

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

In summary

- There are three main types of primary arrhythmogenic disorders:
 - ◇ Long QT syndrome (LQTS)
 - ◇ Brugada syndrome (BrS)
 - ◇ Catecholaminergic polymorphic ventricular tachycardia (CPVT)
- Heart palpitations, dizziness and fainting/blackouts, cardiac arrest and sudden cardiac death are all possible symptoms of a primary arrhythmogenic disorder or another genetic heart disease.
- First-degree relatives (parents, siblings and children) of an individual who has a primary arrhythmogenic disorder are usually at a 50% risk of also developing the condition.
- Cardiac arrest and sudden cardiac death can be a complication of primary arrhythmogenic disorders therefore it is very important that everyone with a family history be seen by a cardiologist and considers genetic testing where available.

WHAT ARE PRIMARY ARRHYTHMOGENIC DISORDERS?

Arrhythmia refers to an abnormal rhythm of the heart which can lead to ineffective pumping of blood around the body. These arrhythmias can be of many different types and can occur for many different reasons. If they develop spontaneously they are known as **primary arrhythmias**, or if they are a result of another condition such as structural heart disease they are known as **secondary arrhythmias**. Therefore a **primary arrhythmogenic disorder** is a condition in which abnormal heart rhythms develop in otherwise healthy individuals without prior warning.

These disorders can be **idiopathic**, meaning that they occur for no known reason, or **inherited**, meaning that they have an underlying genetic cause. Arrhythmias may affect the lower chambers of the heart, known as **ventricles**, or the upper chambers known as **atria** (Figure 58.1). Terms used to describe abnormal heart rhythms may include **tachycardia** (beating very fast), **bradycardia** (beating very slow), or **fibrillation** (rapid, unco-ordinated beating).

The heart rhythm is generated by the heart itself via electrical signals or **impulses**. These are 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 an **electrocardiogram (ECG)** 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 58.1).

Interruptions to the heart's electrical impulses cause the normal contraction-relaxation cycle of the heart to become abnormal, resulting in arrhythmias that may make the heart beat unusually fast, unusually slow or very irregularly.

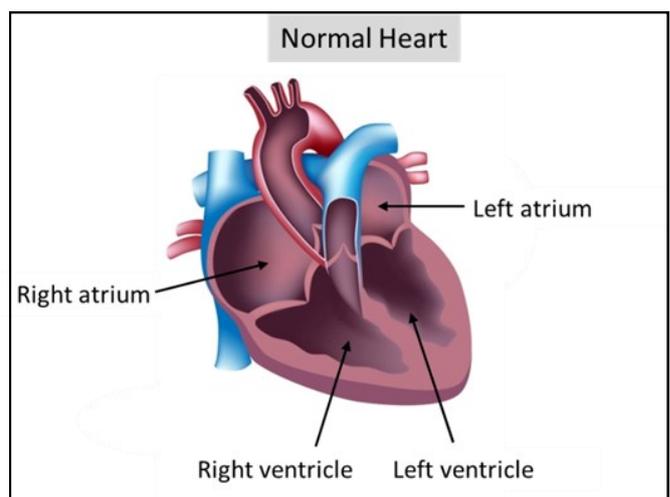


Figure 58.1: Healthy human heart showing lower chambers known as ventricles, and upper chambers known as atria. Adapted from the Australian Genetic Heart Disease Registry <http://www.heartregistry.org.au/>

