Bio Factsheet

www.curriculumpress.co.uk Number 110

Genetic Disease in Humans

This Factsheet covers the following topics:

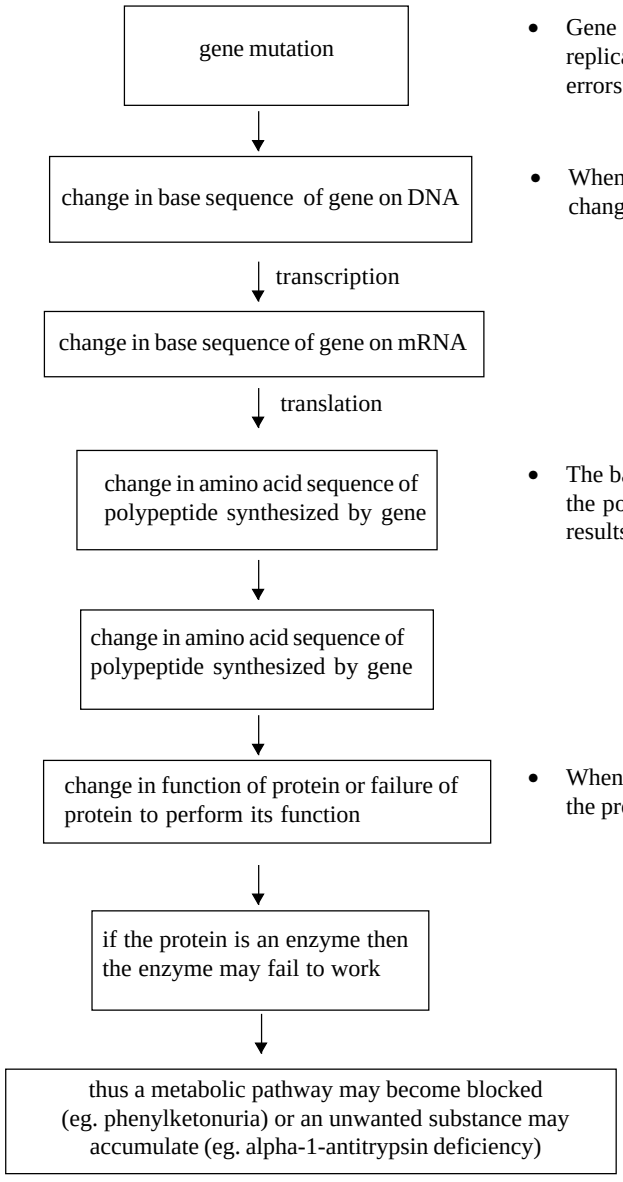
- **how a change in the base sequence of a gene can result in genetic disease;**
- **descriptions of specific diseases caused by gene mutation, for example, sickle-cell anaemia, cystic fibrosis, phenylketonuria, alpha-1 antitrypsin deficiency, Huntington's chorea, haemophilia and colour blindness;**
- **possible treatment of genetic disease by gene therapy;**
- **chromosomal defects and their results, for example, Down's syndrome;**
- **the need for genetic screening and counselling and the implications of the Human Genome Project for sufferers of, and people at risk of, genetic disease.**

***Exam Hint**: - The candidate should check which of the diseases referred to above is on the specification they are studying and learn the named examples. If the specification contains a synoptic essay component, it could be useful to learn all the examples for use in any essay question about genetic diseases.*

How a change in the base sequence of a gene can result in genetic disease

This is illustrated in Fig 1.

