

Important points

- 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
- The thick and sticky mucus is caused by a problem with the transport of salt across the cells of the lungs and pancreas
- As a result of early diagnosis and treatment, over 50% of those with CF now live into their 4th decade but the condition can severely affect their quality of life
- CF most commonly affects people who are of Northern European or UK descent, and is also fairly frequent in people whose ancestry is Southern European and Middle Eastern, but is rare or absent where the ancestry is Asian
- About 1 in every 2,500 babies, male or female, are born with CF in Australia or New Zealand each year
- Everyone has **two copies** of the gene that contains the information for the production of the protein that transports salt in and out of the cells. This gene can be thought of as the 'salt-transport' gene and is called the CFTR gene
- Individuals with CF have **faulty copies of both their salt-transport genes**: they cannot produce the important salt-transport protein
- Individuals who have one working copy of the salt-transport gene and one that is faulty are called 'carriers' of the change that makes the gene faulty ie. **genetic carriers for CF**
- Genetic carriers for CF do not have CF because they can still produce enough salt-transport protein
- About 1 in 25 Australians are genetic carriers for CF
- The pattern of inheritance in families of the faulty gene causing CF is described as **autosomal recessive inheritance**
- When **both parents** are carriers of the faulty gene, they have 1 chance in 4 (or 25% chance) in every pregnancy of having a child with CF
- If only **one parent** is a carrier of the faulty gene, they will not have a child with CF
- All babies in Australia are screened for CF shortly after birth
- Genetic **testing** to determine if a person is a carrier of the faulty CFTR gene may be available pre-pregnancy and in pregnancy and is appropriate when there is a family history of CF or a blood relative is a genetic carrier for CF
- Genetic **screening** may also be available as part of pre-pregnancy planning for those people with a high chance of being a genetic carrier for CF based on their ancestry. The screening will only pick up those who are carriers of one of the more common changes in the CFTR gene
- Where both parents are genetic carriers, they can find out information about the condition, their chance of having an affected child and discuss their reproductive options with a genetic counsellor (see Genetics Fact Sheet 3)

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.

CF 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 or absent where the ancestry is Asian.

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What are the characteristic features of cystic fibrosis (CF)?

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 lessen 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 4th decade but the condition can severely affect their quality of life.

What causes CF?

The cells of the body contain information, in the form of genes, for the body to make all the necessary structural components and chemicals to ensure normal function (see Genetics Fact Sheet 1).

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).

The information for our cells to make an important protein that transports salt in and out of our cells (the 'salt-transport' protein) is contained in a gene located on chromosome number 7. This gene is called the CFTR gene.

We all have two copies of chromosome number 7 in all our body cells and therefore two copies of the gene that codes for the protein that removes the salt.

- Everyone therefore has two copies of the 'salt-transport' gene ie. the CFTR gene, in their body cells.

As there are two copies of each gene, if a person has a change in one copy of their CFTR gene, and the other is a working copy, they will still produce sufficient amounts of the salt-transport protein for normal body function

- Individuals who have one working copy of the salt-transport gene and one that is faulty are called 'carriers' of the variation that makes the gene faulty or '**genetic carriers for CF**'
- Genetic carriers for CF do not have cystic fibrosis because they can still produce enough salt-transport protein
- Individuals with **CF have faulty copies of both their CFTR genes** cannot produce the important salt-transport protein. When the CFTR gene is faulty, it is sometimes called the CF gene.

What does it mean to be a genetic carrier for CF?

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 (including from the United Kingdom).

- Individuals who are genetic carriers for CF have one working copy of their *CFTR* gene and one copy that is faulty in every cell
- 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
- Genetic carriers for CF do not carry CF in their bodies and cannot pass it on to others like a virus. They can however, pass the faulty gene on to their children as described below

There are several theories as to why the number of Australians affected with the condition, and therefore the number of genetic carriers for CF is high in people who are of Northern European ancestry.

- Once a variation occurs in a gene contained in an egg or sperm cell, the faulty gene may be passed down through the generations of a family
- One theory is that geographic barriers would have meant that people from close villages who had the faulty gene were more likely to have children together and this would have kept the change in the *CFTR* gene within the local populations. There would be a higher chance of both parents being genetic carriers for CF. Therefore the number of children born with CF, and the number who are genetic carriers for CF (just like the parents) would increase
- Another theory is that being a genetic carrier for CF provides protection against cholera, an infectious disease due to unclean water, and it also leads to less diarrhoea in childhood. 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 would have had a better chance of surviving cholera and childhood mortality, and be able to have children of their own

How does a person inherit CF?

