

Important points

- Cardiomyopathies are abnormalities of the heart muscle. There are many types and causes of cardiomyopathy: it may also occur as part of other syndromes with a genetic basis such as Noonan syndrome. Two types of cardiomyopathy involve inherited predisposition:

Familial hypertrophic cardiomyopathy (FHCM) is a condition in which part of the heart muscle surrounding the ventricles—in particular the left—is thicker than normal. This may cause problems such as palpitations, breathlessness and chest pain, but some people are symptom-free.

- Estimated to affect 1 in 500 in the Australian population but symptoms start from as early as birth up to the 10th decade
- Variations in at least 11 different genes have been identified; most commonly variations in genes that instruct the cells in the heart to produce the proteins involved in contractions of the heart muscle (*sarcomere proteins*)
- The pattern of inheritance in families of the *sarcomere* protein genes causing predisposition to FHCM is described as **autosomal dominant inheritance**
- When one of the parents has FHCM or is a genetic carrier for FHCM, **in every pregnancy** they have 1 chance in 2 (or 50% chance) of having a child who is at increased risk for FHCM
- The usual method of diagnosis of FHCM is by ultrasound, ECG and examination by a cardiologist. Close blood relatives of affected individuals should have regular cardiac screening
- For those with a strong family history of FHCM, genetic counselling may be useful to assess their risk of developing FHCM and for advice about genetic testing if available (see Genetics Fact Sheet 3). Predictive genetic testing is complex and time consuming and first requires a mutation to be identified in an affected family member

Familial dilated cardiomyopathy (FDCM) affects the heart muscle differently: the ventricle, mainly the left ventricle, is dilated, thin-walled and contracts poorly.

- Affects about 1 in 2,000 people including newborns, children, adolescents, adults, and the elderly
- About 30% of cases of DCM are inherited (familial DCM)
- Over 30 genes have been identified. Depending on the gene(s) involved, FDCM may follow a pattern of autosomal dominant, autosomal recessive, X-linked, or mitochondrial inheritance
- The usual method of diagnosis of FDCM is by ultrasound, ECG and examination by a cardiologist. Close blood relatives of affected individuals should have regular cardiac screening

Cardiovascular disease (*cardio* refers to the heart and *vascular* refers to the blood circulation system) is the general term given to conditions that include:

- Problems with the blood vessels that supply the heart muscle (*coronary artery disease*)
- High blood pressure (*hypertension*)
- Problems with the blood vessels that supply the brain (*stroke*)
- Abnormalities in the structure of the heart affecting the valves and muscle of the heart (eg *cardiomyopathy*) and other heart 'defects'; when these are present at birth they are called *congenital heart defects*
- Problems with the 'electrical' system in the heart that controls the heart beat (*arrhythmias*)
- Problems with other arteries in the body, such as the *aorta* (the main artery that leads from the heart)

In some cases, the information in the genes contributes to the development of cardiovascular disease. This is more likely when there are a number of affected members of a family and symptoms of the condition occur at an early age.

In most cases where there is a family history of cardiovascular disease, the genetic component appears to be a 'susceptibility' factor, rather than a direct cause. That is, the disease is a multifactorial condition (see Genetics Fact Sheet 11) where both inherited genetic predisposition to develop the condition and environmental triggers are involved.

What is inherited predisposition to cardiovascular disease?

Our genes are part of chromosomes and provide the information for our bodies to grow and develop, and to work properly throughout our life (see Genetics Fact Sheet 1).

When the information in the genes is changed in some way, the information sent to the cells may be different.

A gene that contains a variation in the information that stops it working properly is described as faulty. The variation that makes the gene faulty is called a *mutation*. The information contained in the faulty gene, and its product, is impaired (see Genetics Fact Sheets 4 & 5).

Genetic predisposition means that an individual has inherited from a parent a faulty gene copy that does not cause a problem directly but makes them more susceptible to developing the condition later in life when particular environmental factors that trigger the condition are present (see Genetics Fact Sheet 11).

We all have two copies of the genes in our cells and when one copy of the gene is faulty, it may not cause a problem as the other gene copy still sends the right message to the cells to make the gene product. Even if the variation in the genetic information is major, other genes in the cell may still enable the cell to function normally.

