Fact sheet **41**

CYSTIC FIBROSIS

This fact sheet talks about the genetic condition cystic fibrosis and includes details about the symptoms, causes and any treatments or testing available.

IN SUMMARY

- Cystic fibrosis (CF) is a genetic condition that causes respiratory and/or digestive problems
- CF is caused by variations in the *CFTR* gene on chromosome 7, and follows an autosomal recessive pattern of inheritance
- Genetic carriers for cystic fibrosis have one non-working copy and one working copy of the *CFTR* gene, and do not show symptoms of the condition
- Couples where both partners are genetic carriers for CF have a 1 in 4 (25%) chance of having a baby with the condition.

WHAT IS CYSTIC FIBROSIS?

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

CF is a highly variable condition with some experiencing more severe symptoms and others a milder form of the condition. This may be to do with the particular genetic causes that the person has, treatments they have and other unknown reasons. Even amongst siblings with the same genetic cause for CF, there may be some degree of variability. 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. Usually, 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.

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

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 where the ancestry is Asian.

Our body is made up of billions 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 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.

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Since all our chromosomes come in pairs, all our genes also come in pairs. The genes provide the instructions for proteins, which are the building blocks of the cells that make up our body. Although we all have variation in our genes, sometimes this can affect how our bodies grow and develop. Generally, gene variations that have no impact on our health are called benign variants or polymorphisms. These variants tend to be more common in people. Less commonly, variations can change the gene so that it sends a different message. These changes may mean that the gene does not work properly or works in a different way that is harmful. A variation in a gene that causes a health or developmental condition is called a pathogenic variant or mutation. Gene variants may be inherited from a parent, or happen for the first time in a person. Once you have a gene variant, however, it may be passed on to future generations. This is referred to as genetic inheritance.

WHAT CAUSES CYSTIC FIBROSIS?

CF is caused by changes in both copies of the *CFTR* **gene.** 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 working properly.

For some people, one copy of the *CFTR* gene has a variant whilst the other copy is still working. They are known as **genetic carriers** for CF. Genetic carriers for CF will not have any signs or symptoms of the condition.

There are over 2,000 known variants in the *CFTR* gene that may have an impact on the way the gene works. *CFTR* stands for *C*ystic *F*ibrosis *T*ransmembrane *R*egulator *G*ene. The most common variant is called **Phe508del (also known as 'delta F508')** and is found in about 75% of people affected with CF in Australia.

Other variants are much rarer, and some combinations may result in a milder form of cystic fibrosis. For example, a combination of two 'milder' CF variants in a person may only cause male infertility because of a difference called congenital bilateral absence of the vas deferens (CBAVD).

HOW IS CYSTIC FIBROSIS INHERITED?

CF is a genetic condition that follows a pattern of **autosomal recessive inheritance**.

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

- 1 in 4 (25%) chance that they will have a child who inherits both copies of the recessive gene variant from their parents. In this case, no working protein will be made and their child will have CF
- 1 in 4 (25%) chance that their child will inherit both copies of the working gene and will not have CF and is not a genetic carrier
- 1 in 2 (50%) chance that their child will inherit the recessive gene variant and the working copy of the gene from their parents and will be an unaffected genetic carrier for CF, just like the parents.

If only one parent is a carrier for CF and the other parent is unlikely to be a carrier (*Figure 41.2*) in every pregnancy there is:

- Very low chance that the couple will have a baby affected with CF. We cannot exclude the possibility entirely as sometimes the other parent may be a genetic carrier for CF that was not found via genetic screening
- 1 in 2 (50%) chance that their child will inherit the recessive gene variant and the working copy of the gene from the parents and they will be an unaffected genetic carrier for CF
- 1 in 2 (50%) chance that they will have a child who inherits both copies of the working gene from their parents. The child will not have CF.

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

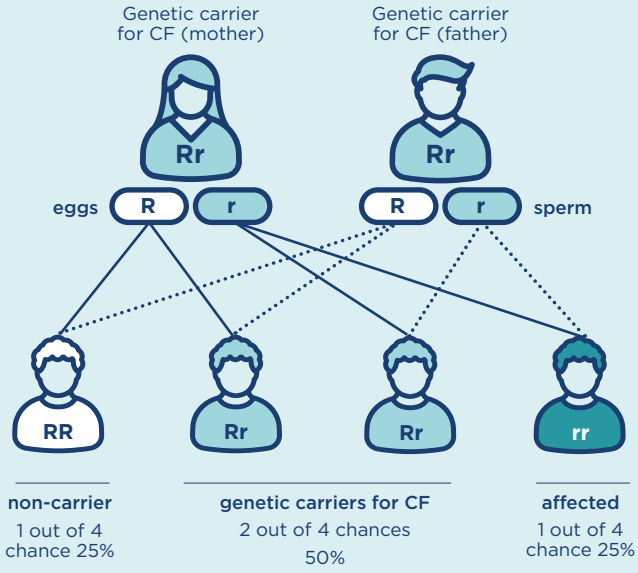
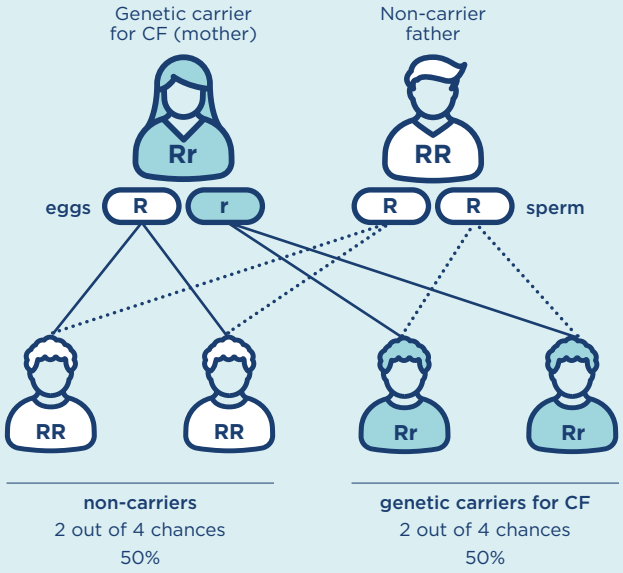


