

This fact sheet describes the genetic condition cystic fibrosis and includes the symptoms, cause and any treatment or testing which is available.

In summary

- Cystic fibrosis (CF) is a genetic condition that causes respiratory and/or digestive problems
- CF is caused by mutations in the *CFTR* gene on chromosome 7 and is inherited in an autosomal recessive pattern
- Genetic carriers for cystic fibrosis have one faulty copy and one working copy of the *CFTR* gene, and do not display symptoms of the condition.

WHAT IS CYSTIC FIBROSIS?

Cystic fibrosis (CF) is a genetic condition that affects many organs in the body: especially the lungs, pancreas and sweat glands. A build-up of thick, sticky mucus in these organs leads to respiratory problems, incomplete digestion and increased salt loss from the sweat glands.

How CF affects people is highly variable, even within families. Generally, however:

- In the lungs, the mucus that is produced is thick and sticky, clogging the small air passages and encouraging bacteria to grow. Repeated infections and blockages can cause severe lung damage
- The ducts from the pancreas to the intestine can also become blocked. Normally, these ducts carry enzymes that are important for the digestion of food. Incomplete digestion results in weight loss in spite of a hearty appetite
- The sweat glands also secrete sweat that is very high in salt, thereby depleting the body of this important substance.

Daily physiotherapy to reduce the load of mucus in the lungs and taking enzyme and nutrient supplements slow down the progression of the condition. As a result of early diagnosis and treatment, 50% of those with CF now live into their fourth decade but the condition can severely affect their quality of life.

About 1 in every 2,500 babies, male or female, is born with cystic fibrosis in Australia and New Zealand each year.

Cystic fibrosis affects most commonly people who are of Northern European or UK descent, fairly frequently people whose ancestry is Southern European and Middle Eastern populations, but is rare where the ancestry is Asian.

WHAT CAUSES CYSTIC FIBROSIS?

The gene involved in cystic fibrosis is called the *CFTR* gene, located on chromosome 7. This gene makes an important protein that transports salt in and out of our cells (the 'salt-transport' protein). We all have two copies of the *CFTR* gene, and in most of us both copies of the *CFTR* gene is functioning normally.

For some people, one copy of the *CFTR* gene has a mutation, whilst the other copy is still functioning normally. Because at least one copy of the *CFTR* gene is working properly, they will still produce sufficient amounts of the salt-transport protein for the body to function normally, and are known as **genetic carriers** for cystic fibrosis. Genetic carriers for cystic fibrosis will not have any signs or symptoms of the condition.

To be **affected** with cystic fibrosis, both copies of the *CFTR* gene must be faulty. Without a working copy of the *CFTR* gene, the body is unable to produce the important salt-transport protein, resulting in the build-up of thick, sticky mucus characteristic of cystic fibrosis.

The *CFTR* gene is a long instruction and there are over 1,500 different variations that may impact on the function of the gene to varying degrees. The most common variation is called **Phe508del**, and is found in about 75% of people affected with cystic fibrosis in Australia. Other variations are much rarer, and some combinations may result in a milder form of cystic fibrosis. For example, a combination of two milder CF variations may result only in male infertility, caused by *congenital bilateral absence of the vas deferens (CBAVD)*.

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.

HOW IS CYSTIC FIBROSIS INHERITED?

Cystic fibrosis is a genetic condition that follows a pattern of **autosomal recessive inheritance**. Autosomal refers to the fact that the *CFTR* gene is located on chromosome 7, which is one of the numbered chromosomes, and therefore affects males and females equally. Recessive means that, in order to develop signs and symptoms of the condition both copies of the *CFTR* gene must be faulty.

If a couple are both genetic carriers for CF (Figure 41.1), in every pregnancy there is:

- 1 chance in 4 (25% chance) that they will have a child who inherits both copies of the recessive gene mutation from his/her parents. In this case, no working gene product will be produced and their child will be affected by CF
- 1 chance in 4 (25% chance) that their child will inherit both copies of the working gene and will be unaffected by CF and not a genetic carrier
- 1 chance in 2 (2 chances in 4 or 50% chance) that their child will inherit the recessive gene mutation and the working copy of the gene from the parents and he/she will be an unaffected genetic carrier for CF, just like the parents.

If only one parent is found to be a carrier for CF (Figure 41.2) in every pregnancy there is:

- Very low risk that the couple will have a baby affected with CF. However, we cannot exclude the risk entirely as sometimes the other parent may be a genetic carrier for CF that was not identified via genetic screening
- 1 chance in 2 (2 chances in 4 or 50% chance) that their child will inherit the recessive gene mutation and the working copy of the gene from the parents and he/she will be an unaffected genetic carrier for CF
- 1 chance in 2 (2 chances in 4 or 50% chance) that they will have a child who inherits both copies of the working gene from his/her parents. In this case, the child will be unaffected by CF.

What does it mean to be a genetic carrier?

On average about 1 in 25 Australians and New Zealanders are genetic carriers for CF but they are more likely to be a carrier if they are of Northern European descent.

- Being a genetic carrier for CF is not like being a carrier of an infectious virus such as hepatitis where the hepatitis virus is carried in the body and can be passed on through contact
- Genetic carriers for CF can however pass the faulty gene on to their children through the egg or sperm cells.

