.

Prenatal Testing and PGD

For couples where the familial mutation is identified, testing may be available during a pregnancy to determine whether or not the baby has inherited the mutation. It may also be possible to undergo **pre-implantation genetic diagnosis** (PGD) on an embryo created using in vitro fertilisation (IVF). These options are best discussed and considered before pregnancy, when possible, in order to ensure all possible risks, benefits and outcomes are explored.

Treatment Options

All affected individuals as well as currently well gene carriers are recommended to take beta-blockers, a tablet that helps to stabilise the heart rhythm. Your cardiologist may recommend an implantable cardioverter defibrillator (ICD) if they feel you are at an increased risk of cardiac arrest, which is a small device surgically implanted in the chest wall which detects abnormal heart rhythms and delivers an electric shock to 'reset' the heart rhythm back to normal.