

Cystic Fibrosis *our focus*

Family Genetic Testing: the family cascade screening programme for cystic fibrosis.

Factsheet – August 2015

Family Genetic Testing: the family cascade screening programme for cystic fibrosis.

Published by the Cystic Fibrosis Trust with assistance originally from the late Dr Maurice Super, formerly of the Department of Clinical Genetics & CF Clinic, Royal Manchester Children's Hospital, and by Dr Martin Schwarz, Honorary Consultant Clinical Molecular Geneticist at Central Manchester & Manchester Children's Foundation Trust.

Date of publication August 2015

Contents

Introduction	5
What is cystic fibrosis?	5
What is cascade screening?	6
Why is a baby born with cystic fibrosis?	6
The cystic fibrosis gene	7
What is the risk for relatives?	7
Are carriers healthy?	7
Can I find out if my partner and I are both carriers?	8
Who else can have a carrier test?	10
How will I receive the test results?	10
Is urgent testing available?	10
What are the options if my partner and I are both carriers of the cystic fibrosis gene?	10
Home testing	11
The future	11
Who can I contact about carrier testing?	12
Further information	15

Introduction

Cascade screening is the process of offering screening for the cystic fibrosis (CF) gene to the family members of someone who has been diagnosed with cystic fibrosis. This factsheet explains:

- what CF is,
- how cascade screening works,
- who can have carrier testing,
- the odds of being a carrier of the CF gene,
- what it means to be a carrier, and
- where you can go for testing and further information.

This is a complicated topic; if you have any questions about the content of this factsheet please discuss it with a CF team, a specialist CF geneticist or your regional genetics centre.

What is cystic fibrosis?

CF is an inherited disease caused by a faulty gene that affects the flow of salt and water into and out of cells. It affects vital organs in the body, particularly the lungs and digestive system, by clogging them with thick, sticky mucus. It is one of the UK's most common life-shortening inherited conditions, affecting around one in 2,500 live births – around 10,000 people in the UK.

Symptoms often appear immediately or soon after birth. Persistent infections can lead to chronic lung problems, and there is poor digestion of fat and protein. Serious symptoms and complications include infection and inflammation of the lungs, malnutrition, diabetes, liver failure and osteoporosis. The lungs can be treated with physiotherapy and drugs. Poor digestion is controlled with the help of specially developed enzymes and particular attention to diet.

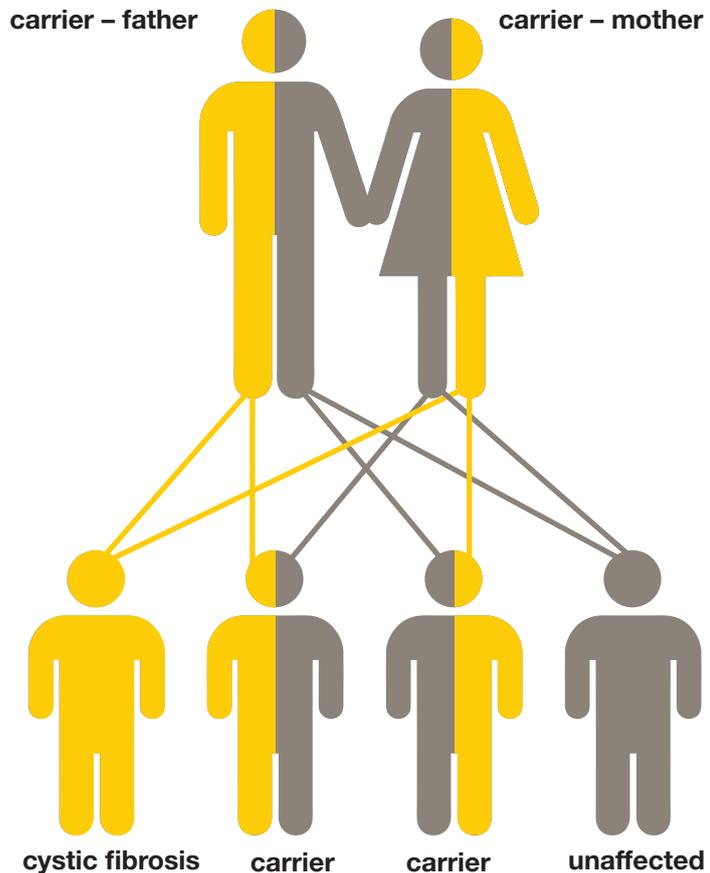
Men with CF are usually infertile due to absence of, or blockages in, the ducts that carry sperm. However, medical advances have allowed some men with CF to father children using a technique called intra-cytoplasmic sperm injection.

