Bio Factsheet

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Cystic Fibrosis

Cystic fibrosis(CF) is a common genetic disorder that occurs worldwide. It is the commonest inherited disease among white North Americans and Northern Europeans.

Genetic basis

Cystic fibrosis is caused by a single mutant **recessive** allele, on chromosome 7. It is inherited by simple Mendelian monohybrid inheritance. In the United Kingdom about one person in 25 is heterozygous for the condition i.e. they are a **carrier**. Heterozygous carriers have normal phenotypes because they do not develop the condition because the recessive CF-allele is masked by the dominant normal allele. However, carriers can of course pass on the CF-allele to their children. Individuals who are double recessive (homozygous) for the CF-gene usually die young and so do not reproduce to pass on the CF-allele. (although treatments for the condition are becoming increasingly successful and some individuals have a life expectancy of about 30 years). Cystic fibrosis has an overall birth incidence of about 1 in 2500.

Fig.1. Inheritance of cystic fibrosis

C = normal allele **c** = CF-allele

Parents:	Normal	X	Carrier
	CC		Cc
Gametes:	C		C and c
Possible offspring:	CC		Cc
	Normal		Carrier
Genotypic ratio:	1	:	1
Phenotypic ratio:	1 normal	:	1 normal
	both normal		

Parents:	Carrier		X		Carrier	
	Cc				Cc	
Gametes:	C and c				C and c	
Possible offspring:	CC	Cc		Cc		cc
	Normal	Carrier		Carrier		Sufferer
Genotypic ratio:	1	: 1	:	1	:	1
Phenotypic ratio:	3 Normal : 1 Sufferer					

Exam Hint: *Careless layout of genetic diagrams costs marks. Whether you use a layout as above, or a punnet square, always ensure that parental and offspring genotypes and phenotypes and gametes are clearly labelled. Phenotypes must be written next to their genotypes, not in a separate list.*

The normal allele controls the synthesis of a cell membrane protein called **cystic fibrosis transmembrane protein (CFTP)**. This protein is essential for the proper activity of epithelial cells. The allele was first cloned in 1989 and over 230 mutations of it have so far been identified worldwide, all resulting in the development of cystic fibrosis.

Some mutations only give rise to mild forms of the disease, but about 80% of mutations involve **deletion of three bases** which result in a loss of a single **phenylalanine** molecule from the CFTP. This causes severe cystic fibrosis to develop.

Symptoms

CFTP is a carrier protein which transports chloride ions out of epithelial cells into mucus. As the chloride ions leave the cell, water has to follow by osmosis and this makes the normal mucus watery. In CF-sufferers, because CFTP is absent, chloride ions and water remain in the cells so the mucus becomes thick and sticky and is difficult to remove. This produces several symptoms in the body:-

- The normal mucus of the tracheal epithelium traps dust and microorganisms in the air flow, and the contaminated mucus is then carried up to the throat by ciliary action. This mucus is either swallowed or blown out of the mouth or nose. In CF-sufferers the mucus is too thick and sticky for the cilia to clear. It progressively blocks up the airways and becomes a breeding ground for bacteria. This causes a severe cough, wheezing, blocked sinuses and difficulty in breathing. The chest may develop into a barrel-shape due to increased effort to breathe properly.
- Thick, sticky mucus in the pancreatic juice becomes surrounded by fibrous tissue forming cysts within the pancreas. These cysts sometimes block the pancreatic duct system, reducing or preventing passage of pancreatic juice into the duodenum. Digestion of food is thus impaired and the CF-sufferer may become malnourished. Similar problems occur in other mucus-secreting organs of the body, for example, the salivary glands, the intestinal glands and the gall bladder.
- An early symptoms in babies suffering from cystic fibrosis is that they produce copious amounts of abnormal, very salty sweat. As the sweat dries the baby becomes coated with a white deposit of salt.
- Young babies with cystic fibrosis may get intestinal blockage due to the intestinal contents (meconium) being too thick and sticky to expel.
- Children with cystic fibrosis tend to have stunted growth, have a delayed onset of puberty, and because of breathing difficulties find it hard to participate in games and sport.
- Most males with cystic fibrosis are sterile and so could not pass on the allele.

