This fact sheet describes thalassaemia and includes the symptoms, cause and any treatment or testing which is available.

In summary

- Thalassaemia is a common inherited red blood cell condition that may cause lifelong anaemia, often requiring regular blood transfusions
- There are two main types: alpha (α) thalassaemia and beta (β) thalassaemia
- It is caused by changes in the alpha globin or beta globin genes that code for the oxygen carrying protein haemoglobin in our red blood cells
- Thalassaemia is inherited in an autosomal recessive pattern and genetic carriers for thalassaemia usually do not have any symptoms.

WHAT IS THALASSAEMIA?

Thalassaemia is a common inherited red blood cell condition that causes lifelong anaemia. People affected with thalassaemia have small, pale red blood cells due to reduced level of functioning haemoglobin (a protein inside the red blood cells). This is known as anaemia and may cause tiredness, lethargy, pale skin (pallor) and other serious complications. The two main types of thalassaemia are:

1. **Alpha (α) thalassaemia:** more common in people whose ancestry is from China, South East Asia, Eastern Mediterranean, Africa, the Pacific Islands and New Zealand (Maori).
2. **Beta (β) thalassaemia:** more common in people whose ancestry is from the Middle East, Mediterranean, Africa, Indian Subcontinent, Central and South East Asia and the Caribbean.

Alpha (α) Thalassaemia

There are two forms of alpha thalassaemia that may cause health problems:

- **Haemoglobin H (HbH) disease**: is a mild form of alpha thalassaemia that causes mild to moderate anaemia that may require treatment with blood transfusions (either intermittently or on a regular basis), an enlarged spleen and jaundice (yellowing) of the eyes and skin.
- **Haemoglobin Barts hydrops fetalis (Hb Barts) syndrome:** is a severe form of alpha thalassaemia where excess fluid builds up in the developing baby due to severe anaemia and the baby usually does not survive long after birth. There may also be complications for the pregnant mother carrying an affected baby, including dangerously high blood pressure (preeclampsia) health problems. It is also possible to be a genetic carrier for alpha thalassaemia, known as al**pha plus thalassaemia trait** or **alpha zero thalassaemia trait**, but neither of these pose any significant health problems.

Beta Thalassaemia

There are two forms of beta thalassaemia that may cause health problems:

- **Beta Thalassaemia Intermedia:** is a milder version of beta thalassaemia major, causing mild to moderate anaemia. Symptoms may appear in early childhood or later in life and blood transfusions may be required. Other symptoms include slow growth and bone changes.
- **Beta Thalassaemia Major:** also known as Cooley's anaemia is the more severe form of beta thalassaemia. Children develop life-threatening anaemia within the first year of life and require regular blood transfusions throughout their life. A build-up of iron due to regular transfusions may cause health complications and medications are needed to remove the excess iron. Other symptoms may include failure to thrive, jaundice (yellowing) of the eyes and skin, enlarged spleen, bone changes and developmental delay.

It is also possible to be a genetic carrier for beta thalassaemia, known as **beta thalassaemia trait** or **beta thalassaemia minor**; neither of these pose any significant health problems.

WHAT CAUSES THALASSAEMIA?

Inside our red blood cells there are proteins called haemoglobin, whose job is to transport oxygen from the lungs to all parts of the body. Haemoglobin is what gives our red blood cells their red colour and is made up of four chains, two alpha globin chains and two beta globin chains.

Variations in the genes that code for the alpha globin chains and beta globin chains may result in the haemoglobin not functioning properly. Symptoms will vary depending on whether it is the alpha globin chain or beta globin chain that is faulty.

Our body is made up of millions 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 little 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.

Since all our chromosomes come in pairs, all our genes also come in pairs. Sometimes, a gene may have a variation in the instruction that causes the gene to no longer function properly. This variation is called a **mutation** or **pathogenic variant**, and means that the product produced by the gene, called a protein, is impaired or even absent.

Gene mutations may be inherited from a parent, or occur for the first time in an individual. Once you have a gene mutation however, it may be passed on to future generations. This is referred to as genetic inheritance.