- In some cases, variations can occur during life in the other gene copy or to the other genes, caused by as yet largely unknown environmental factors
- In other cases, it is not clear how the environmental factors interact with the inherited faulty gene copy

It is clear however, that if the environmental triggers can be identified where there is a genetic susceptibility to develop a cardiac condition, manipulation of the factor or preventing its interaction with the genetic make-up will enable preventive strategies for cardiac conditions to be developed.

It is therefore important to both determine the genetic basis of cardiovascular conditions to be able to identify those who may wish to know of their susceptibility as well as determine the environmental triggers.

This Fact Sheet discusses a form of cardiovascular disease in which genes are known to be involved: an inherited tendency to have high cholesterol that leads to coronary artery disease. It also covers the role of genetics in predisposition to cardiomyopathies.

- Genetics Fact Sheet 53 discusses an inherited tendency to have high cholesterol that leads to coronary artery disease (familial hypercholesterolaemia)
- Genetics Fact Sheet 55 discusses the role of genetics in predisposition to cardiovascular conditions where there is a problem with the electrical control of the heart beat (arrhythmias)

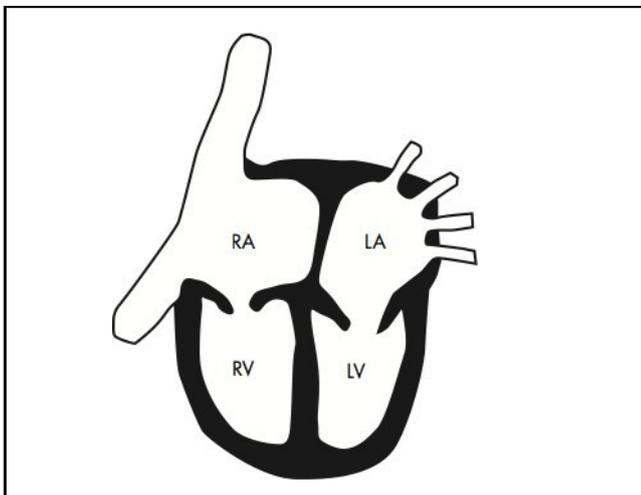


Figure 54.1: (a) Normal heart. RA = right atrium, LA = left atrium, RV and LV = right and left ventricles

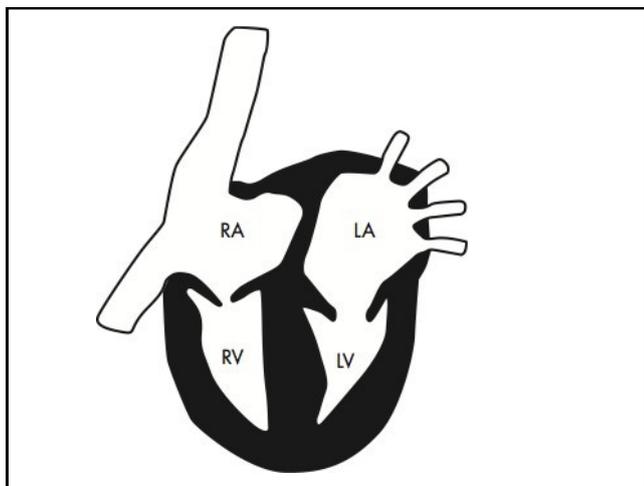


Figure 54.1: (b) A heart affected by hypertrophic cardiomyopathy with thickened muscular wall and smaller ventricular chambers

- Genetics Fact Sheet 56 discusses the genetic aspects of hypertension, congenital heart defects and inherited conditions of connective tissue with cardiovascular effects

Cardiomyopathies

Cardiomyopathies are abnormalities of the heart muscle. The name comes from the Greek or Latin languages: *hyper* (greater than normal), *trophic* (growth), *cardio* (heart), *myo* (muscle) and *pathy* (disease).

There are many types and causes of cardiomyopathy; it may also occur as part of other syndromes with a genetic basis such as Noonan syndrome.

Two types of cardiomyopathy involve inherited predisposition:

- Familial hypertrophic cardiomyopathy (FHCM)
- Familial dilated (congestive) cardiomyopathy (FDCM)

(a) Familial hypertrophic cardiomyopathy (FHCM)

Of the four chambers of the heart – the left and right atrium and the left and right ventricles – the ventricles are largely responsible for pumping the blood through the blood vessels (*Figure 54.1a*).