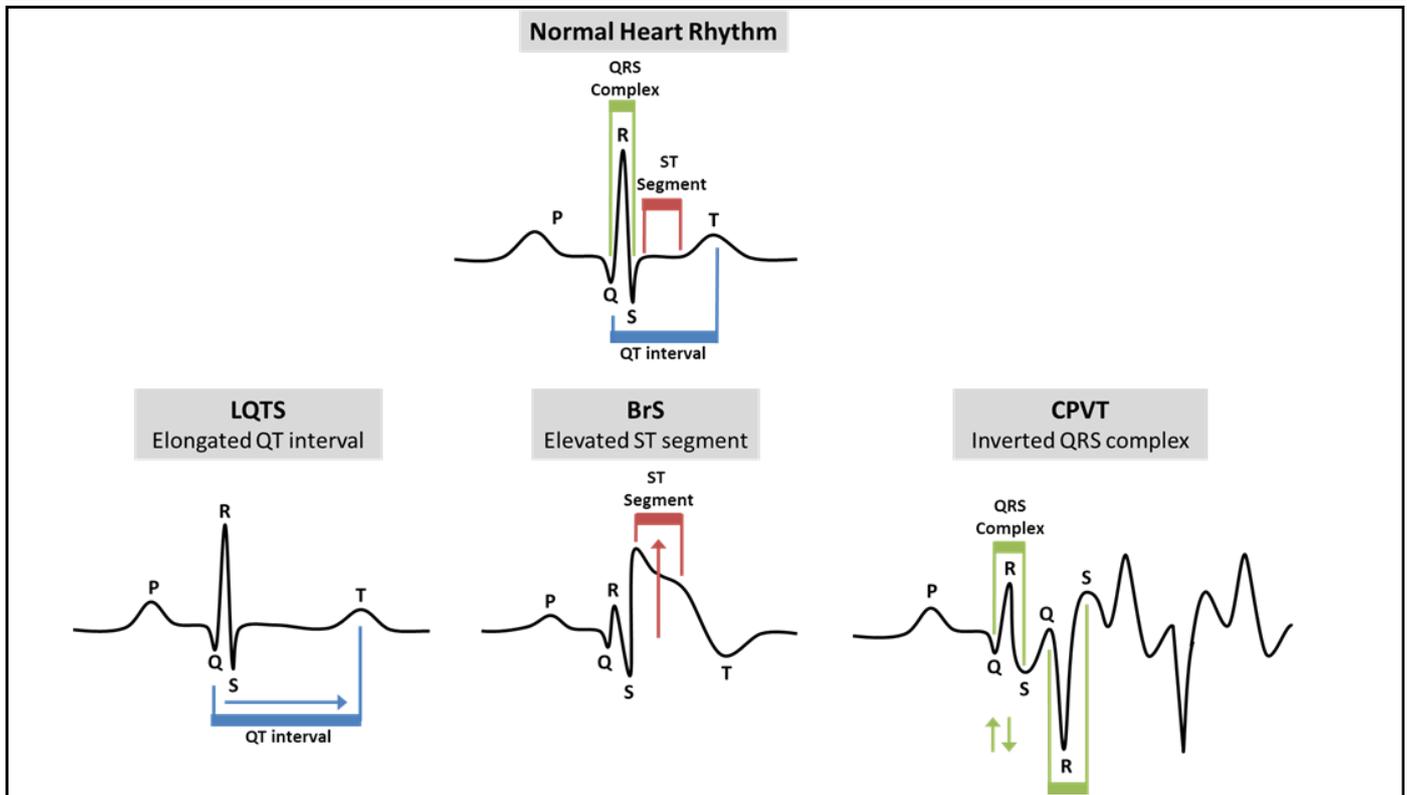


Figure 58.2: ECG patterns seen in primary arrhythmogenic disorders

There are three main inherited primary arrhythmogenic disorders:

1. **Long QT syndrome (LQTS)**
2. **Brugada syndrome (BrS)**
3. **Catecholaminergic polymorphic ventricular tachycardia (CPVT)**

Some common aspects across these three conditions include:

- They all affect the rhythm of the heart but differ in the type of arrhythmia they produce and what triggers these abnormal rhythms
- They may present with common symptoms such as palpitations, dizziness, chest pain and fainting
- Each carries a small but significant risk of cardiac arrest or sudden cardiac death if undiagnosed and untreated
- Close relatives of an individual with a primary arrhythmogenic disorder have a 1 in 2 (50%) chance of also being affected and should have regular cardiac screening
- Genetic testing is available in some, but not all cases and can help to clarify who in the family is at risk
- Some affected individuals can have no symptoms but should have regular screening and check-ups with a cardiologist.

1. Long QT syndrome (LQTS)

Long QT syndrome (LQTS) is a condition 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 known as **ventricular fibrillation** meaning fast, chaotic heartbeats due to rapid, uncoordinated contractions 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.

2. Brugada syndrome (BrS)

BrS is a condition in which the ventricles of the heart beat abnormally fast and irregularly and this can affect the blood supply around the body. This can cause heart palpitations, dizziness and fainting if the arrhythmia persists for only a short time, or may cause cardiac arrest or sudden death if the arrhythmia is not corrected. Diagnosis is made by detection of a characteristic arrhythmia on ECG – called a type 1 Brugada ECG pattern – in which the ST segment is elevated.

Certain drugs are known to exacerbate symptoms and should be avoided. Fever is also a risk factor and may trigger abnormal heart rhythms.

3. Catecholaminergic polymorphic ventricular tachycardia (CPVT)

CPVT is a condition in which arrhythmias are triggered by physical or emotional exertion. A characteristic ECG pattern known as **polymorphic ventricular tachycardia** is used to diagnose CPVT. In particular, **bidirectional ventricular tachycardia** is a type of polymorphic ventricular tachycardia in which the QRS complex flips on each alternating beat to form a unique M-shaped pattern.

WHAT CAUSES PRIMARY ARRHYTHMOGENIC DISORDERS?

LQTS, BrS and CPVT are all caused by changes in genes that control ion channels and are sometimes referred to as **cardiac ion channelopathies**.

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. Long QT Syndrome (LQTS)

LQTS can be caused by mutations in around 15 different genes, with the most commonly implicated genes being *KCNQ1* (LQTS type 1), *KCNH2* (LQTS type 2), and *SCN5A* (LQTS type 3). These genes are involved in making the ion channels that are involved in the electrical impulses controlling our heart rhythm. Mutations result in altered structure or function of these channels and impacts on the flow of ions, such as sodium and potassium, between cells – this changes how cells can communicate and results in arrhythmia.