CF is a genetic condition (see Genetics Fact Sheet 2). Therefore it is passed from parents to children in their genes.

Two factors influence the pattern of inheritance of the faulty salt-transport gene causing CF in families.

1. The *CFTR* gene is located on chromosome 7, an autosome (one of the numbered chromosomes)
2. The effect of the change in the gene is 'recessive' or hidden by the presence of the working copy of the gene (see Genetics Fact Sheets 1, 4 & 5)

The pattern of inheritance in families of the faulty gene causing CF is therefore described as **autosomal recessive inheritance** (see Genetics Fact Sheet 8).

In *Figures 33.1* and *33.2* which illustrate the pattern of inheritance, the faulty *CFTR* gene is represented by 'r'; the working copy by 'R'. There are four possibilities, **in every pregnancy**, for the combinations of genes passed from the parents.

As shown in *Figure 33.1*, **if a couple are both carriers** of the *CFTR* gene, in every pregnancy there is a

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

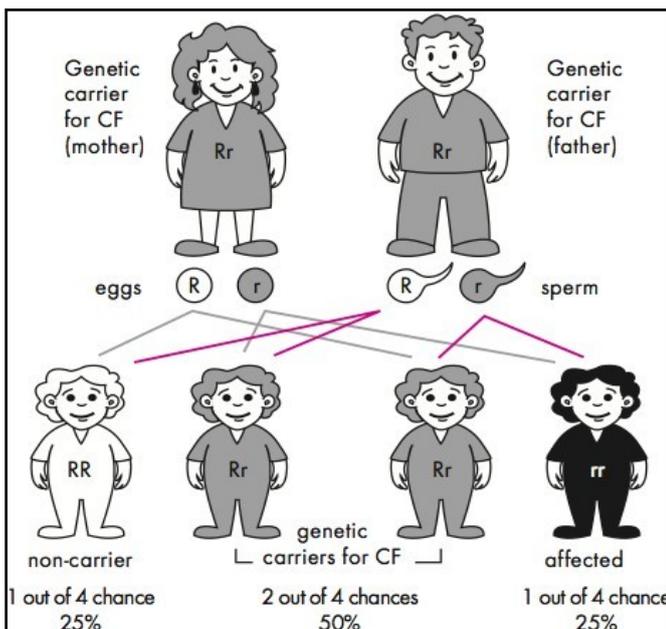


Figure 33.1: Autosomal recessive inheritance where both parents are carriers of the faulty salt-transport *CFTR* gene. The faulty salt-transport gene copy is represented by 'r'; the working copy by 'R'.

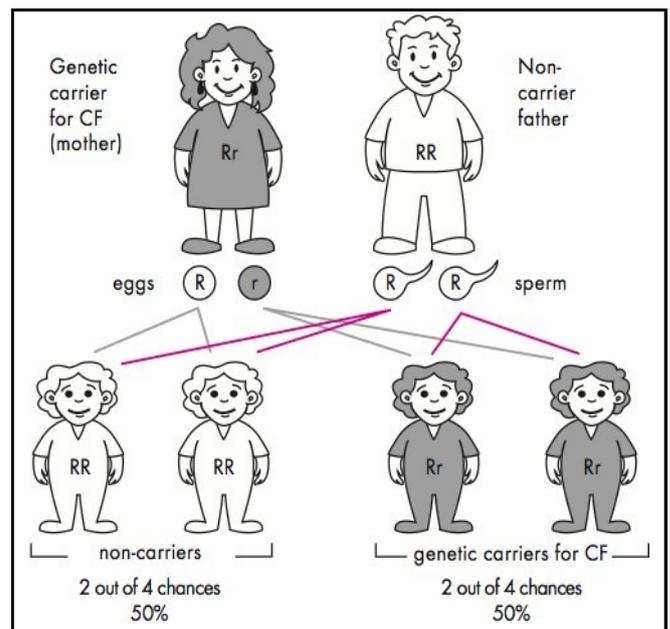


Figure 33.2: Autosomal recessive inheritance where only one parent is a carrier of the faulty salt-transport *CFTR* gene. The faulty salt-transport gene *CFTR* represented by 'r'; the working copy by 'R'.