New treatments have been developed that have improved the quality and length of life of people with CF, but the condition still remains serious and burdensome. There is no cure at present, but a new generation of pharmaceuticals is being developed that will target specific mutation types at the molecular level. The first of these is called Kalydeco™ and is used in patients with at least one copy of the G551D mutation. Other, similar treatments are in the pipeline. In addition, research into gene therapy to cure the effect of the disease on the lungs is ongoing.

What is cascade screening?

Cascade screening is used to see whether someone is a carrier of the CF gene, and can be offered to relatives (and their partners) of a person diagnosed with cystic fibrosis. Whenever a carrier is detected, carrier testing is then made available to the carrier's relatives and their partners in a cascade fashion.

Why is a baby born with cystic fibrosis?



For a baby to be born with CF, both parents must be carriers of the faulty CF gene. The child will have inherited the faulty gene from each parent.

The carrier parents, who are not themselves affected by cystic fibrosis, have one unaffected gene and one faulty cystic fibrosis gene. If both parents are carriers, a child has:

- A one-in-four chance of being born with cystic fibrosis,
- A two-in-four chance of being a carrier, like their parents, but not having the disease, and
- A one-in-four chance of being completely free of the condition – neither having cystic fibrosis nor being a carrier of the faulty CF gene

Note that the odds are the same for each successive pregnancy.

The CF gene

The gene responsible for CF was discovered in 1989. More than 2,000 mutations (different forms of the gene) have been discovered, but only a few are common. In the UK, one mutation accounts for the majority of CF cases. For example, 81% of CF carriers in the North West of England have the most common mutation in the UK. This mutation plus a further 49 mutations account for more than 95% of the total mutations in the UK in native British people. The ethnic origin of a person can also influence which mutations are most common. People of Ashkenazi Jewish origin have a different, but overlapping, spectrum of common mutations to that of Europeans. People from the Indian sub-continent have an entirely different range of mutations.

What is the risk of carrying the faulty gene for relatives?

In the general population in the UK 1 in 25 people without a family history of cystic fibrosis carries a faulty CF gene. Relatives of someone with cystic fibrosis have a much higher chance of being carriers. The chart below gives the statistical chances of relatives (who have not been tested) of being carriers and their risk of having a child with cystic fibrosis.

Before testing

Relationship to person with CF	Chance of being a carrier	Risk of having a child with CF with an untested partner
Parents	100%	1 in 4 (with each other)
Person with CF	100%	1 in 50
Parent with new partner	100%	1 in 100
Child of woman with CF	100%	1 in 100
Brother or sister	2 in 3	1 in 150
Aunt or uncle	1 in 2	1 in 200
Grandparent	1 in 2	1 in 200
First cousin	1 in 4	1 in 400
Second cousin	1 in 8	1 in 800

Are carriers healthy?

People with only one faulty copy of the gene that causes cystic fibrosis will not have the condition and are not at risk of developing it. Carriers do not experience any detrimental symptoms as a result of their status, although any children they have with another carrier could be born with cystic fibrosis.

Can I find out if my partner and I are carriers?