Alpha Thalassaemia

There are two pairs of alpha globin genes on chromosome 16 (a total of four alpha globin genes, two on each chromosome), that code for the alpha globin chains. Alpha thalassaemia occurs when one or more of the four alpha globin gene copies are faulty.

- **Genetic carriers for alpha thalassaemia**: have one or two faulty copies of the alpha globin genes. As there are at least two working gene copies, enough alpha globin chains are created to prevent any serious health complications. People with one faulty gene copy have *alpha plus thalassaemia trait* and may not have any indication of being a genetic carrier for thalassaemia from routine blood tests.

  People with two faulty gene copies have *alpha zero thalassaemia trait* and usually have small, pale red blood cells on routine blood tests.
- **People affected with alpha thalassaemia**: have three or four faulty copies of the alpha globin genes. *Haemoglobin H disease* is caused by three faulty gene copies and causes a mild to moderate anaemia. *Haemoglobin Barts hydrops fetalis* has all four alpha globin genes not working properly and affected babies usually do not survive long after birth.

The different alpha thalassaemias and the gene changes that result in each form of alpha thalassaemia are shown in *Figure 43.1*.

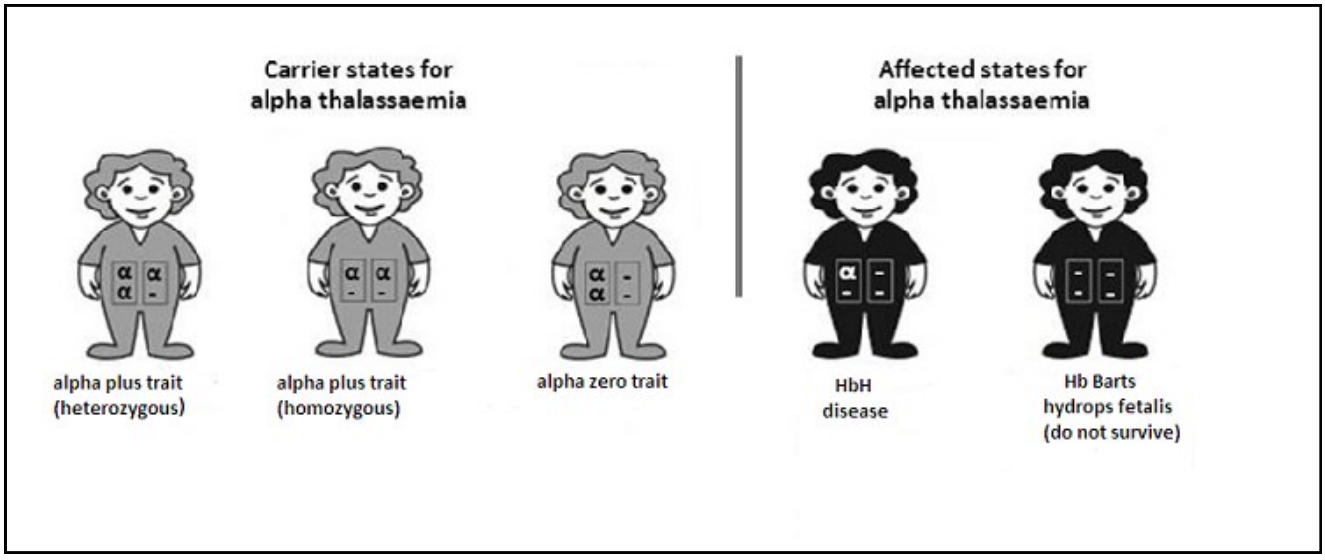

Figure 43.1: *The different possible carrier states for alpha thalassaemia (alpha plus trait and alpha zero trait) and affected states (HbH disease and Hb Barts hydrops fetalis) are shown in this figure. The faulty alpha globin gene copies on chromosome 16 are indicated by a minus sign (-) and working copies of the gene by 'a'.*

Beta Thalassaemia

There is one pair of beta globin genes on chromosome 11 (a total of two beta globin genes, one on each chromosome pair), that code for the beta globin chains. Beta thalassaemia occurs when one or both copies of the beta globin gene copies are faulty.

