The haemoglobin protein, found in red blood cells, transports oxygen from the lungs to all parts of the body and gives blood its red colour.

A number of different genetic conditions are due to inheriting one or more faulty copies of the gene(s) that contain the information for the cells to make the globin protein chains.

The haemoglobin gene(s) are located on the long arm of chromosome number 11. There are two copies of each of these chromosomes in every body cell. The genetic information for the body to make the two different haemoglobin chains is contained in two different haemoglobin genes located on two different chromosomes:

- Two identical α-globin genes code for the α globin chains located on chromosome number 16
- The β-globin gene codes for the beta β globin chain located on chromosome number 11

There are two copies of each of these chromosomes in every body cell.

Everyone therefore has four copies of the alpha globin gene and two copies of the beta globin gene in their body cells. Inherited variations in the information that make the alpha or beta globin genes faulty or where the genes are missing (deleted) can lead to haemoglobinopathy conditions.

The World Health Organization (WHO) estimates that globally at least 5% of adults are genetic carriers for a haemoglobin condition: About 2.9% for thalassaemias and About 2.3% for sickle cell disease

The chance of being a genetic carrier for a haemoglobin condition is influenced by the person’s ancestry (see below). Some population groups are more likely to be a genetic carrier for a haemoglobin condition than others. Most countries have an uneven distribution of genetic carriers in their population because the population is made up of people with different ancestries.

What is thalassaemia?

In thalassaemia, one of the haemoglobin chains is either missing, produced in greatly reduced amounts, or has an abnormal structure. As a result, the haemoglobin in the red blood cells of people affected with thalassaemia, does not function normally.

The genetic information for the body to make the two different haemoglobin chains is contained in two different haemoglobin genes located on two different chromosomes:
There are two different types of thalassaemia based on which of the globin chains are affected.

- **Alpha (α) thalassaemia**
- **Beta (β) thalassaemia**

In some cases, an individual can be a genetic carrier for both alpha and beta thalassaemia. Nevertheless, they are no more severely affected than if they were a genetic carrier for one type of thalassaemia only.

### Alpha (α) thalassaemia

There are two pairs of alpha thalassaemia gene copies (a total of four gene copies). Alpha thalassaemia occurs when one or more of the four alpha globin gene copies are faulty. There are four different types of alpha thalassaemia depending on how many of the four alpha globin gene copies are faulty. Two types of alpha thalassaemia are known as carrier states and are not associated with any significant health problems. The other two types of alpha thalassaemia are associated with significant health problems.

#### Carrier states of alpha thalassaemia

- When only one of the four alpha globin gene copies is faulty there is only a small reduction in the amount of alpha globin protein produced by the body. This type of thalassaemia does not cause any health problems. A person with this condition is known as a silent carrier because this type of alpha thalassaemia is not usually detectable by a routine blood test.
- When two of the four alpha globin gene copies are faulty the body produces less alpha globin protein. Individuals with this are generally healthy but may have smaller red blood cells and at worst may have some mild anaemia. This type of thalassaemia is usually detectable on a routine blood test. The two alpha globin gene faults can occur on the same chromosome (alpha zero trait) or on one of each of the chromosome pair (alpha plus trait).

#### Affected states of alpha thalassaemia

- If three of the four alpha globin gene copies are faulty, this may cause a significant health problem. Individuals with this condition have lifelong anaemia that may require treatment with blood transfusions. This condition is an intermediate form of alpha thalassaemia and is also known as haemoglobin H disease or HbH disease.
- When all four of the alpha globin gene copies are faulty this results in a severe form of alpha thalassaemia where babies with the condition usually do not survive long after birth. This is because no alpha globin protein is produced and there is build up of an abnormal haemoglobin protein. This condition is also known as Hb Barts hydrops fetalis.

The different alpha thalassaemias and the gene changes that result in each form of alpha thalassaemia are shown in Figure 34.3a.

### Beta (β) Thalassaemia

There are only two gene copies for beta thalassaemia (one on each chromosome). Beta thalassaemia exists in two states, either as a carrier, (beta thalassaemia minor), or affected (beta thalassaemia major).

#### Beta (β) thalassaemia minor

Beta thalassaemia minor (also known as beta thalassaemia trait) is a condition caused by one of the two beta globin gene copies being faulty. Individuals with this condition are generally healthy, but may have smaller red blood cells and may have mild anaemia. They are carriers for beta thalassaemia.

