

Important points

- Cardiovascular disease with either an inherited predisposition or cause is associated with high blood pressure (*hypertension*), congenital heart defects and with some rare inherited conditions of connective tissue

Hereditary Hypertension is most likely due to the interaction of changes in a number of different genes that leads to a susceptibility to the condition, triggered by environmental factors that may include diet, obesity and stress.

- When there are two or more affected relatives, the increased risk is three times the population risk
- *Primary pulmonary hypertension* is a very rare form of hypertension caused by an obstruction of the pulmonary arteries (arteries that lead to the lungs) Inheriting a faulty *BMPR2* gene causes a predisposition to developing this condition
- People with a strong family history of primary pulmonary hypertension can seek advice from their local genetic counselling service (see Genetics Fact Sheet 3)
- Genetic testing for mutations in the *BMPR2* gene involves first identifying the mutation in a family member who has or had primary pulmonary hypertension (**mutation search**) and may take considerable time. Second, and only if a mutation is found, **predictive genetic testing** may be possible for other family members without primary pulmonary hypertension, to determine their risk of developing the condition

Congenital heart defects are abnormalities of the structure and/or function of the heart that are present at birth that may be so slight that the baby appears healthy for many years after birth; others are so severe that they are life threatening.

- In most cases, the cause is unknown
- It affects about 1 in every 100 newborn babies
- Factors that increase the risk for a child having a congenital heart defect include
 - A family history of congenital heart defects
 - Exposure of the mother to certain environmental factors in pregnancy including contracting German measles (*rubella*) and certain chemicals or drugs (*teratogens*) such as high levels of alcohol, cocaine, lithium and some everyday medications
 - The child has a chromosomal abnormality such as Down syndrome
 - The condition is due to a change in a single gene (rarely)
- Genetic counselling is important to identify a possible genetic cause

Inherited conditions of connective tissue with cardiovascular effects A number of connective tissue conditions that follow a pattern of autosomal dominant inheritance are characterised by cardiovascular manifestations and include:

- **Marfan syndrome** is caused by inheriting a faulty *FBNI* gene copy that contains the information for the protein *fibrillin-1* found in the aorta, the lens of the eye and in connective tissue of bone; cardiovascular problems include cardiomyopathy and heart failure, aortic rupture and problems with an important valve in the heart (*mitral valve*)
- **Ehlers Danlos syndrome Type 4** caused by inheriting a faulty *collagen type 3* gene copy that contains the information for a component of collagen found in the skin, bones and blood vessels. There is an increased risk for spontaneous rupture of the aorta or the large to medium-sized arteries in the individual's 20s or 30s due to an abnormality in the arterial walls
 - A cardiologist can make a clinical cardiac assessment
 - Genetic counselling is important regarding implications for family members and discussion of predictive genetic testing, if available

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 heartbeat (*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.

If the information is changed so that the gene product in the cell is impaired, reduced or absent, the gene change is described as a mutation. Mutations are changes in genes that make the gene faulty (see Genetics Fact Sheet 4).

Genetic predisposition means that a person has inherited from a faulty gene copy from a parent, 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 gene change is major, other genes in the cell may still enable the cell to function normally.

- In some cases, changes can occur spontaneously during life in the second gene copy, or to other genes, caused by as yet largely unknown environmental factors.
- It is not clear how environmental factors interact with the inherited faulty gene copy to cause cardiovascular disease. It is however, clear that if the environmental triggers can be identified where there is a genetic susceptibility to develop a cardiac condition, manipulation of the environmental 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 determine both the genetic basis of cardiovascular conditions to be able to identify those who may wish to know of their susceptibility, as well the environmental triggers.

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

- Genetics Fact Sheet 53 discusses an inherited tendency to have high cholesterol that leads to coronary artery disease (familial hypercholesterolaemia).
- Genetics Fact Sheet 54 discusses the role of genetics in predisposition to cardiomyopathies.
- 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 heartbeat.

Hypertension

What is high blood pressure (hypertension)?

Blood pressure is the measure of the pressure or tension made by the blood on the walls of the arteries.

It is usually expressed as two numbers eg. 120/80 (ie. 120 over 80). The first number (120) represents the pressure in the arteries when the heart contracts (*systolic* blood pressure). The second

number represents the pressure in the arteries between heart contractions or heart beats (*diastolic* blood pressure).