- **Genetic carriers for beta thalassaemia:** have one faulty copy and one working copy of the beta globin gene. This is called *beta thalassaemia trait or beta thalassaemia minor.* Genetic carriers are generally healthy but usually have slightly small, pale red blood cells.
- **People affected with beta thalassaemia:** have both faulty copies of the beta globin gene. The severity of the symptoms may vary depending on the genetic variation, and may be classified as either *beta thalassaemia major* or *beta thalassaemia intermedia.*

HOW IS THALASSAEMIA INHERITED?

Thalassaemia is a genetic condition that follows a pattern of **autosomal recessive inheritance.** Autosomal refers to the fact that the alpha and beta globin genes are located on the numbered chromosomes (16 and 11), and therefore affects males and females equally.

Recessive means that, in order to develop signs and symptoms of the condition, both copies of the globin genes must be faulty (or at least 3 out of 4 alpha globin genes).

For Alpha Thalassaemia:

If a couple are both genetic carriers for alpha zero thalassaemia trait (*Figure 43.2*), in every pregnancy there is:

- 1 chance in 4 (25% chance) that they will have a child who inherits both copies of the recessive gene mutation from his/her parents. In this case, no working gene product will be produced and their child will have Hb Barts hydrops fetalis and will not survive.
- 1 chance in 4 (25% chance) that their child will inherit both copies of the working gene and will be unaffected by alpha thalassaemia and not a genetic carrier
- 1 chance in 2 (2 chances in 4 or 50% chance) that their child will inherit the recessive gene mutation and the working copy of the gene from the parents and he/she will be an unaffected genetic carrier for alpha thalassaemia, just like the parents.

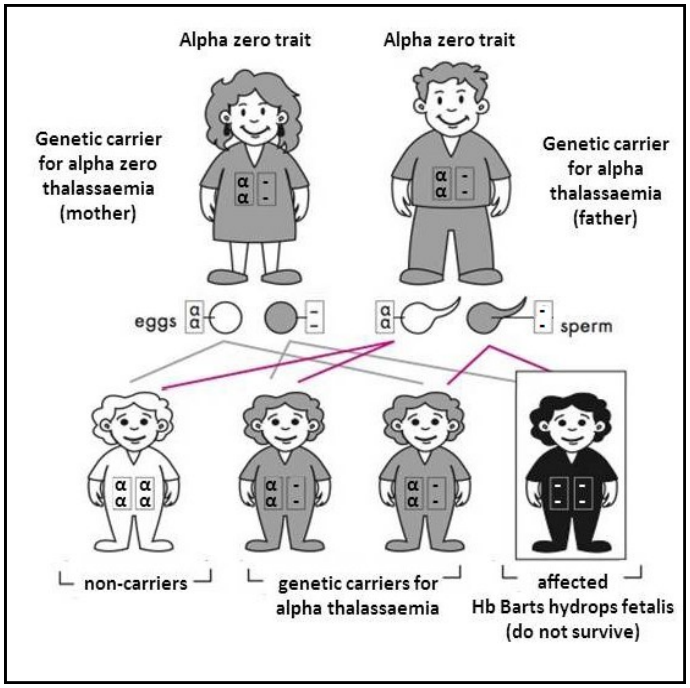

Figure 43.2: *Autosomal recessive inheritance where both parents are carriers of two faulty alpha globin gene copies on one of their copies of chromosome 16 (alpha zero trait). There is one chance in four of having a child with a severe form of alpha thalassaemia major, Hb Barts hydrops fetalis. The faulty alpha globin gene copies are indicated by a minus sign (-) and working copies of the gene by 'a'.*

