

Important points

- Many forms of cardiovascular disease are caused by interruptions to the heart's normal contract-relax cycle and cause abnormally fast or unusually slow heart rates and changes in the waveform produced on an electrocardiogram (ECG)
- These conditions are called *cardiac arrhythmias*: the heart pumps less effectively; not enough blood reaches the brain and other vital organs. When the body's blood flow is inadequate, the person can faint or suffer chest pain
- The soundwave generated by the heart beat is divided into 'intervals' given the letters P, Q, R, S & T
- In some people, it takes longer for the electrical signal to activate and inactivate the lower chambers of their heart (the ventricles); described as a longer Q-T interval on the ECG – they have long QT syndrome (LQTS)
- Having a longer Q-T interval increases the risk for ventricular '*fibrillation*' which means that the heart cannot pump enough oxygen-rich blood to the rest of the body, causing the symptoms of LQTS which include fainting and in some cases, cardiac arrest and sudden death during or following exercise in otherwise fit and healthy young people
- LQTS usually develops during childhood, but may occur at any age and affects around 1 in 5000 people; it is an important cause of unexpected sudden death, especially in children and young adults
- Variations in the information in 12 different genes (*LQTS1-LQTS12*) that make the genes faulty (mutations) result in increased risk for developing this form of LQTS
- Individuals who have one faulty *LQTS* gene, and one working copy on their other partner chromosome, are carriers of the faulty gene for LQTS. ie. genetic carriers for LQTS. They are at increased risk for developing ventricular fibrillation leading to cardiac arrest and sudden death but may never do so unless other triggering factors are present that may include certain medications, illnesses that could result in low blood potassium levels and strenuous exercise
- The pattern of inheritance in families of the faulty gene(s) causing predisposition to LQTS is described as **autosomal dominant inheritance**.
 - When one of the parents has LQTS or is a genetic carrier for LQTS, **in every pregnancy** they have 1 chance in 2 (or 50% chance) of having a child who is at increased risk for LQTS
- The usual method of diagnosis of LQTS is by a cardiologist, involving ECG and exercise tests
- People with a strong family history of LQTS can seek advice from their local genetic counselling service (see Genetics Fact Sheet 3).
 - Genetic testing for mutations in the LQTS genes involves first identifying the mutation in a family member who has or had LQTS (**mutation search**) and may take considerable time
 - Second, and only if a mutation is found, testing may be possible for other family members without LQTS, to determine if they have inherited the faulty gene (**predictive genetic testing**)

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 of LQTS, 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 of LQTS, 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 meant by 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 all our genes in our cells and when one copy of a gene is faulty, it may not cause a problem as the other gene copy still sends the correct 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, 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

However, it is 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 role of genetics in predisposition to cardiovascular conditions where there is a problem with the electrical control of the heartbeat.

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

The heartbeat

The heartbeat is a sound generated by the contraction and relaxation rhythm of the four chambers of the heart: two atria and two ventricles (Figure 55.1). This sound is powered by an electrical signal (*impulse*). An average heart beats 100,000 times a day, pumping some 500 litres of blood through its chambers to the rest of the body and then back to the heart.

The electric signal, generated by the heart itself as it contracts, is produced by the flow of charged chemicals (potassium, sodium and calcium) called ions, within the cells of the heart. The ions flow in and out of the heart's cells through ion channels.

Doctors can record the electrical signal produced by the ions on a machine called the electrocardiogram (ECG, or EKG) by placing electrodes on the skin of the chest. The machine makes a tracing of the signal, called a waveform.

The different parts of the waveform are represented by the letters P, Q, R, S and T (Figure 55.2).