- High blood pressure, also called **hypertension**, is usually classified as a level that is greater than 140/90 on several different days. If high blood pressure is not treated, it can lead to heart disease and stroke.

What causes hypertension?

Research is continuing into the cause of hypertension in families.

The contribution to its cause will most likely not be from changes in a single gene but involve the interaction of changes in a number of different genes that lead to an inherited susceptibility and environmental triggers that include diet, obesity and stress (see Genetics Fact Sheet 11).

Close relatives in families where there are a number of members with high blood pressure need to be aware that they may be at increased risk of cardiovascular disease. Early treatment to reduce blood pressure and avoidance of environmental risk factors can be initiated if necessary.

For individuals with two or more affected relatives, there is a three times increased risk over the population risk for developing hypertension.

Inherited predisposition to primary pulmonary hypertension

One very rare form of hypertension caused by an obstruction of the pulmonary arteries (arteries that lead to the lungs) referred to as primary pulmonary hypertension, has been linked to changes in the **BMPR2 gene** (*bone morphogenetic protein receptor type 2*).

Inheriting a faulty **BMPR2** gene copy increases the risk for developing this form of hypertension. If an individual has one faulty **BMPR2** gene copy and the other partner **BMPR2** gene copy is working, they are carriers of the faulty **BMPR2** gene: they are genetic carriers for primary pulmonary hypertension.

- Genetic carriers for **BMPR2** are susceptible (predisposed) to primary pulmonary hypertension
- Just having a faulty **BMPR2** gene is not enough for the hypertension to develop

Two factors influence the pattern of inheritance of the faulty **BMPR2** gene causing predisposition to primary pulmonary hypertension in these families.

1. The **BMPR2** gene is located on chromosome 2, which is an autosome (one of the numbered chromosomes)
2. The effect of the change in the **BMPR2** gene is 'dominant' over the information in the working copy of the gene on the partner chromosome 2 (see Genetics Fact Sheets 1, 4 & 5)

The pattern of inheritance in families of the faulty **BMPR2** gene is therefore described as **autosomal dominant inheritance** (see Genetics Fact Sheet 9).

In *Figure 56.1* the autosomal dominant faulty gene causing predisposition to primary pulmonary hypertension is represented by 'D'; the working copy by 'd'. Where one of the parents has **BMPR2** (or is predisposed to primary pulmonary hypertension) due to the faulty **BMPR2** gene, there are four possible combinations of the genetic information that is passed on by the parents.

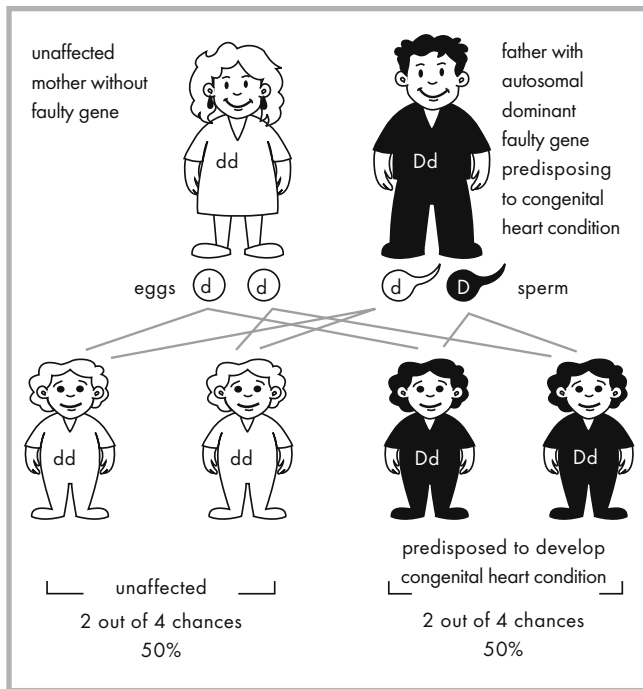


Figure 56.1: Autosomal dominant inheritance when one parent has the faulty gene copy. The faulty gene copy is represented by 'D'; the working copy by 'd'.