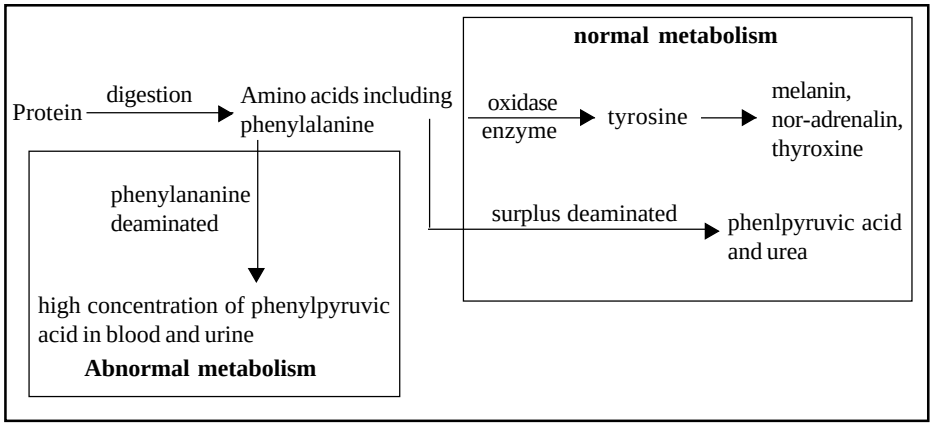
Fig 1. How a gene defect can cause genetic disease



- Gene mutations are small errors in the base sequence of DNA which occur when it replicates to form new DNA. Mutagens e.g. radiation increase the frequency of such errors.
- When the altered DNA replicates to form messenger RNA, (by transcription), the change in the base sequence is copied onto the messenger RNA.
- The base sequence on the messenger RNA determines the sequence of amino acids in the polypeptide synthesized (by translation), thus the altered base sequence results in an incorrect amino acid sequence and thus an incorrect structure.
- When this abnormal polypeptide binds with other polypeptides, (in the Golgi body), the protein formed will have an abnormal structure.

A good example of a metabolic defect is phenylketonuria (PKU). This is a symptom of several metabolic diseases, caused by defects in enzymes involved in the metabolic pathways of the amino acids phenylalanine and tyrosine.

Phenylpyruvica imbecilitus



Normal metabolism

1. much of the phenylalanine absorbed from food is oxidised by an oxidase enzyme to tyrosine.
2. This is then further oxidised resulting in products such as adrenaline, nor-adrenaline, thyroxine and melanin (the dark pigment in skin).
3. surplus phenylalanine is deaminated forming the excretory products, phenylpyruvic acid and urea.

Abnormal metabolism

1. About 1 in 10,000 babies are born with a mutation which makes the oxidase enzyme catalysing the change of phenylalanine to tyrosine inoperative.
2. Instead of forming tyrosine, large quantities of phenylalanine are deaminated forming very high concentrations of phenylpyruvic acid in the blood and urine.
   Phenylpyruvic acid belongs to a class of compounds called phenyketone bodies and the presence of larger than normal concentrations of these in urine is called phenylketonuria.
3. These high concentrations cause serious irreversible brain damage if allowed to persist.

All new-born babies have their urine tested for the presence of PKU and if diagnosed positive, to avoid developing phenylpyruvica imbecilitus, must feed on a special low content phenylalanine diet throughout life.

***Remember** – fortunately, most gene mutations are recessive and so if the sufferer of a genetic disease does have children it is unlikely that the disease will develop in the children because the mutant allele will be usually be masked by a normal dominant allele from the other parent. However, the children will be carriers of the mutant allele.*

Other mutations may adversely affect:

- an oxidase in the pathway from tyrosine to melanin making it impossible for melanin to be made. This condition is called **albinoism**, characterised by white hair and skin and pink eyes.
- an oxidase in the pathway from tyrosine to thyroxine making it impossible for normal quantities of the growth hormone, thyroxine, to be made. This condition is called **cretinism** and is characterised by a lack of physical and mental development in the child.

Sickle cell anaemia

1. Caused by gene mutation.
2. In one single instance, instead of the base **thymine** appearing, **adenine appears** (i.e. a base occurs)
3. The result is that during translation the amino acid **valine** is incorporated into the β – polypeptide chain of haemoglobin instead of **glutamic acid**
4. This small change, which produces abnormal haemoglobin S, results in the red blood cells collapsing into sickle shapes (Fig 3).