Speak with your GP if you would like to have carrier testing. It is now possible to test for the gene using a simple mouthwash or blood test. In the case of a mouthwash test, cells lining the cheek are collected by spitting saliva into a special tube; DNA can be extracted from these cells and then analysed. In relatives of people diagnosed with CF, the exact gene alterations found in their affected family member are established wherever possible, no matter how rare the alteration. A test for the more common gene alterations is performed on the partner who does not have a family history of the condition.

Because the test for common mutations only detects about 90 – 95% of mutations, a negative result does not entirely rule out the possibility of the person being a CF carrier, but the statistical likelihood is reduced to less than 1 in 250. Depending on the number of genetic CF alterations tested for in your health region, this figure may differ slightly. A positive result shows that the person is definitely a carrier, even if there is no family history.

Very occasionally, neither CF gene alteration is identified in the person with CF, because the mutations may be very rare ones that are not detected in the routine test. In these cases, testing for carriers in a relative becomes a little more complicated, but is generally still possible by testing the entire CF gene for mutations. Once the CF-carrying gene from each parent has been identified, it is then possible to test for that pattern in the relative. Except in the case of a full brother or sister of someone with CF, a negative result does not confirm with 100% certainty that you are not a carrier, but it does mean that you have a much lower risk. The chart on the next page shows how the level of risk of having a child with CF can be estimated once testing has taken place and suggests possible courses of action.

After tests that detect 90% of cf genes

Results	Risk of having a child with CF	Action
Both partners are carriers	One in four	Genetic counselling. Options are discussed including tests and support available in current or future pregnancy. Pre-implantation genetic diagnosis is also explained.
Relative carrier, partner negative	Less than 1 in 1,000	Reassurance. Low Risk. Tests are not routinely offered in pregnancy. Check offspring for CF if sickly (routine screening of newborn babies was introduced in 2007 and picks up the majority of CF cases).
Relative negative, partner carrier *	Less than 1 in 2,000 Unless the relative is a full brother or sister of the person with CF, when a negative test means non-carrier (risk zero).	Re-test to ensure there is no sample mix-up. Reassure – low risk. No routine tests in pregnancy. Check offspring for CF if sickly.
Both partners negative	Less than 1 in 250,000	Strong reassurance.

*The reason the chances are different if the relative of someone with cystic fibrosis is a negative rather than someone not related to anyone with CF, is that the relative will be known to be free of the CF gene known to be in the family. In the case of someone whose full brother or sister has CF, the known mutations in that family will have been tested for and the brother/sister found to be free of any CF genes.

Is there a charge for testing?

Not if you are a relative of someone with cystic fibrosis. The cascade scheme is offered as an NHS service to people with a family history of CF and their partners.

Who else can have a carrier test?

Testing is offered to close relatives (and their partners) of people with cystic fibrosis. Also, the relatives of anyone found to be a carrier will be offered testing. Anyone who has a family history of CF can ask for a test, ideally through his or her GP. The name 'cascade' arises because whenever a carrier is detected, the offer of testing cascades out to their relatives. If you are not a relative of someone with CF and wish to have the carrier status test it may be difficult to obtain on the NHS. Details of where private testing is available are included at the end of this leaflet.

How will I receive the test results?

This may differ from region to region within the NHS. The contact person in your local genetics department will be able to explain their procedures to you. In many health regions, results are given in writing, stating whether the person has been discovered to be a carrier or is negative on testing. It must be remembered that a negative result does not absolutely rule out the possibility of being a carrier, although it typically reduces the likelihood at least tenfold. Details of the chances of still being a carrier are given to people who test negative, and a statistical level of risk of having a child with CF is given to couples. Results are generally available within ten working days of the sample arriving in the laboratory.

Couples or individuals found to be carriers will be invited to make contact with genetic counsellors, by telephone and in person, to explain and discuss the situation and future options. The genetic field worker will also provide further explanation and discussion. Carriers are informed that there are no major health risks to them from being a carrier. Specialist genetic counselling is offered in all cases where both partners are carriers.