This means that, in every pregnancy, there is

- An equal chance ie. 1 chance in 2 (or 50% chance) that their child will inherit a copy of the faulty *BMPR2* gene and will therefore be susceptible to primary pulmonary hypertension
- An equal chance ie. 1 chance in 2 (or 50%) that their child will inherit the correct copy of the gene from his/her affected parent as well as a working copy from his/her unaffected parent. In this case, the child will not be any more susceptible to hypertension than anyone in the community. Importantly, children who have not inherited the faulty gene cannot pass it on to their own children

While Figure 56.1 shows the father as the parent carrying the faulty *BMPR2* gene, the same situation would arise if it was the mother.

What can be done if an individual thinks he or she may be at risk for developing primary pulmonary hypertension?

'Predictive' genetic testing may be possible for those families where a member has been identified as having primary pulmonary hypertension due to a faulty *BMPR2* gene (see Genetics Fact Sheet 21).

Genetic testing however, is complex

- First the change in the *BMPR2* gene has to be identified in a family member affected with primary pulmonary hypertension
- Second, and only if a mutation is found, predictive genetic testing may be possible for other family members without primary pulmonary hypertension, to determine their risk of developing the condition

Genetic counselling can enable discussion of the availability, appropriateness and implications of such testing (see Genetics Fact Sheet 3).

Table 56.1: Risks for relatives of family members affected with a congenital heart condition

Family situation	Risk for the family member to be affected
General population risk	0.5% to 1%
For the brother or sister of first case in the family	2% to 3%
Where parent is affected: Father Mother	2% to 3% 5% to 6%
Where there are two affected brothers/sisters	10%
Where a brother or sister and parent are affected	10%
Where there are more than 2 affected first degree relatives (i.e. parent, brother/sister)	About 50%

Congenital heart defects

What is a congenital heart defect?

A congenital heart defect is an abnormality of the structure and/or function of the heart that is present at birth, affecting about 1 in every 100 newborn babies.

The abnormality may be so slight that the baby appears healthy for many years after birth while others are so severe that they are life threatening.

What is the chance of having a baby with a heart defect?

For everyone, the chance of having a child with a congenital heart condition is 0.5% (1 chance in 100).

- Relatives of a family member affected with a congenital heart condition are at increased risk for having a child with a congenital heart condition (see Table 56.1)
- Where there is a family history, risks for a family member having a congenital heart defect increases with the number of affected relatives and their degree of relatedness

What causes congenital heart defects?

In most cases, the cause is unknown.

In some cases both genetic and/or environmental factors cause congenital heart defects (see Genetics Fact Sheet 11).

While the environmental factors are largely unknown, it is clear that exposure of the mother to certain environmental factors increases the risk for a baby being born with a heart defect. These include:

- Contracting German measles (*rubella*) during the first three months of pregnancy
- Taking certain chemicals or drugs (called *teratogens*) during pregnancy such as high levels of alcohol, cocaine, lithium and other medications

Sometimes a congenital heart defect is part of a genetic condition due to a chromosomal abnormality such as Down syndrome (see Genetics Fact Sheet 28).

In a small number of cases the heart defect is inherited following a specific pattern of inheritance and is due to a change in

a single gene. The risk that a child will be born with a heart defect depends upon the type of defect, its cause and the family history of the condition. Familial conditions however, caused by a change in just one gene or changes in chromosomes are rare.

- The severity of the condition and the symptoms are highly variable perhaps because of the effects of 'modifier' genes and/or environmental influences
- Genetic counselling is important to identify a possible genetic cause (see Genetics Fact Sheet 3)

Inherited conditions of connective tissue with cardiovascular effects

A number of connective tissue conditions that follow a pattern of autosomal dominant inheritance are characterised by cardiovascular manifestations. These include Marfan syndrome and Ehlers Danlos syndrome Type 4.

(a) Marfan syndrome

Marfan syndrome affects about 1 individual in 10,000 in the general population.

Three major systems in the body are affected: the eyes (*ocular*), skeleton (the bones and supporting tissues called connective tissues) and the cardiovascular system. The effects include short sightedness (myopia); unusually long, slender limbs and fingers and joint hypermobility.