Fig 3. Normal and sickled red blood cells

The gene which controls the molecular structure of haemoglobin has two recessive alleles, Hb^A (for normal haemoglobin A) and the mutant Hb^S (for abnormal haemoglobin S).

Individuals could have one of the following three genotypes and phenotypes:

- Hb^AHb^A normal phenotype with normal haemoglobin
- Hb^AHb^S heterozygous carrier with normal phenotype with 50% normal haemoglobin A and 50% abnormal haemoglobin S. The red cells only become sickle shaped in conditions of oxygen deficiency. This condition is called 'sickle-cell trait'.
- Hb^SHb^S abnormal phenotype with 100% haemoglobin S. The red cells permanently sickle, become sticky on their surfaces and clump together to cause blockages in the blood circulation. They are rapidly destroyed, causing a severe anaemia. This is full 'sickle-cell anaemia' and sufferers usually die in childhood or soon afterwards.

Sickle cell anaemia is more prevalent in areas of the world where malaria is common. The malarial parasite, (*Plasmodium sps*) feeds on the haemoglobin within the sufferer's red cells and is transmitted between sufferers by the female *Anopheles* mosquito when it sucks blood. The parasite can use normal haemoglobin A as a source of food but cannot use abnormal haemoglobin S. There is insufficient haemoglobin A in the red cells of individuals with genotype Hb^AHb^S to support the parasitic growth and so these individuals are resistant to malaria. Normal individuals will succumb to malaria and some of them will die from it. Thus there is an overall higher percentage of Hb^AHb^S individuals in malarial zones than in non-malarial zones.

***Exam Hint:** – A common error made by candidates is to write 'more sickle cell sufferers survive in malarial regions than in non-malarial regions'. This is not so – the higher incidence of sickle cell sufferers in malarial areas is because some normal individuals are killed by malaria and so there are fewer normal individuals.*

Cystic fibrosis

Cystic fibrosis (CF) is the commonest recessive genetic disorder in the UK Caucasian population. It has an overall birth frequency of about 1 in 2500. The condition is due to a mutation in the allele coding for the **cystic fibrosis transmembrane conductance regulator** (CFTR). This is a protein which regulates the transport of chloride across cell membranes. The mutant allele is recessive and heterozygotes do not exhibit symptoms. The mutant allele occurs in 4% of the population and arises by deletion of three adjacent DNA nucleotides coding for the amino acid phenylalanine.

The disease affects nearly all the exocrine (externally secreting) glands of the body, including the salivary glands, intestinal glands, the pancreas, the lung and bronchial tree surfaces, and the gall bladder. Lack of the CFTR protein means that the cells of these glands cannot transport chloride ions of the cells. The raised chloride content in the cells draws water osmotically into the cells, from the mucus which the cells secrete. Thus these glands produce a very sticky concentrated mucus causing severe respiratory and pancreatic problems. Treatments, by physiotherapy to remove the mucus from the airways, by taking tablets of pancreatic enzymes to remove accumulated protein, DNA and cells, and by antibiotics to minimise infection, can increase the life expectancy to about 30 years. Death is usually due to respiratory failure. Males with CF are usually sterile.

Cystic fibrosis can now be treated, with considerable success, by gene therapy. The normal allele for CFTR protein synthesis is cloned and incorporated into either liposomes or into adenoviruses. The liposomes or adenoviruses are then sprayed into the nasal passages and transport the normal alleles into the lungs and lung cells. These cells can then produce the CFTR protein. (For more details about gene therapy, see Factsheet 51, September 1999, Gene Therapy).