Diagnosis of cystic fibrosis

- This can be made by the recognition of symptoms in the sufferer, for example, production of copious quantities of very salty sweat in babies.
- In newborn babies a biochemical test for an immunoreactive trypsin (IRT), which is present in the plasma of sufferers, is performed if CF is suspected.
- Cloning and sequencing the CF-gene has enabled geneticists to develop screening methods for the detection of the mutant/recessive alleles in prospective parents, sufferers and their relatives. Cells for DNA analysis are collected by a simple mouthwashing technique. The DNA is extracted, amplified using the polymerase chain reaction, and the DNA screened, using gene probes, to check for the presence of recessive CF-alleles. The test can identify most, but not all, adult carriers of the disease.

Remember *– the* ***polymerase chain reaction*** *enables small quantities of extracted DNA to be copied exactly, forming large quantities of the DNA. A* ***gene probe*** *is a sequence of known nucleotides, labelled with a radioactive tracer. In the case of CF-testing the probes will contain complementary base sequences to the CF-genes and so will attach to them, enabling recognition.*

In April 1997 the National Institutes of Health in the USA recommended that the screening test for CF should be offered to all couples planning to have a child. (A child of two symptomless heterozygous carriers has a 25% chance of having CF).

Genetic screening tests for CF are very expensive (for example, antenatal (before birth) screening is currently around £46,000 - £53,000 per single CF pregnancy detected – each individual test costs between £1500 and £2200). Thus a financial restraint prevents screening of the total reproductive population.

When prospective parents are tested, the woman is tested first. The man will be tested only if the woman is a carrier. If the woman is not a carrier then even if the man is a carrier they could not produce CF-sufferers.
If a carrier is detected it is advisable to test for other carriers amongst the carrier's relatives.

Genetic screening can thus reduce the incidence of the disease, providing both parents, if both diagnosed as carriers, refrain from having children. However, many carrier parents want a family so badly that they take the calculated risk of a 1 in 4 chance of having a CF-baby.

Treatment of cystic fibrosis

- The mucus blocking the trachea and bronchial passages periodically (up to 5 times a day) has to be removed by the sufferer lying face down, with head and thorax sloping lower than the abdomen, while a physiotherapist or nurse slaps the back to dislodge the mucus which can be coughed up and spat into disinfectant.

- Drug therapy can be used to reduce the incidence of the bacterial infections associated with CF. Antibiotics inhibit bacterial growth. Recombinant human deoxyribonuclease (produced by genetic engineering) is used to digest bacterial DNA and dead white blood cell DNA. Tablets containing pancreatic enzymes may be given to boost digestion in the duodenum and ileum.