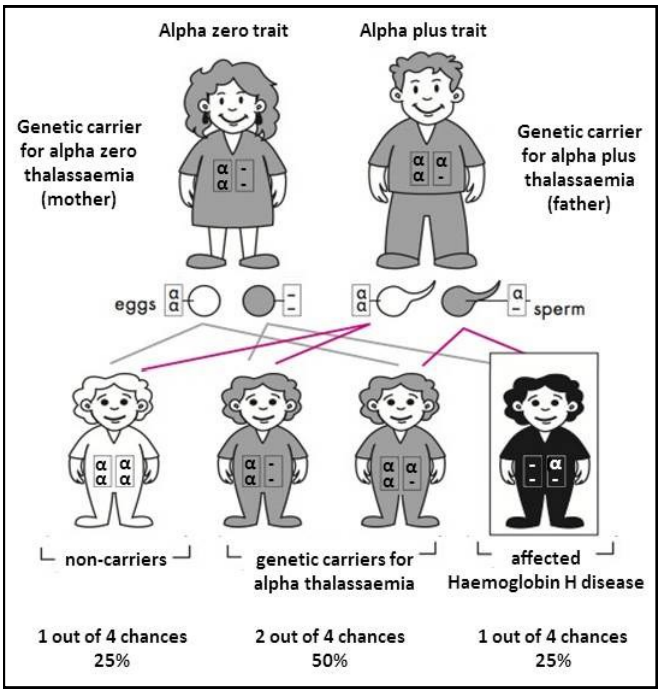

Figure 43.3: *Autosomal recessive inheritance where parent is a carrier of two faulty alpha globin gene on one of their copies of chromosome 16 (alpha zero trait) and the other parent is a carrier of one faulty alpha globin gene.on one of their copies of chromosome 16 (alpha plust trait). There is one chance in four of having a child with a mild form of alpha thalassaemia, Haemoglobin H disease. The faulty alpha globin gene copies are indicated by a minus sign (-) and working copies of the gene by 'a'.*

If a couple where one parent is a carrier for alpha zero thalassaemia trait and the other parent is a carrier for alpha plus thalassaemia trait (*Figure 43.3*), in every pregnancy there is:

- 1 chance in 4 (25% chance) that they will have a child who inherits both copies of the recessive gene mutation from his/her parents. In this case, a reduced working protein will be produced and their child will be affected by Haemoglobin H disease
- 1 chance in 4 (25% chance) that their child will inherit both copies of the working gene and will be unaffected by alpha thalassaemia and not a genetic carrier
- 1 chance in 2 (2 chances in 4 or 50% chance) that their child will inherit the recessive gene mutation and the working copy of the gene from the parents and he/she will be an unaffected genetic carrier for alpha thalassaemia, just like the parents.

If a couple are both genetic carriers for alpha plus thalassaemia trait, then, at worst, the baby has a 1 chance in 4 (25%) of inheriting both single gene mutations, one on each chromosome.

As there are still two working copies of the alpha globin gene, enough haemoglobin protein is created to prevent any significant health problems. The baby will therefore be a healthy genetic carrier.

Likewise, If only one parent is a carrier for either alpha zero thalassaemia trait or alpha plus thalassaemia trait, then at worst the baby has a 1 chance in 2 (50%) of also being a genetic carrier. In all these cases, there is no chance that the baby will be affected with alpha thalassaemia.