Exam Hint: *- In questions about genetic diseases examiners may ask about one or more of three possible factual areas: (i) the genetic basis of the disease, (ii) the symptoms/implications of the disease and (iii) the treatment of the disease.*

Genetic screening and counselling

Genetic screening and counselling is becoming increasingly important in society. This is because the mapping of the human genome by the 'Human Genome Project', the ability to copy large quantities of specific DNA in the 'Polymerase Chain Reaction' and the ability to clone and recognise alleles, has improved methods of diagnosis of genetic disease and accurate prediction of genetic disease. For example:

- **diagnosis** – gene tests are becoming available commercially which can detect mutant alleles in people suspected of having specific diseases or at risk of developing them. For example, tests are available to determine the presence of mutant alleles for cystic fibrosis, Huntington's chorea, sickle cell anaemia, alpha-1-antitrypsin deficiency, juvenile diabetes and haemophilia. These tests may be carried out on the DNA of prospective parents or on DNA obtained from babies in the uterus in the early stages of pregnancy.
- **prediction** – by detecting mutant alleles in a person's genome it may be possible to predict the onset of disease in later life. The onset of such disease may be a certainty, as with the Huntington's chorea allele, or just a probability, as with the juvenile diabetes allele. The detection of mutant alleles in a person will have implications for that person and also for that person's family because the alleles may been received from parents or passed on to children during the normal course of inheritance.

Various **ethical** problems arise out of the new ability to diagnose and forecast genetic disease. For example:

- decisions have to be made whether to abort fetuses that are shown to have serious genetic defects or whether to let them survive so that parents or society then have to take responsibility for their care throughout life.
- decisions have to be made regarding the privacy of an individual's DNA profile. For example, if an individual shows a potential for developing diabetes should that information be made available to interested parties with the result that the individual might be refused employment, pensions rights, life insurance or a mortgage?

Other genetic diseases caused by gene mutation

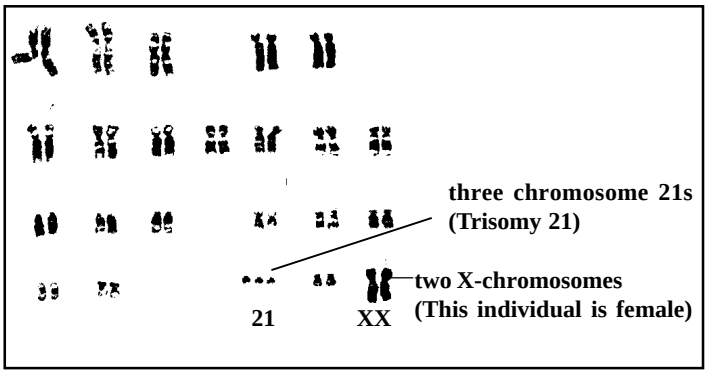
Genetic disease	Genetic basis	Symptoms	Implications/treatment
α – 1 – antitrypsin deficiency	Mutated recessive allele which acts in Mendelian fashion.	A failure of liver cells to make the enzyme á – 1 – antitrypsin means that unwanted proteases in tissues are not destroyed by antitrypsin. The accumulating proteases damage lung and liver tissues.	Affected children develop emphysema (damage to the elastic tissue in the lungs) and cirrhosis (damage to liver cells). Children can be treated by gene therapy or given a nasal spray containing α–1–antitrypsin made by transgenic sheep.
Huntington's chorea	Mutated dominant allele which acts in Mendelian fashion.	Death of brain cells in certain brain centres results in involuntary twitching movements of the face and body (chorea), alternating periods of excitement and depression followed by development of severe dementia.	The disease has its onset in the thirty year old age group and sufferers usually require institutional care. The dominant mutation is passed on to all children and this happens before the parent realises he or she has the condition.
Haemophilia	Sex-linked mutated recessive allele on the X-chromosome	A failure of liver cells to synthesize a clotting factor protein causes a failure of the blood to clot efficiently. This can lead to severe haemorrhage and death.	Females tend to be carriers of the defective allele and sufferers are nearly always male. Sufferers are kept alive by treatment with clotting factors. A drug is now available to correct the mutation in liver cells.
Red-green colour blindness	Sex-linked mutated recessive allele on the X-chromosome	Sufferers have an inability to distinguish certain shades of red and/or green.	Females tend to be carriers of the recessive allele and sufferers are usually male. Sufferers may be refused entry to professions like the police force, fire service, air force. There is no available treatment because gene therapy would be too expensive or risky to use on this harmless condition.