Hypertrophic cardiomyopathy (HCM) is a condition in which part of the heart muscle surrounding the ventricles – in particular the left – is thicker than normal (*hypertrophic*) (*Figure 54.1b*).

When there is a family history of HCM, it is referred to as *familial hypertrophic cardiomyopathy* (FHCM) which is:

- Characterised by increased muscle thickening and changes in the heart muscle structure that may cause problems such as palpitations, breathlessness and chest pain. Some people may be symptom-free
- Variable with respect to in the age at which it can be diagnosed, or at which symptoms start: from as early as birth up to the 10th decade
- Estimated to affect 1 in 500 in the Australian population
- Usually diagnosed by detection of the increased muscle thickness on an ultrasound scan of the heart and by an electrocardiogram (also known as an ECG, which is an electrical tracing of the heart)

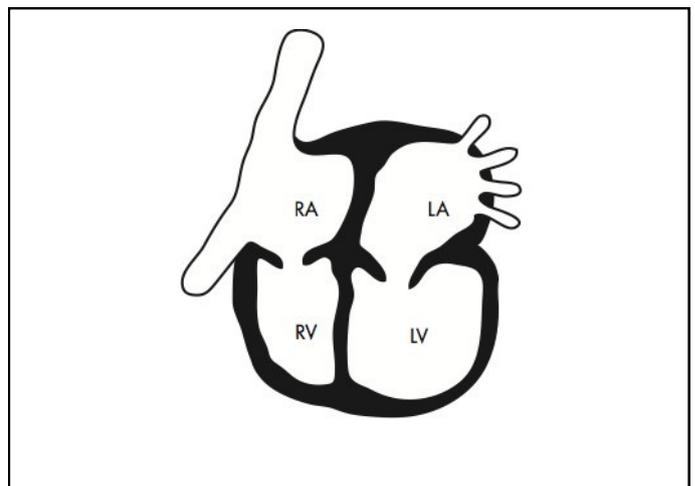


Figure 54.1: (c) A heart affected by dilated cardiomyopathy with left ventricular (LV) chamber enlarged and thin walled

Genes and familial hypertrophic cardiomyopathy (FHCM)

More than 1400 variations in the information in at least 11 different genes have been identified as associated FHCM.

- The most common genes identified instruct the cells in the heart to produce the proteins involved in contractions of the heart muscle (*sarcomere proteins*)
- Variations that make the sarcomere protein genes faulty result in enlargement of the part of the heart muscle that does most of the work of pumping blood around the body. The degree and extent of this enlargement, as well as the age of onset, varies considerably between individuals
- There may be other genes that modify the ‘expression’ of the faulty sarcomere genes, and may therefore help to explain the variable degree of severity seen in this condition
- Research is underway to investigate these ‘modifying’ genes

When inherited predisposition is involved in FHCM, what is the pattern of inheritance of the condition in families?

In these cases, two factors influence the pattern of inheritance of most FHCM in families.

1. The genes are located on autosomes (one of the numbered chromosomes)
2. The effects of variations in the genes involved are ‘dominant’ over the information in the working copy of the genes on the partner chromosomes (see Genetics Fact Sheets 1, 4 & 5)

The pattern of inheritance in families of the faulty genes causing predisposition to FHCM is therefore described as **autosomal dominant inheritance** (see Genetics Fact Sheet 9).

In *Figure 54.2* the autosomal dominant faulty gene, causing predisposition to FHCM is represented by ‘D’; the working copy by ‘d’.

Where one of the parents has or has the faulty gene that predisposes them to FHCM, there are four possible combinations of the genetic information that is passed on by the parents.

This means that, **in every pregnancy**, there is:

- 1 chance in 2 or 50% chance that their child will inherit a copy of the faulty gene from one parent and a working copy from the other and will therefore be at increased risk for hypertrophic cardiomyopathy
- An equal chance (ie. 1 chance in 2) or 50% chance that their child will inherit the working copy of the gene from both parents. In this case, the child will not develop hypertrophic cardiomyopathy and cannot pass on the faulty gene copy to any of his/her children

While *Figure 54.2* shows the father as the parent carrying the faulty FHCM gene, the same situation would arise if it was the mother. A faulty FHCM gene can be inherited from either the mother or the father.

The environmental factors that cause the mutations in the FHCM gene(s) are still largely unknown. The identification of these factors and preventing their action paves the way for the prevention of the condition.

Can a person determine if they have inherited a faulty FHCM gene?