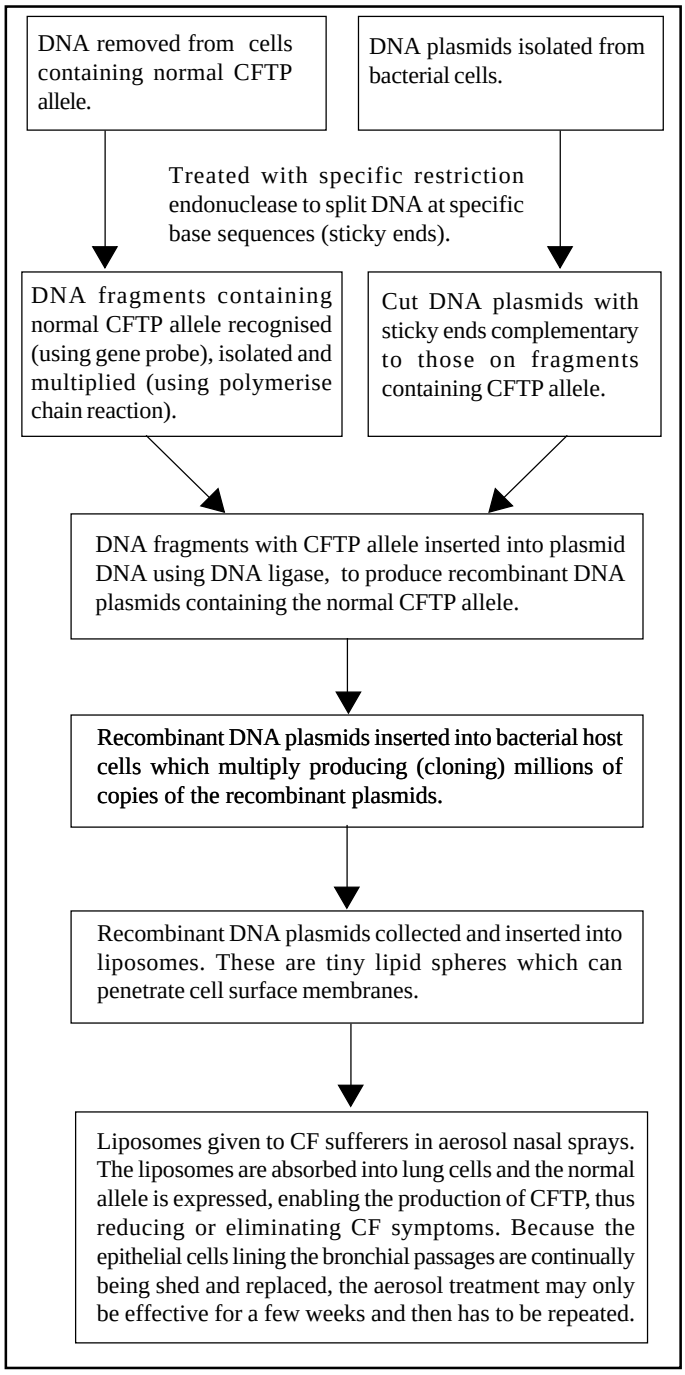
- Gene therapy is now being used to treat cystic fibrosis. This therapy may involve **gene replacement** (replacing the mutant allele with a normal one) or **gene supplementation** (adding copies of normal alleles to the cell without removing the pre-existing mutant alleles). The added alleles are dominant and so mask the effects of the recessive alleles. Dependant on which cells are treated, the gene therapy may be **germ-line gene therapy** or **somatic-cell gene therapy**.

Germ-line gene therapy
In germ-line therapy the dominant genes would be added to the sperm or egg cells so that after fertilisation and development every cell of the offspring would function normally. The alteration would also be passed on to the next generation. This procedure is, at present, banned in Britain on ethical grounds, although it would be a better way of controlling cystic fibrosis than somatic-cell therapy.

Somatic-cell gene therapy
In somatic-cell gene therapy (Fig2), the normal dominant genes are given to somatic cells of the body. Thus the germ cells will not receive the normal genes and so the alteration will not be passed on to the next generation. Also there is no guarantee that all the somatic cells involved will receive the normal genes and so recovery may not be complete.

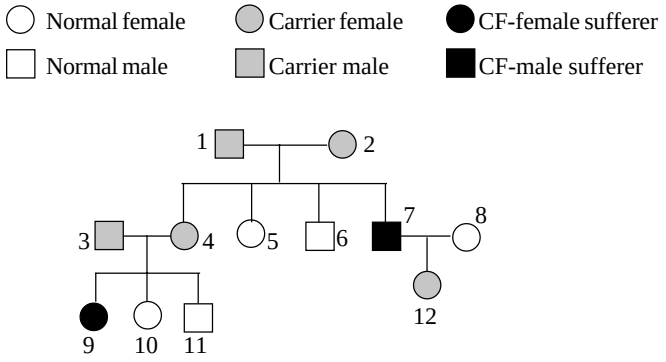
Exam Hint: *it is unlikely you will be asked a question solely on cystic fibrosis, but you may need to use the information you have about cystic fibrosis in other questions - for example, questions on inheritance, family trees, nature and effects of mutation, genetic engineering, gene therapy and ethical aspects of modern biology.*

Fig. 2. Somatic-cell gene therapy to treat cystic fibrosis



Practice Questions

1. The diagram below is a family tree of a family in which cystic fibrosis (CF) has occurred. Study the tree and then answer the questions below.