Is urgent testing available?

In case of queries or anxieties arising in pregnancy, testing of couples with results within a few days can be organised.

What are the options if my partner and I are both carriers of the CF gene?

All available options will be explained during your counselling session, so that you can decide what is right for you. All decisions are for you to make, and there will be trained staff available in the genetics department to clarify the situation and to discuss the implications of all possible courses of action. Antenatal tests, with the options of ending or continuing the pregnancy, are discussed, including any risks that may be associated with the tests. Pre-implantation genetic diagnosis using IVF techniques to ensure that only an embryo free of CF is implanted into the womb are also explained.

Home testing

The Cystic Fibrosis Trust recommends that genetic testing is undertaken with professional clinical support and that the results of a genetic test are discussed with a genetic counsellor, who can explain in full the results you may get and the options available to you as an individual.

Using a home genetic testing kit would mean that you do not have professional support available to you if and when you need it, as well as being less reliable. For these reasons, the Cystic Fibrosis Trust advises against the use of home genetic testing kits.

The future

As our ability to detect more CF genes improves, it will be possible to test for the rarer mutations that currently make the carrier status test less than 100% accurate due to missed, rare or previously unidentified mutations. This is called a false-negative result. Those people with a positive test have been proved to be carriers and that will not change. Work is being carried out on techniques capable of detecting CF cells in the embryo using a sample of the mother's blood. This would avoid the need for chorionic biopsy (where a piece of the developing placenta is taken at 10 – 12 weeks) or amniocentesis (where a sample of the fluid surrounding the foetus is taken), the current tests available for antenatal diagnosis.

Who can I contact about carrier testing?

Genetics centres in the UK offer CF carrier tests to people with a family history of CF. Your GP will be able to refer you to your local genetics centre to be seen by a genetics counsellor. We have listed them below but it is best to ask your GP for a referral rather than contact them directly.

England

Bristol Regional Genetics Service

Level B, St Michael's Hospital,
Southwell Street, Bristol BS2 8EG
0117 342 5115

Clinical Genetics Unit

Birmingham Women's Hospital,
Edgbaston, Birmingham B15 2TG
0121 627 2630

Department Of Clinical Genetics

St George's University Of London,
Cranmer Terrace,
London SW17 0RE
0208 725 5297

Department of Genetic Medicine St Mary's Hospital

Hathersage Road, Manchester M13 0JH
0161 276 6506

East Anglian Medical Genetics Service

Department of Medical Genetics,
Clinical Genetics Box 134,
Level 6, Addenbrooke's Treatment Centre,
Cambridge University Hospitals NHS Foundation Trust,
Hills Road, Cambridge CB2 2QQ
01223 216 446

Great Ormond Street Children's Hospital Clinical Genetics Unit,

Great Ormond Street Hospital, Great Ormond Street,
London WC1N 3JH
020 7762 6845 / 6831 / 6856

Guy's Hospital Genetics Service

7th Floor Borough Wing Guy's Hospital,
Great Maze Pond, London SE1 9RT
020 7188 1364

Merseyside Regional Clinical Genetics Service

Liverpool Women's NHS Foundation Trust,
Crown Street, Liverpool L8 7SS
0151 802 5001

Northern Genetics Service Institute of Human Genetics

Central Parkway, Newcastle upon Tyne NE1 3BZ
0191 241 8721

North West Thames Regional Genetics Service

Molecular Genetics Laboratory

Level 8V, Northwick Park Hospital and St Mark's NHS Trust,
Watford Road, Harrow HA1 3UJ
0208 869 2795

Nottingham University Hospitals City Hospital Campus

The Gables, Gate 3 Hucknall Road,
Nottingham NG5 1PB
0115 962 7728 or 0115 969 1169