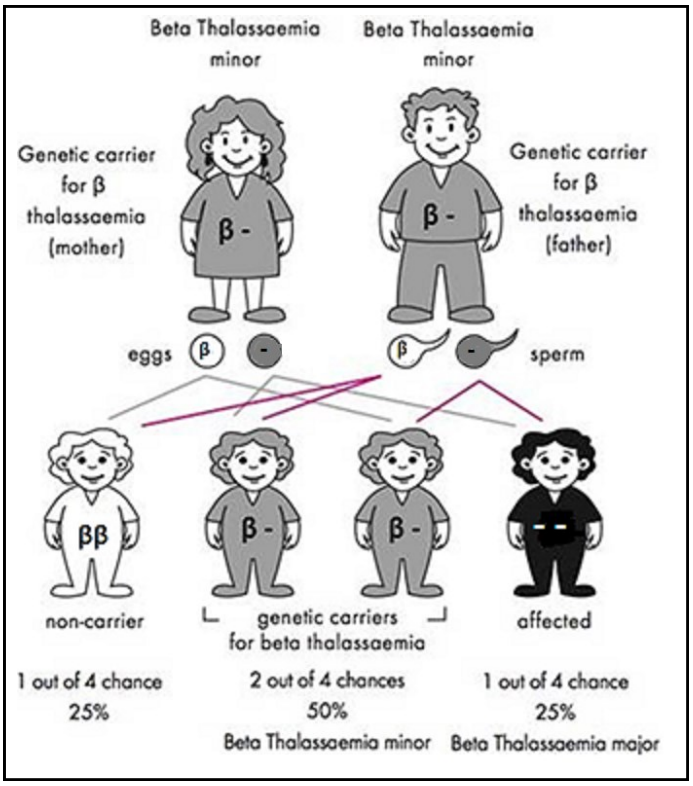

Figure 43.4: *Autosomal recessive inheritance where both parents are carriers of the faulty beta globin gene copy on chromosome 11. There is one chance in four of having a child with beta thalassaemia major. The faulty haemoglobin beta chain gene copy is represented by a minus sign (-); the working copy by 'B'.*

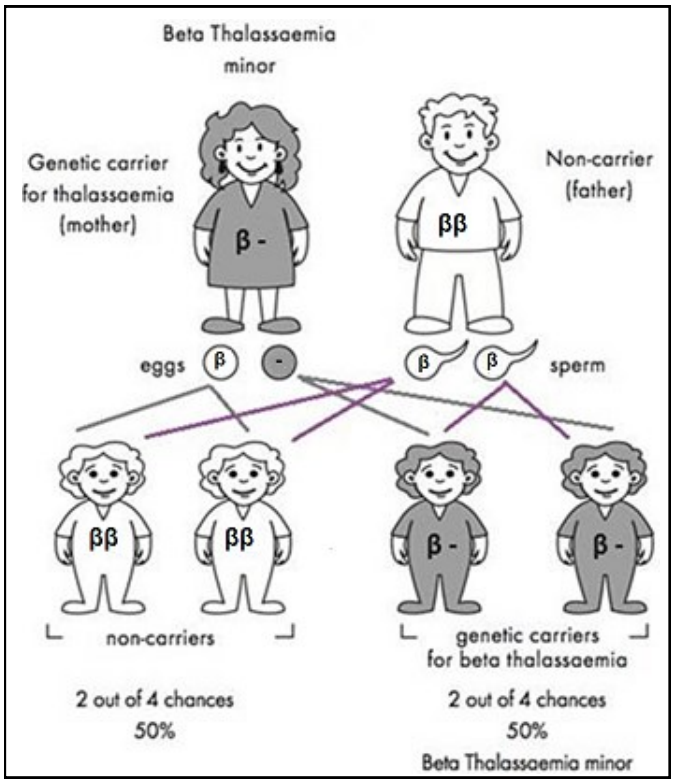

Figure 43.5: *Where only one parent is a carrier of the faulty beta globin gene copy on chromosome 11, there is no chance of having a child with beta thalassaemia major. The faulty haemoglobin beta chain gene copy is represented by a minus sign (-); the working copy by 'B'.*

For Beta Thalassaemia:

If a couple are both genetic carriers for beta thalassaemia (*Figure 43.4*), in every pregnancy there is:

- 1 chance in 4 (25% chance) that they will have a child who inherits both copies of the recessive gene mutation from his/her parents. In this case, no working gene product will be produced and their child will be affected by beta thalassaemia
- 1 chance in 4 (25% chance) that their child will inherit both copies of the working gene and will be unaffected by beta thalassaemia and not a genetic carrier
- 1 chance in 2 (2 chances in 4 or 50% chance) that their child will inherit the recessive gene mutation and the working copy of the gene from the parents and he/she will be an unaffected genetic carrier for beta thalassaemia, just like the parents.