The usual methods of diagnosis of FHCM are by ultrasound, ECG and examination by a cardiologist. Close blood relatives of affected individuals should have regular cardiac screening.

People with a strong family history of FHCM can also seek advice from their local genetic counselling service. Their risk of developing FHCM, based on their family history, can be estimated and discussed in more detail (see Genetics Fact Sheet 3).

The genetic counselling team may be able to:

- Clarify their chance of developing FHCM based on their family history
- Answer any questions they may have about their family history of cancer
- Discuss what medical check-ups are appropriate
- Discuss the limitations, potential benefits, disadvantages and appropriateness of genetic testing if available (see Genetics Fact Sheet 21)

Genetic testing for mutations in the FHCM genes, where available, is complex and involves

- **First**, identifying the variation that is making the gene faulty (a mutation) in a family member who has or had FHCM. This **mutation searching** may take considerable time.
- **Second**, and only if a mutation is found, testing other family members without FHCM, to determine if they have inherited the faulty gene. This is called **predictive genetic testing** (see Genetics Fact Sheet 21).

(b) Familial dilated cardiomyopathy (DCM)

Dilated cardiomyopathy (DCM) affects the heart muscle differently: the ventricle, mainly the left ventricle, is dilated, thin-walled and contracts poorly (*Figure 54.1c*).

Affected individuals will require regular cardiac investigations and monitoring of symptoms.

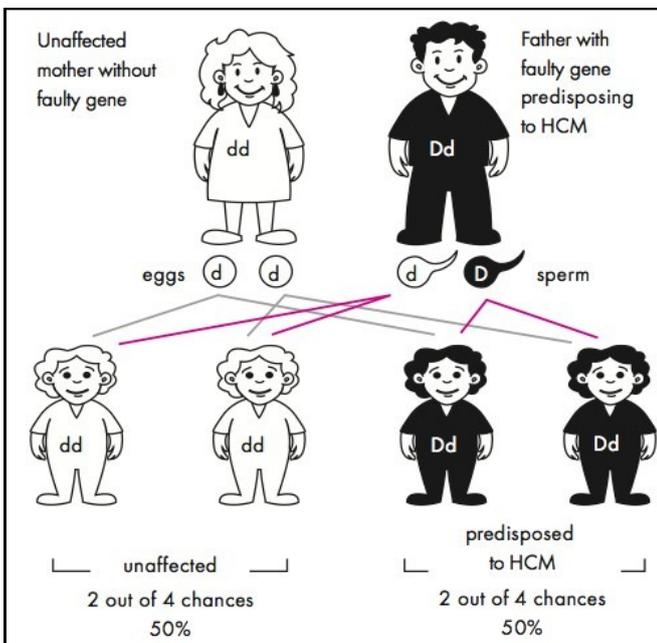


Figure 54.2: Autosomal dominant inheritance when one parent has a faulty FHCM gene copy. The faulty FHCM gene copy is represented by ‘D’; the working copy by ‘d’.

The condition:

- Can affect newborns, children, adolescents, adults, and the elderly
- Affects about 1 in 2000 people born in Australia
- May be the result of damage from a variety of agents, such as alcohol, viruses and some other conditions
- Where there is a family history of DCM, it is referred to as familial dilated cardiomyopathy (FDCM). At least 30% of cases of DCM are inherited (familial DCM)

Up to 50% of people with DCM of unknown cause have other family members with the condition (a positive family history) and the condition is considered to be familial DCM.

- There are no specific symptoms that reliably distinguish the familial form of DCM from the non-familial form.

Genes and familial dilated cardiomyopathy (FDCM)

Over 30 genes have been identified that when faulty cause FDCM. These genes contain the information for a variety of proteins. These findings indicate that diverse molecular mechanisms may underlie familial DCM.

Depending on the gene(s) involved, FDCM may follow a pattern of autosomal dominant, autosomal recessive, X-linked, or mitochondrial inheritance (see Genetics Facts Sheets 8-10 & 12).

- Close blood relatives of affected individuals should have cardiac screening including investigations such as echocardiography and ECG
- The frequency of follow up assessment should be determined by the average age of onset of the disease in symptomatic family members and 'suspicious' ECG changes, and may range from 6-12 months to 5 years

Other Genetics Fact Sheets referred to in this Fact Sheet: 1, 3, 4, 5, 9, 11, 21, 53, 55, 56