#### Beta (β) thalassaemia major

- **Beta thalassaemia major**
- **This form of the condition is**
  - Also known as Cooley anaemia
  - Evident after birth, usually within 6 to 12 months
  - A condition in which the main symptom is severe anaemia (a blood condition that makes people tired and pale: not enough oxygen is available to the cells)
    - The anaemia develops during the first few years of life and frequent blood transfusions must be given to maintain the life of a person who has this type of thalassaemia
    - Since iron is an important part of the haemoglobin protein, the transfusions cause a build-up of iron in the person’s heart, liver and other organs. Special treatment is necessary to remove the iron
    - Other features include pallor, lethargy, poor appetite, developmental delay, failure to thrive, growth failure with bone changes and fractures
  - Caused by reduced or absent production of the beta-globin chain of the haemoglobin due to having a loss (deletion) or a change in both copies of the beta globin chain gene
  - More common in people whose ancestry is from the Middle East, Southern Europe, Indian Subcontinent, Central and South East Asia and Africa

### What is sickle cell disease?

Sickle cell disease is also known as HbS disease. The condition is

- Usually characterised by chronic anaemia and also blockage of blood vessels by the sickle-shaped red blood cells, causing bone and chest pain and damage to other organs, failure to thrive, repeated infections and painful swelling of the hands or feet
- Caused by changes in the structure of the beta-globin chains of haemoglobin, i.e. a haemoglobin variant, that result in red blood cells that form an irreversible sickle shape
- More common in people whose ancestry is from Africa, the Middle East, Southern Europe, India, Pakistan, South America and the Caribbean

#### Sickle cell trait

This condition is caused by having one faulty beta-globin gene and one working copy.

People with sickle cell trait are ‘carriers’ of a faulty beta haemoglobin gene: they are genetic carriers for sickle cell disease.

### What does it mean to be a genetic carrier for thalassaemia or sickle cell disease?

While being a carrier for thalassaemia or sickle cell disease may cause a mild anaemia, genetic carriers usually have good health and their bodies function normally. Genetic carriers for sickle cell disease however, may also have problems when having an anaesthetic, the result being that the red blood cells of a carrier can undergo ‘sickling’.
The chance of being a genetic carrier for one of these conditions depends on an individual’s ancestry. The chance of being a carrier is higher in people of certain backgrounds:

- For alpha thalassaemia: China and South East Asia, Southern European countries, the Middle East, the Indian Subcontinent, Pakistan, Africa, the Pacific Islands or New Zealand (Maori)
- For beta thalassaemia: the Middle East, Southern Europe, Indian Subcontinent, Central and South East Asia or Africa
- For sickle cell disease the risk is high if an individual’s ancestry is from Africa, the Middle East, Southern Europe, India, Pakistan, South America or the Caribbean

There are several theories as to why the frequency of the condition, and the number of genetic carriers for thalassaemia, is high in these populations:

- Once a mutation occurs in the haemoglobin chain gene of an egg or sperm cell, it is passed down through the generations of a family
- Geographic barriers would have meant that people from close villages who had the faulty gene would marry and this would have kept the mutation in the haemoglobin chain gene within the local populations. There would be a higher chance of both parents being genetic carriers for one of the types of thalassaemia and therefore the number of children born with thalassaemia, and genetic carriers for thalassaemia would increase
- It is thought that being a genetic carrier for thalassaemia provides protection against malaria, a mosquito-borne disease.

Throughout history, those who were genetic carriers for thalassaemia would have had a better chance of surviving malaria and have children of their own

**How does a person inherit beta thalassaemia or sickle cell disease?**

Haemoglobin conditions are genetic conditions (see Genetics Fact Sheet 2). Therefore they are passed from parents to children in their genes.

Two factors influence the pattern of inheritance of the faulty globin genes causing beta thalassaemia or sickle cell disease in families.

1. These particular globin genes are located on chromosome 11 which is an autosome (a numbered chromosome)
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 of the faulty or missing haemoglobin gene in families is therefore described as **autosomal recessive inheritance** (see Genetics Fact Sheet 8).

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**Figure 34.1a:** Autosomal recessive inheritance where both parents are carriers of the faulty beta globin gene copy. There is one chance in four of having a child with beta thalassaemia major. The faulty haemoglobin beta chain gene copy is represented by ‘r’; the working copy by ‘R’.

**Figure 34.1b:** Autosomal recessive inheritance where both parents are carriers of the faulty haemoglobin globin gene copy. The faulty haemoglobin chain gene copy is represented by ‘r’; the working copy by ‘R’.
In Figures 34.1a&b and 34.2a&b which illustrate the pattern of inheritance, the faulty globin gene copy is represented by ‘r’; the correct copy by ‘R’. There are four possibilities, in every pregnancy, for the combinations of the genes passed from the parents.