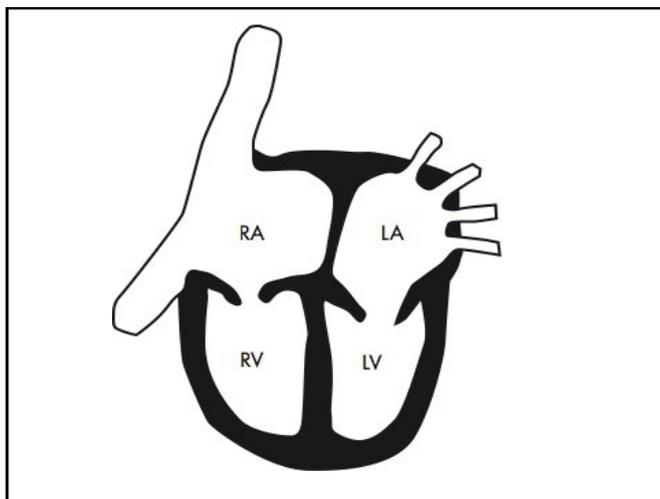


Figure 55.1: Normal heart. RA = right atrium, LA = left atrium, RV and LV = right and left ventricles.

Many forms of heart disease are caused by interruptions to the normal contract-relax cycle and cause abnormally fast or unusually slow heart rates and changes in the waveform produced on the ECG.

- These conditions are called *cardiac arrhythmias*: the heart pumps less effectively, so that not enough blood reaches the brain and other vital organs. When the body's blood flow is inadequate, the person can faint or suffer chest pain
- For example, by looking at the waveform, doctors can see the time it takes for the electrical signal to activate and inactivate the lower chambers of the heart (the ventricles). This is called the Q-T interval (Figure 55.2)

Long QT syndrome (LQTS)

What is long QT syndrome?

Long QT syndrome (LQTS) is a group of conditions where there is a longer QT interval on an ECG than usual. This prolonged Q-T interval can increase the risk for a type of arrhythmia that can lead to *ventricular fibrillation*: fast, chaotic heartbeats due to rapid, uncoordinated contractions in the muscle fibres of the ventricles.

Ventricular fibrillation means that the heart cannot pump enough oxygen-rich blood to the rest of the body, causing the symptoms of LQTS which include fainting (*syncope*) and, in some cases, cardiac arrest and sudden death.

This can occur during or following exercise in otherwise fit and healthy young people. LQTS is an important cause of unexpected sudden death, especially in children and young adults. Symptoms usually develop during childhood, but may occur at any age.

LQTS affects about 1 in 2500 people.

What causes long QT syndrome?

LQTS is a group of cardiac arrhythmias due to problems in the ion channels of the heart cells. The condition can be caused by more than 50 medications, many of them common, as well as part of other medical conditions.

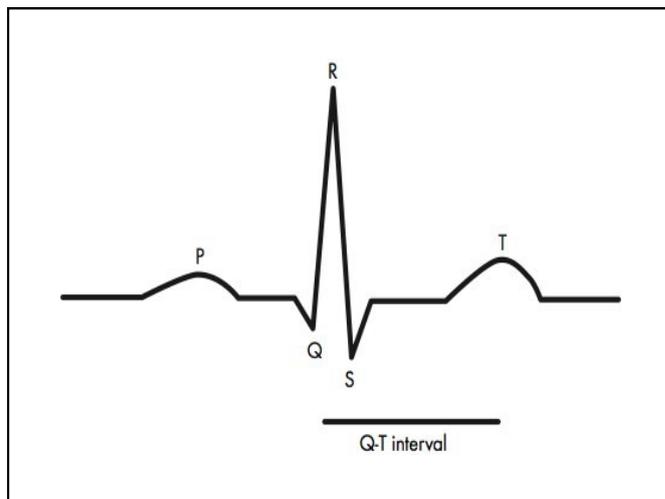


Figure 55.2: Normal heart signal as measured by an ECG. The Q-T interval is longer in long QT syndrome.

In other cases of LQTS there is an inherited predisposition. Variations in at least 12 genes (*LQTS1-LQTS12*) have been identified as causing predisposition to LQTS. The condition however may never develop unless triggered by environmental factors. These factors may include certain medications, illnesses that could result in low blood potassium levels and strenuous exercise.