2. Brugada Syndrome

The most common causative gene is *SCN5A*, which is also a LQTS gene. This gene provides instructions for making a sodium channel, which normally transports positively charged sodium ions into heart muscle cells. Mutations change the structure and function of sodium channels and leads to arrhythmia.

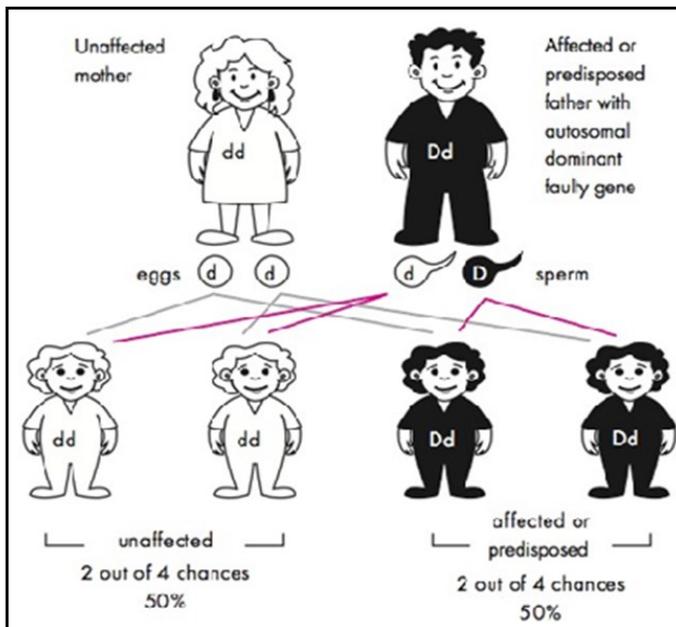


Figure 58.3: Autosomal dominant inheritance when one parent carries the autosomal dominant faulty gene copy. The autosomal dominant faulty gene copy is represented by 'D'; the working copy of the gene by 'd'.

3. Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

Five genes are currently implicated in CPVT with the greatest contribution from *RYR2*, which accounts for almost 90% of cases, and is associated with calcium ion channels. Mutations in CPVT genes leads to inappropriate calcium handling within heart muscle cells, and during times of physical or emotional exertion this can lead to inappropriately rapid contraction of the heart and arrhythmia.

HOW ARE PRIMARY ARRHYTHMIC DISORDERS INHERITED?

Most primary arrhythmogenic disorders 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 58.3*). For every pregnancy in this situation there is:

- 50% chance that a child, either male or female, will inherit only working copies of a gene from each of their parents and be healthy
- 50% chance that they will inherit one copy of the faulty gene, and one working copy and have a primary arrhythmogenic disorder.

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

Some Exceptions

LQTS, BrS and CPVT can all be inherited in the autosomal dominant pattern explained above, however 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 primary arrhythmia may be inherited or passed on in their family.

IS THERE ANY TESTING AND TREATMENT AVAILABLE FOR PRIMARY ARRHYTHMOGENIC DISORDERS?

Clinical Testing

Primary arrhythmogenic disorders are diagnosed through clinical tests which look at the heart rhythm (electrocardiogram, ECG).

Sometimes a stimulus, like a drug infusion or exercise, is needed to unmask arrhythmias in affected individuals.

Because most primary arrhythmogenic disorders 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.

The benefit of genetic testing is to conclusively identify family members that have inherited a primary arrhythmogenic disorder so that they can receive the appropriate cardiac care.

While those that are found to not carry the familial mutation can be released from regular cardiac screening and are not at any increased risk.

Genetic Testing

Genetic testing to identify the causative mutation in a family may be available, however 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 which is called **predictive testing**.

If a mutation cannot be found, no further genetic testing can be offered in the family and all first-degree relatives should see a cardiologist for regular cardiac review.

Currently, there are significant limitations to genetic testing technologies 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). Where possible, these options are best discussed and considered before pregnancy, in order to ensure all possible risks, benefits and outcomes are explored.

Treatment Options

In some cases, affected individuals and gene carriers may recommend you to take a medication called a beta blocker, 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. This is a small device (like a pacemaker) which is surgically implanted in the chest wall. The ICD will monitor your heart rhythm and if it detects an abnormal (life threatening) heart rhythm will deliver an shock to 'reset' the heart rhythm back to normal. For BrS and LQTS additional treatment recommendations include avoidance of drugs known to exacerbate symptoms. A list of these drugs can be found at:

- www.brugadadrugs.org
- www.qtdrugs.org

It is important if you have a diagnosis of BrS or LQTS to check all medications on this list prior to taking them, this includes over the counter cold and flu medication. If in doubt you should consult your cardiologist or pharmacist.

Fever is known to aggravate Brugada syndrome. Therefore fever should be aggressively treated with paracetamol.

For CPVT a procedure known as left cardiac sympathetic denervation may be indicated and should be discussed with your cardiologist. This procedure is also sometimes considered in other arrhythmogenic disorders particularly when patients are unresponsive/ intolerant to beta blockers.