If on genetic testing however, only one parent is found to be a carrier of the faulty *CFTR* gene (Figure 33.2) in every pregnancy

- It is unlikely that the couple will have a baby affected with CF
- 1 in 2 chance (ie. 2 chances in 4) or 50% that the baby will be an unaffected genetic carrier for CF, just like his/her parents

What is the variation in the salt-transport gene that causes CF?

The salt transport gene that causes CF is called the *CFTR* gene

- The most common variation that makes the *CFTR* gene faulty (mutation) is found in about 75% of people affected with CF in Australia.
 - The common *CFTR* gene mutation is called the $\Delta F508$ (deltaF508) mutation. This means that, at position 508 along the gene's length, there is a deletion of a code word for phenylalanine, an amino acid, which is one of the building blocks of the protein responsible for removing salt from the cells. For more information about changes in the genetic code, see Genetics Fact Sheets 4 & 5
- There are however over 1,500 other rarer changes that in some way impact upon the function of the *CFTR* gene that have been identified at different places along the length of this gene
 - Some combinations of changes may result in a milder form of CF. For example, a cause of male infertility (*congenital bilateral absence of the vas deferens*, CBAVD) can result from various combinations of uncommon changes within the *CFTR* gene

Changes in other unknown gene(s) appear to modify the impact of the faulty *CFTR* gene, contributing to the variability in expression of the features of CF, even within families.

How is CF detected?

Newborn screening

In Australia, every newborn baby is screened for the presence of several inherited conditions of which CF is one. A small blood sample is taken from the baby's heel in the first few days after birth and sent to a Newborn Screening Laboratory for analysis. Newborn screening will detect the majority (95%) of babies born with CF in Australia (see Genetics Fact Sheets 20).

- This screening test, in conjunction with genetic testing, can determine if the baby has both copies of his or her *CFTR* gene altered by the common mutation (*df508*). These babies will have CF
- Babies who have only one copy of their salt-transport protein gene changed by this common mutation may also give a positive result on the screening test. The babies will be given diagnostic test called 'sweat testing' in which the salt content of the baby's sweat is measured to determine if they have CF
- Some of these babies:
 - **Will not be diagnosed** with cystic fibrosis with sweat testing. While they only have one of their gene copies has the common mutation, the other partner gene copy has one of the many rarer mutations. These changes mean that both of their *CFTR* gene copies send a wrong message to the cells so that the essential protein will not be produced by the cells at all, or in enough quantity, and the baby is affected with the condition

- **Will not be diagnosed** with CF with sweat testing. These babies are genetic carriers for CF and do not have the condition. Although these babies are usually unaffected with CF, the families should seek genetic counselling regarding their risk for having children affected with the condition as both parents may be genetic carriers and, by chance, did not have an affected baby (see Genetics Fact Sheet 3)

In other cases

If a person has clinical symptoms of CF (regardless of whether newborn screening was done at birth) a sweat test may be done to clarify the presenting condition.

In investigations of male infertility, CF may be diagnosed where it affects sperm production.

How can a person find out if they are a genetic carrier for CF?

There is an increased chance that someone is a carrier of a faulty salt-transport *CFTR* gene (ie. a genetic carrier for CF) if they have a family history of CF or a blood relative who is known to be a genetic carrier for CF.

Genetic testing to determine if a individual is a carrier of the faulty gene running in the family may be available and can be discussed with their doctor or a genetic counsellor (see Genetics Fact Sheet 3).

Genetic **screening** may also be available for those individuals with a high chance of being a genetic carrier for CF based on their ancestry, even if there is no family history of the condition. The screening test looks at the information in the *CFTR* gene in an individual's DNA obtained from a sample of their cheek cells using a swab and will only pick up those who are carriers of one of the more common changes in the *CFTR* gene (see Genetics Fact Sheet 21).

How can knowing about having the faulty CF gene help?

If both partners in a couple are genetic carriers for CF, they can find out information about the condition, their chance of having a child with CF and discuss their reproductive options with a genetic counsellor (see Genetics Fact Sheet 3).

Prenatal testing for CF in pregnancy is possible if both parents have been identified as genetic carriers for CF (see Genetics Fact Sheet 17C).

It may also be possible to undergo preimplantation genetic diagnosis (PGD) screening for CF on an embryo created using in vitro fertilisation (IVF). If the embryo does not have the condition it may be transferred to the uterus and allowed to develop normally (see Genetics Fact Sheet 18).

Other Genetics Fact Sheets referred to in this Fact Sheet: 1, 2, 3, 4, 5, 8, 17C, 18, 20, 21

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