If only one parent is found to be a carrier for beta thalassaemia (*Figure 43.5*) in every pregnancy there is:

- No chance that the couple will have a baby affected beta thalassaemia
- 1 chance in 2 (2 chances in 4 or 50% chance) that they will have a child who inherits both copies of the working gene from his/her parents. In this case, the child will be unaffected by beta thalassaemia
- 1 chance in 2 (2 chances in 4 or 50% chance) that their child will inherit the recessive gene mutation and the working copy of the gene from the parents and he/she will be an unaffected genetic carrier for beta thalassaemia.

What happens if an alpha thalassaemia carrier and a beta thalassaemia carrier have a family?

It is possible that one parent may be a genetic carrier for alpha thalassaemia and the other parent is a genetic carrier for beta thalassaemia.

There is a 1 chance in 4 (25%) that the baby will inherit both genetic mutations and be a carrier for both alpha thalassaemia and beta thalassaemia. As the genes involved are different and have different roles in the production of haemoglobin, the baby will not develop any signs or symptoms of anaemia, and will only be a healthy genetic carrier for both conditions.

What about haemoglobin variants and thalassaemia?

Haemoglobin variants is a term used to describe a specific change in the alpha or beta globin genes that alters the *structure* of the haemoglobin produced, rather than reduce the amount of haemoglobin. Some common examples include Haemoglobin S (also known as sickle cell disease), or Haemoglobin E.

Sometimes one parent may be a genetic carrier for thalassaemia and the other parent is a genetic carrier for a haemoglobin variant. Depending on the combination, it is possible that a baby will have some thalassaemia-like symptoms. It is best to discuss the possible outcomes with your genetic health professional based on you and your partner's genetic carrier status.

What does it mean to be a genetic carrier?

Being a genetic carrier for thalassaemia is quite common in different ethnicities, and may be as high as 1 in 10 in certain populations.

- Being a genetic carrier for thalassaemia is not like being a carrier of an infectious virus such as hepatitis where the hepatitis virus is carried in the body
- Genetic carriers for thalassaemia do not carry thalassaemia in their bodies and cannot pass it on to others like a virus. They can however, pass the faulty gene on to their children as described above.

There is a high proportion of thalassaemia genetic carriers found in countries where the mosquito-borne disease malaria is more common. Being a genetic carrier for thalassaemia is believed to provide some natural protection against severe forms of malaria.

Many children used to die from malaria, and it was noted that children who were thalassaemia genetic carriers were more likely to survive the disease and, in turn, pass on their genetic carrier status to their children. Hence, there are now many genetic carriers for thalassaemia in areas where malaria is (or was) more common.

IS THERE ANY TESTING AVAILABLE FOR THALASSAEMIA?

People who are affected with thalassaemia have chronic anaemia, and this may be detected through specialised blood tests through your family doctor. These blood tests may also identify genetic carriers for thalassaemia, although some milder forms like alpha plus thalassaemia trait are not always identified on these blood tests alone. Genetic testing of the alpha globin genes or beta globin gene may be performed to confirm a diagnosis of thalassaemia, or to confirm the genetic carrier status of a person.

Testing for genetic carrier status

When a person is identified as a genetic carrier for thalassaemia, their first degree relatives (parents, children, brothers and sisters) all have a 1 chance in 2 (50%) of also being a genetic carrier. Screening may be performed through specialised blood tests through your family doctor, or genetic testing may be offered if the gene mutations have been identified in your family.

Prenatal testing and PGD

For couples who are both known genetic carriers for thalassaemia, testing may be available during a pregnancy to determine whether the baby will be unaffected, affected or a genetic carrier for thalassaemia. It may also be possible to undergo **pre-implantation genetic diagnosis** (PGD) screening for thalassaemia on an embryo created using in vitro fertilisation (IVF). These options are best discussed and considered before pregnancy, when possible, in order to ensure all possible risks, benefits and outcomes to be explored.