As shown in Figures 34.1a and 34.1b, if a couple who are both carriers of the faulty, or missing globin gene have a baby, 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 the haemoglobin condition
- 1 in 4 chance, or 25%, that their child will inherit both copies of the working gene and will be unaffected by the haemoglobin condition 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 the haemoglobin condition, just like the parents

As shown in Figures 34.2a and 34.2b, if only one parent is found to be a carrier of the faulty or missing globin gene, in every pregnancy

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

How does a person inherit alpha thalassaemia?

Alpha thalassaemia is a genetic condition (see Genetics Fact Sheet 2). It is therefore passed down from parents to children in their genes.

Two factors influence the pattern of inheritance of the faulty globin genes causing alpha thalassaemia.

1. These particular globin genes are located on chromosome 16, which is an autosome (a numbered chromosome)
2. The effect of the change in the gene is ‘recessive’ or hidden by the presence of a working copy of the gene (see Genetics Fact Sheets 1, 4, & 5)

The pattern of inheritance of the faulty or missing haemoglobin gene(s) in families is therefore described as autosomal recessive inheritance (see Genetics Fact Sheet 8).

The inheritance of alpha thalassaemia is complicated, however, by there being four alpha globin gene copies; two on each copy of chromosome 16.

Figures 34.3a illustrates the different possible unaffected carrier states for alpha thalassaemia according to how many of the alpha globin genes they have inherited:

- A silent carrier has 3 working copies (2 on one chromosome 16 and only one on the partner chromosome 16; the other gene copy on the partner chromosome 16 is faulty)
- An alpha zero carrier (called trait) has two working copies on one chromosome and only faulty copies on the other
- An alpha plus carrier (trait) has both copies of chromosome 16 containing a working copy and a faulty copy.
A child who has HbH disease will inherit only one working copy of the alpha globin gene. A child with Hb Barts (hydrops fetalis) are has only faulty copies of the alpha gene and will not survive.

An example of a family where parents are carriers for alpha thalassaemia, illustrating the chance of them passing on specific combinations of faulty alpha thalassaemia gene copies to their children, is shown in Figure 34.3b. In this example, there is a possibility that the parents may have a child with the most severe form of alpha thalassaemia, Hb Barts hydrops fetalis. It is important to note that not all the possibilities for carrier parents for alpha thalassaemia have been outlined, and the parents shown in Figure 34.3b are only one such possibility.

**How can people find out if they are genetic carriers for thalassaemia or sickle cell disease?**

A blood test can determine if an individual has a type of alpha thalassaemia trait or has sickle cell trait and is therefore a carrier of the faulty gene involved in that type of haemoglobin condition.

- Even though some of the red blood cells in people with thalassaemia minor or sickle cell trait are abnormal compared to non-carriers, their blood still enables normal body function

There is an increased chance that someone is a carrier of a faulty gene involved in these conditions if they have a family history of the condition or a blood relative who is known to be a genetic carrier for the condition.

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

**How can knowing about having a faulty haemoglobin gene help?**

If both partners in a couple are genetic carriers for thalassaemia, it is important to find out what type of thalassaemia each of them is a genetic carrier for. Both parents must be genetic carriers for the same type of thalassaemia for there to be a chance that they may have a baby with thalassaemia major.

If both partners are genetic carriers for the same type of thalassaemia, or for sickle cell disease, they can find out information about the condition, and their risks, and discuss their reproductive options with a genetic counsellor (see Genetics Fact Sheet 3).

Prenatal testing for thalassaemia or sickle cell disease may be possible in pregnancy where the baby’s haemoglobin chain genes would be examined (see Genetics Fact Sheet 21) and testing in association with assisted reproductive technologies (ART) such as in vitro fertilisation (IVF) may also be possible (see Genetics Fact Sheets 17C and 18).

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

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**Figure 34.3a:** The different possible carrier states for alpha thalassaemia (silent carrier, alpha zero trait and alpha plus trait) and affected states (HbH disease and Hb Barts hydrops fetalis) are shown in this figure. The faulty alpha globin gene copies are indicated by a minus sign (−) and working copies of the gene by ‘a’.

**Figure 34.3b:** Autosomal recessive inheritance where both parents are carriers of two faulty alpha globin gene copies on one of their chromosome 16 (alpha zero trait). There is one chance in four of having a child with a severe form of alpha thalassaemia major, Hb Barts hydrops fetalis. The faulty alpha globin gene copies are indicated by a minus sign (−) and working copies of the gene by ‘a’.

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