Figure 41.2:
Autosomal recessive inheritance where only one parent is a genetic carrier of the *CFTR* gene copy. The non-working *CFTR* gene copy is represented by 'r'; the working copy by 'R'.



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.

Genetic carriers for CF can, however, pass the non-working gene copy on to their children through the egg or sperm cells.

A theory for why being a genetic carrier for CF is more common in people of Northern European ancestry, may be that there was a survival advantage because this provided some degree of protection against cholera infections in earlier European history.

IS THERE ANY TESTING AVAILABLE FOR CYSTIC FIBROSIS?

Diagnostic Testing

If a person shows symptoms of CF, then a **sweat chloride test**, or sweat test, may 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 usually indicates that a person has CF.

Once a person is diagnosed with CF, genetic testing may be performed to identify the variants causing the condition. This involves a blood test (or cheek swab sample) to look for variants in the *CFTR* gene.

As described above, a person with CF will have two variants present, one in each copy of the *CFTR* gene. Genetic testing may involve either a variant panel screen, to look for the more common gene variants, or full gene sequencing where the *CFTR* gene is read to look for possible variants in a more complete way.

Genetic testing may also be done in a stepwise way, with a variant panel performed first, and followed by full gene sequencing if the variant panel does not identify the cause. Your health care practitioner will explain the testing 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 CF. A positive result on newborn screening indicates that a child may have CF, and further tests including a sweat test are required to confirm or exclude the diagnosis.

Testing for carrier status

Genetic testing for carrier status is available for people who have a family history of CF. For example, when a person is found to be a genetic carrier for CF, their first degree relatives (parents, children, brothers and sisters) all have a 1 chance in 2 (50%) of also being a genetic carrier. The testing laboratory will need to know which specific gene variant(s) caused CF in the family, before testing others in the family.

If someone is found to be a genetic carrier, then carrier testing is available for their partner when they are planning a family. Carrier screening for people who do not have a family history may involve either a variant panel screen, where only the more common gene variants are tested for, or full gene sequencing of the *CFTR* gene to look for variants more extensively.

What can results of sequencing the CFTR gene show?

- Pathogenic, or likely pathogenic genetic variants are found, confirming the diagnosis of CF or carrier status for CF
- No variant is found. This does not exclude the diagnosis of CF or carrier status for CF. If there is no variant on sequencing a person who does not show symptoms of CF, their chance of being a carrier of CF is much lower
- A variant of uncertain significance (VUS) is found. This means current testing could not find a likely genetic cause. Unless there is more evidence to say differently, this type of variant cannot be used for managing health risk or testing relatives.

Genetic testing for CF may be covered by Medicare in some instances and guidance on how to test may be sought from laboratory services. You are encouraged to talk about pros and cons with your health care provider before making a decision.

A specialised CF Clinic or Genetics service may help guide the testing process and treatment and management of the condition in families.

Treatment

People with complex conditions like CF need a personalised approach to their care, especially looking after the lungs and digestive system.

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 at least their fourth decade but for many the condition can severely affect their quality of life. Medications are used to help fight lung infections and help keep airways clear. Some people with CF are eligible for a lung transplant, where damaged lungs may be replaced with healthy lungs from a donor. This is major surgery.

For some people with CF, there are approved drugs in Australia available to target their specific class of genetic variation, causing CF in them. Such treatments target the underlying problem and are called CFTR modulators. A number of other ways of personalising treatment are currently being researched including genetic-based therapies. Challenges for such therapies include the delivery of treatment to the most affected parts of the body (e.g. the lungs) and maintaining the effect of the treatment.

Planning a pregnancy

For couples who are both known genetic carriers for CF, testing may be available during a pregnancy. This will work out whether the baby will be unaffected, have CF or is a genetic carrier for CF. Genetic testing in a pregnancy for CF is optional and should be talked about in full with your doctor, midwife or genetic counsellor. It may also be possible to have pre-implantation genetic diagnosis (PGD) to look for CF in an embryo made using in vitro fertilisation (IVF).

Reproductive genetic carrier screening is also available for couples who are planning pregnancy, or are in early pregnancy. This may include genetic screening for CF in many instances.

When planning a family, options for testing are best talked about before pregnancy.

More support and information is available for individuals and families through support organisations including Genetic Alliance Australia.