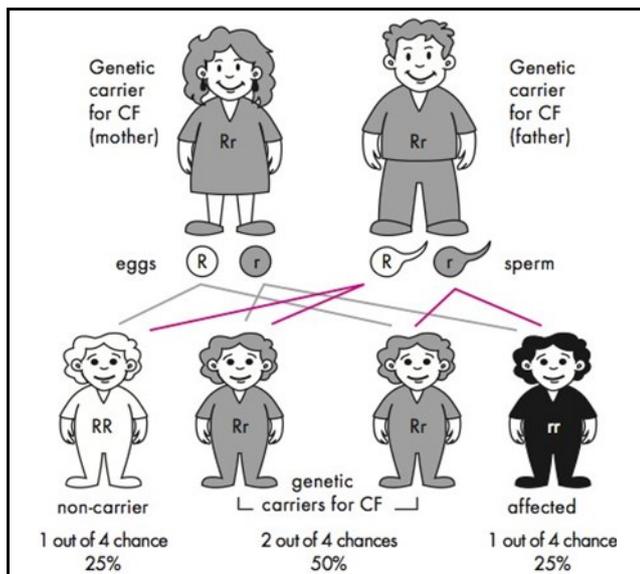


Figure 41.1: Autosomal recessive inheritance where both parents are genetic carriers of the faulty *CFTR* gene. The faulty *CFTR* gene is represented by 'r'; the working copy by 'R'.

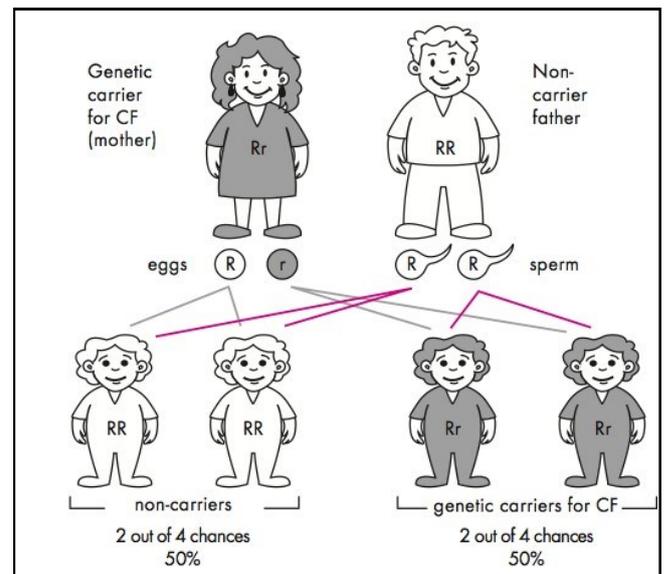


Figure 41.2: Autosomal recessive inheritance where only one parent is a genetic carrier of the *CFTR* gene. The faulty *CFTR* gene is represented by 'r'; the working copy by 'R'.

There are several theories as to why there are a high number of genetic carriers for CF who are of Northern European ancestry. One interesting theory is that being a genetic carrier for CF provides protection against cholera, an infectious disease causing diarrhoea due to unclean water. When people live in unsanitary overcrowded circumstances as occurred during European history, cholera would have spread uncontrollably. People living in Europe at this time who were genetic carriers for CF had a better chance of surviving cholera and childhood mortality.

IS THERE ANY TESTING AVAILABLE FOR CYSTIC FIBROSIS?

Diagnostic Testing

If a person shows symptoms of cystic fibrosis, then a **sweat chloride test**, or sweat test, will be performed to confirm the diagnosis. A sweat test is a simple, painless test that measures the concentration of chloride in a person's sweat. Increased levels of chloride in a sample of sweat indicate that a person is affected with cystic fibrosis.

Once a person is diagnosed with cystic fibrosis, genetic testing may be performed to confirm the diagnosis. This involves a blood test (or cheek swab sample) to look for mutations within the *CFTR* gene.

An affected person will have two mutations identified, one in each copy of the *CFTR* gene. Genetic testing may involve either a mutation panel screen, where only the more common gene mutations are tested for, or a full gene sequencing test where the whole *CFTR* gene is sequenced to look for possible mutations. Your healthcare practitioner will explain the test that is available to you.

Newborn Screening

All children born in Australia and New Zealand are offered newborn screening, which includes a screening test for cystic fibrosis. A positive result on newborn screening indicates that a child *may* be affected by cystic fibrosis, and further tests are required to confirm or exclude the diagnosis.

Testing for carrier status

Genetic testing for carrier status is available for individuals who have a family history of cystic fibrosis. Usually only the mutation identified in the family will be tested. If somebody is identified as a genetic carrier, then carrier testing may be offered to their partner when they are planning a family. Carrier screening for people who don't have a family history may involve either a mutation panel screen, where only the more common gene mutations are tested for, or a full gene sequencing test, where the whole *CFTR* gene is sequenced to look for possible mutations. Mutation panel screens can only *reduce* the risk that a person is a carrier for cystic fibrosis, as not all mutations are tested for.

Prenatal testing and PGD

For couples who are both known genetic carriers for CF, testing may be available during a pregnancy to determine whether the baby will be unaffected, affected or a genetic carrier for CF. It may also be possible to undergo **pre-implantation genetic diagnosis** (PGD) screening for CF 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 can be explored.