Chromosomal defects: Down's syndrome

The commonest form of Down's syndrome is trisomy 21 in which there are three copies of chromosome 21 in each nucleus. This is due to non-disjunction – a failure of chromosome separation in meiosis resulting in a pair of chromosomes or chromatids passing to the same pole of the cell instead of separating to opposite poles. About 70% of non-disjunctions occur in meiosis I and about 30% in meiosis II. The majority of non-disjunctions occur in the egg and only a few occur in the sperm. The frequency of 'non-disjunctive' eggs rises with the age of the mother and mothers over the age of 40 years are particularly at risk. Because of this, all mothers over the age of 40 are advised to undergo genetic screening by amniocentesis during early pregnancy so that the fetal chromosomes can be analysed.

Remember *– If necessary, amniocentesis is performed under local anaesthetic, at 15-16 weeks of pregnancy. It involves passing a fine needle into the uterus and amniotic cavity, observed with an ultrasound image, and withdrawing some amniotic fluid containing fetal cells. The fetal cells are cultured in a suitable growth medium so that chromosome and DNA analysis, can be carried out. The chromosomes can be stained, photographed, cut out from the picture and spread out in their pairs, Such a picture is called a karyotype and an example of a trisomy 21 karyotype is shown in Fig 4.*

Fig 4. Karyotype of Down's syndrome (trisomy 21) chromosomes



Sufferers of Down's syndrome tend to have a round flat face with eyelids that appear to slant upwards. They have varying degrees of learning disability and are at increased risk of lung, ear and other infections. With antibiotics and modern medical care they can expect to live a fairly normal life for several decades. Trisomy 21 sufferers tend to have a gentle, loving disposition.

A rarer form of Down's syndrome is caused by a translocation mutation. Here the end of a chromosome 21 breaks off and becomes attached to the end of a chromosome 15. (In some cases a complete third chromosome 21 becomes attached to a chromosome 15). Down's sufferers with this mutation tend to have an aggressive disposition.

Exam Hint: *– A common error made by candidates is to confuse gene mutation with chromosome mutation. Mutations such as deletion, substitution, translocation and insertion refer to base changes on the DNA in gene mutation, but to gene/allele loci changes on chromosomes in chromosomal mutation. Be careful you know which type of mutation is involved for a particular disease.*

Practice Questions

1. Klinefelter's and Turner's syndromes are due to chromosomal mutations which affect the sex chromosomes but Down's syndrome is due to autosomal chromosomal mutation. Klinefelter males have the sex chromosomes XXY and Turner females have the sex chromosome XO (only one sex chromosome).
   (a) (i) Name the type of mutation which could have resulted in the XXY or XO genotypes. **1**
   (ii) Explain how the genotypes XXY and XO could have arisen. **4**
   (b) Describe the autosomal abnormalities which can result in Down's syndrome. **3**
   Total 8

2. In the inheritance of sickle-cell anaemia, the normal allele is shown as Hb^A and the sickle-cell allele is shown as Hb^S.
   (a) (i) Describe the mutation of Hb^A which results in the formation of Hb^S. **4**
   (ii) What are the effects on individuals of genotypes $Hb^A Hb^S$ and $Hb^S Hb^S$? **4**
   (iii) Write a genetic diagram of a family tree to show the possible children of two parents, both heterozygous for sickle cell trait. **3**
   (iv) The first child born to these parents had sickle cell anaemia. When counselled the parents were told the probabilities of having further children with either sickle-cell anaemia or sickle-cell trait. What are these probabilities? **2**
   (b) Of 12400 adults examined in malarial regions of Africa, 0.24% were $Hb^S Hb^S$, 24.2% were $Hb^A Hb^S$ and 75.56% were $Hb^A Hb^A$. In non-malarial regions of the world the genotype frequencies are $Hb^S Hb^S$ 0.0001%, $Hb^A Hb^S$ 0.0004% and $Hb^A Hb^A$ 99.9995%. Suggest explanations for these statistics. **4**
   Total 17

3. Read through the following passage about cystic fibrosis and then fill in the spaces with the most appropriate word or words.