What is the pattern of inheritance of long QT syndrome in families?

A variation in one of 12 different genes that make the gene faulty results in an increased risk for the most common form of LQTS to develop. If a person has one faulty *LQTS* gene copy and the other partner *LQTS* gene copy is working, they are carriers of the faulty *LQTS* gene: they are genetic carriers for LQTS.

- Genetic carriers for LQTS are susceptible (predisposed) to ventricular fibrillation leading to cardiac arrest and sudden death
- Just having a faulty *LQTS* gene copy is not enough for the syndrome to develop

Two factors influence the pattern of inheritance of LQTS in affected families.

1. The 12 different genes are all located on autosomes (one of the numbered chromosomes)
2. The effects of variations which make the gene in the genes involved faulty 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 LQTS is therefore described as **autosomal dominant inheritance** (see Genetics Fact Sheet 9).

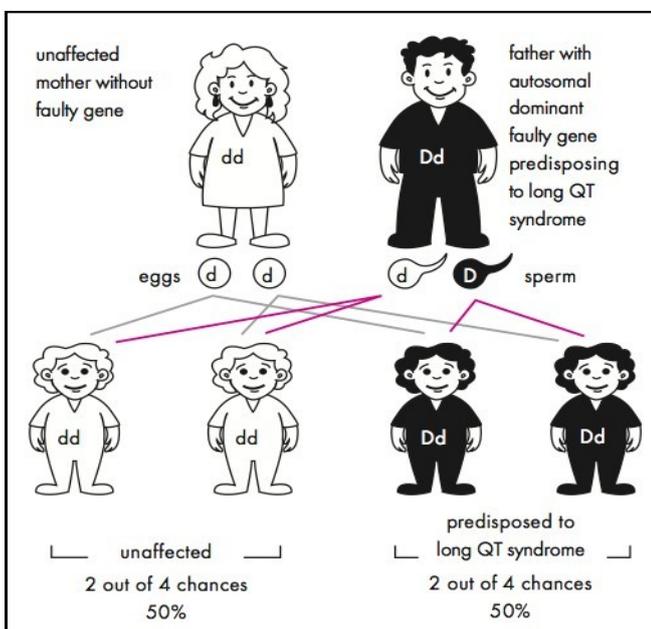


Figure 55.3: Autosomal dominant inheritance when one parent has a faulty Long QT syndrome (*LQTS*) gene copy. The faulty Long QT syndrome (*LQTS*) gene copy is represented by 'D'; the working copy by 'd'.

In *Figure 55.3* the autosomal dominant faulty gene causing predisposition to LQTS is represented by 'D'; the working copy by 'd'. Where one of the parents has LQTS (or is predisposed to LQTS) due to faulty *LQTS* gene, there are four possible combinations of the genetic information that is passed on by the parents.

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 *LQTS* gene and will therefore be susceptible to the syndrome and cardiac arrest
- An equal chance ie. 1 chance in 2 (or 50%) that their child will inherit the working 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 cardiac arrhythmia than anyone in the community

While *Figure 55.3* shows the father as the parent carrying the faulty *LQTS* gene, the same situation would arise if it was the mother. A faulty *LQTS* gene can be inherited from either the mother or the father.

Can a person determine if they have inherited a faulty *LQTS* gene?

The usual method of diagnosis of LQTS is by a cardiologist, involving ECG and exercise tests. Treatment may include drug therapy; an implantable defibrillator may be indicated for some individuals.

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

The genetic counselling team may be able to:

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

Genetic testing for mutations in the *LQTS* genes involves:

- **First**, identifying the variation that is making the gene faulty (a mutation) in a family member who has or had LQTS. 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).

Other Genetics Fact sheets referred to in this Fact Sheet: 1, 3, 4, 5, 9, 11, 21, 53, 54, 56