The cardiovascular problems that are the most life-threatening feature, affect a significant number of people with Marfan syndrome and include:

- A problem with the main artery of the body called the aorta causing problems with the heart muscle (cardiomyopathy), heart failure, and aortic rupture, associated with a breakdown of the elastic fibres in the aortic wall. Exercise and pregnancy, resulting in higher cardiac output, increases susceptibility to aortic rupture
- Problems with an important valve in the heart (mitral valve)

What causes Marfan syndrome?

The condition is caused by changes in the *FBN1* gene which contains the information for the protein called *fibrillin-1*, a major protein found in the aorta, the lens of the eye and in connective tissue of bone. In people with Marfan syndrome the *FBN1* gene is faulty.

- One of several hundred different changes may make the *fibrillin* gene faulty
- Approximately 15% of cases of Marfan syndrome are due to a spontaneous change (mutation) occurring for unknown reasons during or shortly after conception (*de novo* cases)

What is the pattern of inheritance of Marfan syndrome in families?

Two factors influence the pattern of inheritance of the faulty *fibrillin* gene causing Marfan syndrome in these families.

1. The *fibrillin* gene is located on chromosome 15, which is an autosome (one of the numbered chromosomes)

2. The effect of the change in the *fibrillin* gene is 'dominant' over the information in the working copy of the gene on the partner chromosome 15 (see Genetics Fact Sheets 1, 4 & 5)

The pattern of inheritance in families of the faulty *fibrillin* gene is therefore described as **autosomal dominant inheritance** as shown in *Figure 56.1* (also see Genetics Fact Sheet 9).

What can be done if an individual thinks he or she may be at risk of having Marfan syndrome?

A cardiologist may make a clinical cardiac assessment. Clinical genetics services provide counselling regarding implications for family members and discussion of genetic testing, if available (see Genetics Fact Sheet 3). Treatment involves drug therapy, appropriate preventive advice and regular eye examination.

(b) Ehlers Danlos syndrome type 4 (vascular type)

Ehlers Danlos syndrome is a group of conditions. Type 4 of the syndrome (vascular type) is rare.

Ehlers Danlos syndrome type 4 affects both the bones and connective tissues and cardiovascular system. It is characterised by hypermobility of skin and joints, skin fragility and bruising.

Spontaneous rupture of the aorta or of the large to medium-sized arteries may occur in an individual's 20s or 30s due to an abnormality in the walls of the arteries.

What causes Ehlers Danlos syndrome type 4?

The condition is caused by changes in a gene that contains the information for the cells to produce a component of *collagen*, a major protein in the skin, bones, and blood vessels (*collagen type 3*).

The changes make the *collagen type 3* gene faulty.

What is the pattern of inheritance of Ehlers Danlos syndrome type 4 in families?

Two factors influence the pattern of inheritance of the faulty collagen type 3 gene causing Ehlers Danlos syndrome type 4 in these families.

1. The collagen type 3 gene is located on chromosome 2, which is an autosome (one of the numbered chromosomes)
2. The effect of the change in the collagen type 3 gene is 'dominant' over the information in the working copy of the gene on the partner chromosome 2 (see Genetics Fact Sheets 1, 4 & 5)

The pattern of inheritance in families of the faulty collagen type 3 gene is therefore described as **autosomal dominant inheritance** as shown in *Figure 56.1* (also see Genetics Fact Sheet 9).

What can be done if an individual thinks he or she may be at risk for having Ehlers Danlos syndrome type 4?

A cardiologist can make a clinical cardiac assessment. Clinical genetics services provide counselling regarding implications for family members and discussion of genetic testing, if available (see Genetics Fact Sheet 3).

Other Genetics Fact Sheets referred to in this Fact Sheet: 1, 3, 4, 5, 9, 11, 21, 28, 53, 54, 55

Information in this Fact Sheet is sourced from:

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Edit history

June 2007 (7th Ed)

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Acknowledgements this edition: Gayathri Parasivam; Prof David Sullivan; Prof John Emery; A/Prof Sylvia Metcalfe

Previous editions: 2004, 2002, 2000, 1998, 1996, 1994

Acknowledgements previous editions: Mona Saleh; Bronwyn Butler; Prof David Sullivan; Prof David Khoury; Dr David Wilcken; Dr Tony Roscioli