Cystic fibrosis is due to a mutation in the ..... coding for the protein called the ..... . This protein regulates the transport of .....
across plasma membranes ..... cells. The mutation is due to ..... and excludes the amino acid ..... from the protein.
As a result of the cellular ..... of ..... , water is drawn osmotically from the ..... which glandular cells secrete. This secretion becomes very thick and sticky, causing severe .....
problems to the sufferer of this condition. **Total 10**

4. Complete the following table of genetic diseases.

Condition	Autosomal or sex-linked	Dominant or recessive	Main symptom
			Failure of the blood to clot.
Huntington's chorea			
			Absence of pigmentation
Colour blindness			
Phenylpyruvica imbecilitus			

Total 5

Answers

1. (a) (i) non-disjunction; **1**
(ii) pair of sex chromosomes passes to the same pole of the cell during meiosis;
no chromosome passes to the other pole;
thus sperm or egg produced may have the genotypes O, XX or XY;
when fertilisation of these occurs with a normal X or Y gamete, XO, or XXY can be formed; **4**

(b) non-disjunction of chromosome 21 leading to trisomy 21;
translocation of end of chromosome 21 onto end of chromosome 15;
attachment of an extra chromosome 21 onto the end of chromosome 15; **3**

Total 8

2. (a) (i) substitution; of DNA base thymine by adenine; causing glutamic acid to be replaced by valine; (at position 6) in the β–polypeptide chain of haemoglobin; **4**

(ii) **Hb^AHb^S :** heterozygous carrier with normal phenotype;
with 50% normal haemoglobin A and 50% abnormal haem globin S;
red cells become sickle shaped in conditions of oxygen deficiency/ref 'sickle-cell trait'.
Hb^SHb^S : abnormal phenotype with 100% haemoglobin S.
red cells permanently sickle, become sticky and clump together to cause blockages in the circulation;
sickle cells are rapidly destroyed, causing severe anaemia and death; **max 4**

(iii)

Parents:	**Hb^AHb^S**		x	**Hb^AHb^S**	
Gametes:	**Hb^A**	**Hb^S**		**Hb^A**	**Hb^S ;**
Children:	**Hb^AHb^A**	**Hb^AHb^S**		**Hb^AHb^S**	**Hb^SHb^S ;**
	normal	**sickle-cell trait**		**sickle-cell trait**	**sickle-cell anaemia ;** **3**

(iv) sickle-cell anaemia: 1 in 4/25% probability;
sickle-cell trait: 1 in 2/50% probability; **2**

(b) *Plasmodium*/malarial parasites cannot feed on haemoglobin S;
thus sickle-cell trait sufferers do not succumb to malaria and survive;
many normal individuals suffer from and die from malaria;
thus frequency of sickle-cell trait sufferers in population is raised;
these individuals breed thus increasing frequency of sickle-cell anaemia sufferers; **max 4**

Total 17

3. allele/gene; CFTR/(cystic fibrosis) transmembrane conductance regulator; chloride (ions); out of; deletion; phenylalanine; accumulation; chloride; mucus; respiratory/pancreatic; **Total 10**

4.

Condition	**Autosomal or sex-linked**	**Dominant or recessive**	**Main symptom**
Haemophilia	**Sex-linked**	**Recessive;**	Failure of the blood to clot.
Huntington's chorea	**Autosomal**	**Dominant**	**Death of brain cells leading to dementia in later life;**
Albinoism	**Autosomal**	**Recessive**	Absence of pigmentation
Colour blindness	**Sex-linked**	**Recessive**	**Inability to distinguish some shades of red and green;**
Phenylpyruvica imbecilitus	**Autosomal**	**Recessive**	**Phenylketonuria /PKU/ brain damage;**

Total 5

Acknowledgements:
This Factsheet was researched and written by Martin Griffin.

ISSN 1351-5136