(a) (i) Using C for the dominant allele and c for the recessive allele, write down the possible genotypes of individuals 1, 5, 8 and 9. **4**

(ii) Suggest two reasons why it is virtually impossible for individual 12 to be produced. **2**

(b) (i) By means of a genetic diagram show the probability of individuals 3 and 4 having a CF baby. **3**

(ii) How might individuals 3 and 4 easily recognise that their baby has cystic fibrosis? **1**

Total 10

2. (a) Cystic fibrosis sufferers have abnormally thick sticky mucus. Explain why this is so. **4**

(b) What are the main effects of the thick sticky mucus on
(i) the respiratory system, and **3**
(ii) the digestive system? **3**

(c) Before gene therapy became available as a treatment, state two ways in which cystic fibrosis sufferers were treated. **2**

Total 12

3. Gene therapy can be used to treat cystic fibrosis sufferers. Both germ-line gene therapy and somatic-cell gene therapy are possible. However, in Britain the Warnock Committee have ruled that germ-line gene therapy is unethical, and so at present it cannot be used.

(a) Distinguish between germ-line gene therapy and somatic-cell gene therapy. **2**

(b) (i) How are the recombinant plasmids containing the normal CFTP allele given to the CF sufferer in somatic-cell gene therapy? **2**

(ii) Somatic-cell gene therapy does not completely cure cystic fibrosis. Why? **2**

(c) Suggest one reason for and one reason against germ-line gene therapy. **2**

Total 8

Answers

1. (a) (i) individual 1 = Cc; individual 5 = CC or Cc; individual 8 = Cc; individual 9 = cc; **4**

(ii) individual 7 (the father) is a CF-sufferer and male CF-sufferers are usually sterile; until recent years CF sufferers usually died young/before reproductive age; **2**

(b) (i)
parents Cc x Cc (no mark)
gametes C and c ↓ C and c ;
possible offspring CC Cc Cc cc ;
3 Normal : 1 sufferer, = 25% probability; **3**

(ii) the baby would produce large amounts of extremely salty sweat; **1**

2. (a) ref. mutation of gene which codes for cystic fibrosis transmembrane protein/CFTP; ref deletion of three bases resulting in omission of a phenylalanine residue from CFTP; normal CFTP regulates transport of chloride ions and water from epithelial cells into mucus; normal CFTP is not produced in CF sufferers and so the mucus is not diluted with water from the epithelial cells (and so mucus is thicker/stickier than normal); **4**

(b) (i) thick/sticky mucus accumulates in the trachea and bronchial passages causing coughing/wheezing/blockage of airways; becomes heavily infected with microorganisms/bacteria/ becomes full of white blood cells/pus; because breathing is difficult, ribs and chest muscles develop making the chest 'barrel- shaped'; **3**

(ii) cysts develop in the pancreas to encapsulate lumps of sticky mucus; these may block the pancreatic duct drainage system so pancreatic juice fails to reach the duodenum/digestion impaired/ malnutrition results; similar cysts may also develop in salivary glands/intestinal glands/gall bladder blocking flow of secretions from these glands; **3**

(c) by physiotherapy/slapping the back several times a day to dislodge mucus; by antibiotics to reduce infection/ deoxyribonuclease to breakdown DNA in pus/ pancreatic enzyme tablets to increase digestion; **2**

3. (a) in germ-line gene therapy the normal gene is inserted into the sperm/ and or egg cells (before in vitro-fertilisation/artificial insemination) and so prevents development of the condition/cystic fibrosis; in somatic-cell gene therapy the normal gene is inserted into somatic/ lung cells of a cystic fibrosis sufferer and so reduces symptoms; **2**

(b) (i) recombinant plasmids inserted into liposomes/tiny (submicroscopic) lipid spheres; passed into respiratory passages/lungs of sufferer by an aerosol spray and liposomes become absorbed into the epithelial cells; **2**

(ii) some somatic cells may not absorb any liposomes and so still lack the CFTP allele; epithelial cells of the respiratory passages are continually shed and replaced so that the replacement cells would lack the CFTP allele; **2**

(c) if screened couples/carriers wanting a baby are at risk of producing a CF-baby then germ-line gene therapy would enable them to avoid the problem/germ-line gene therapy prevents the development of CF in a baby and also in his/her eventual offspring; germ-line gene therapy is, in effect, producing designer babies/ adults and this is considered immoral/against the present perspectives of most world religions; **2**

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