Oxford Clinical Genetics

The Churchill Hospital, Old Road,
Headington, Oxford OX3 7LE
01865 225931

Peninsula Clinical Genetics Service

Royal Devon & Exeter Hospital,
Gladstone Road, Exeter EX2 5DW
01392 405726

Sheffield Clinical Genetics Service

Outpatients Department 2,
Northern General Hospital,
Herries Road, Sheffield S5 7AU
0114271 7025

Wessex Clinical Genetics Service

Mailpoint 627, Princess Anne Hospital,
Coxford Road, Southampton SO16 5YA
0238 120 6170

Yorkshire Regional Genetics Service

3rd Floor, Chapel Allerton Hospital,
Chapeltown Road, Leeds LS7 4SA
0113 392 4432

SCOTLAND

East of Scotland Regional Genetics Service

Tayside University Hospitals NHS Trust,
Ninewells Hospital & medical School,
Dundee DD1 9SY
01382 632 035

North of Scotland Regional Genetics Service Medical School

Foresterhill, Aberdeen AB25 2ZD
01224 552 120

South East Scotland Clinical Genetics Service Western

David Brock Building, General Hospital,
Crewe Road, Edinburgh EH4 2XU
0131 537 1116

West of Scotland Regional Genetics Service

Southern General Hospital,
Glasgow G51 4TF
0141 354 9200/9201

WALES

All Wales Medical Genetics Service,

Institute of Medical Genetics,
University Hospital of Wales, Heath Park,
Cardiff CF4 4XW
029 2074 2577

NORTHERN IRELAND

Northern Ireland Regional Genetic Service Floor A,

Belfast City Hospital Trust, Lisburn Road,
Belfast BT9 7AB

Contact the Duty Scientist on geneticslabs@belfasttrust.hscni.net.

If you require any more information about having carrier testing then please contact us at the Cystic Fibrosis Trust Helpline. The details are on the last page.

Further information

UK Genetic Testing Network – <http://ukgtn.nhs.uk>

NHS Choices – www.nhs.uk/conditions/genetics

The Cystic Fibrosis Trust provides information about cystic fibrosis through our factsheets, leaflets and other publications.

Most of our publications are available through our helpline and can be downloaded from our website. Visit cysticfibrosis.org.uk/publications.

.....

The Cystic Fibrosis Trust helpline can help you with a range of issues, no matter how big or small. Our trained staff can provide a listening ear, practical advice, welfare/benefits information or direct you to other sources of support. The helpline can be contacted on 0300 373 1000 or helpline@cysticfibrosis.org.uk and is open Monday to Friday, 9am – 5pm.

Calls to 0300 numbers cost no more than 5p per minute from a standard BT residential landline. Charges from other landlines and mobile networks may vary, but will be no more than a standard geographic call and are included in all inclusive minutes and discount schemes. If you are worried about the cost of the call please let us know and we'll call you back.

You can also find more information at our website cysticfibrosis.org.uk.

Cystic Fibrosis Trust
2nd Floor One Aldgate
London
EC3N 1RE
020 3795 1555

cysticfibrosis.org.uk



More factsheets available at:
cysticfibrosis.org.uk/publications

© Cystic Fibrosis Trust 2017. This factsheet may be copied in whole or in part, without prior permission being sought from the copyright holder, provided the purpose of copying is not for commercial gain and due acknowledgement is given.

The information included in this publication is not intended to replace any advice you may receive from your doctor or CF multidisciplinary team and it is important that you seek medical advice whenever considering a change of treatment.

Cystic Fibrosis Trust, registered as a charity in England and Wales (1079049) and in Scotland (SC040196). A company limited by guarantee, registered in England and Wales number 3880213. Registered office: 2nd Floor, One Aldgate, London EC3N 1RE.

Cystic Fibrosis Trust

cysticfibrosis.org.uk

© Cystic Fibrosis Trust 2017. Registered as a charity in England and Wales (1079049) and in Scotland (SC040196). A company limited by guarantee, registered in England and Wales number 3880213.
Registered office: 2nd Floor, One Aldgate, London EC3N 1RE.