Fact sheet **43**

THALASSAEMIA

This fact sheet talks about a group of genetic conditions called thalassaemia and includes details of symptoms, causes and treatments or testing available.

IN SUMMARY

- Thalassaemia is a common inherited red blood cell condition that may cause lifelong anaemia, often requiring regular blood transfusions and/or medications
- 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 way and genetic carriers for thalassaemia usually do not have any signs or symptoms
- Couples where both partners are genetic carriers for the same type of thalassaemia have a 1 in 4 (25%) chance of having a baby with thalassaemia

WHAT IS THALASSAEMIA?

Thalassaemia is a common inherited red blood cell condition that causes lifelong anaemia. People 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, 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. Treatment may be needed with blood transfusions (either now and then or on a regular basis). Other features include a larger than usual spleen (organ that filters blood) 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 in pregnancy due to severe anaemia. 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). It is also possible to be a genetic carrier for alpha thalassaemia, known as **alpha plus thalassaemia trait** or **alpha zero thalassaemia trait**, but neither of these are likely to pose any significant health problems on their own.

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 start in early childhood or later in life and blood transfusions may be needed. 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 serious anaemia within the first year or two of life and require regular blood transfusions throughout their life.

Content updated November 2021
NOV21/V1 NS12676
SHPN: (HETI) 241007

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 generally pose any significant health problems on their own.

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 working properly. Symptoms will vary depending on whether it is the alpha globin chain or beta globin chain that is not working.

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 happens when one or more of the four alpha globin gene copies are not working.

- **Genetic carriers for alpha thalassaemia:** have one or two non-working copies of the alpha globin genes. As there are at least two working gene copies, enough alpha globin chains are made to prevent any serious health complications. People with one non-working 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 non-working gene copies have *alpha zero thalassaemia trait* and usually have small, pale red blood cells on routine blood tests.

Our body is made up of billions of cells, and in each cell there are instructions, called genes, that make all the necessary structural components and chemicals for the body to work properly. These genes are packaged onto 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. The genes provide the instructions for proteins, which are the building blocks of the cells that make up our body. Although we all have variation in our genes, sometimes this can affect how our bodies grow and develop. Generally, gene variations that have no impact on our health are called benign variants or polymorphisms. These variants tend to be more common in people. Less commonly, variations can change the gene so that it sends a different message. These changes may mean that the gene does not work properly or works in a different way that is harmful. A variation in a gene that causes a health or developmental condition is called a pathogenic variant or mutation.

Gene variants may be inherited from a parent, or happen for the first time in a person. Once you have a gene variant, however, it may be passed on to future generations. This is referred to as genetic inheritance.

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 non-working alpha globin gene copies on chromosome 16 are indicated by a minus sign (-) and working copies of the gene by 'a'.

- **People with alpha thalassaemia:** have three or four non-working copies of the alpha globin genes. *Haemoglobin H disease* is caused by three non-working gene copies and causes a mild to moderate anaemia that is treatable. *Haemoglobin Barts hydrops fetalis* is where all four alpha globin genes are not working properly and babies with this 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*.

Beta Thalassaemia

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

- **Genetic carriers for beta thalassaemia:** have one non-working gene 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 copies of the beta globin gene not working. 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 non-working (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 in 4 (25%) chance that they will have a child who inherits both copies of the recessive gene variant from their parents. In this case, no working gene product will be made and their child will have Hb Barts hydrops fetalis and will not survive.
- 1 in 4 (25%) chance that their child will inherit both copies of the working gene and will not have alpha thalassaemia and is not a genetic carrier
- 1 in 2 (50%) chance that their child will inherit the recessive gene variant and the working copy of the gene from the parents and they 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 non-working 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 non-working alpha globin gene copies are indicated by a minus sign (-) and working copies of the gene by 'a'.

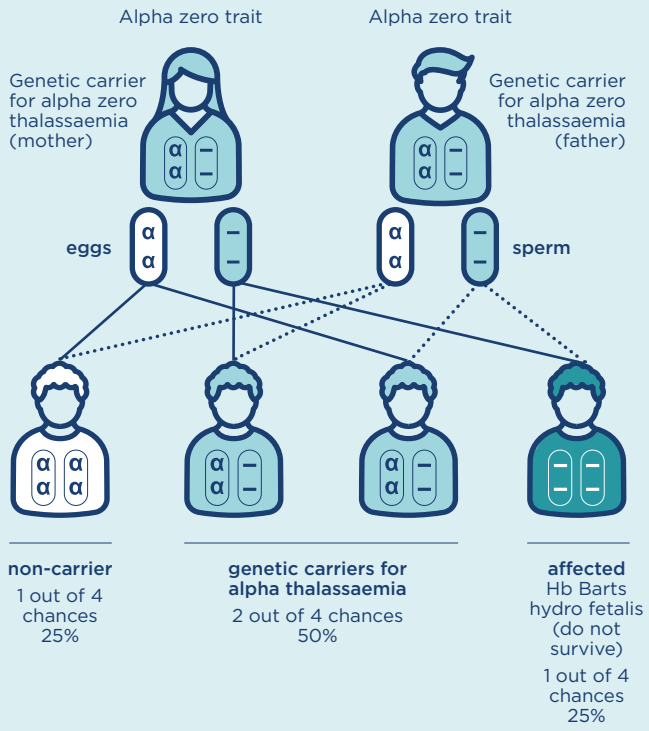
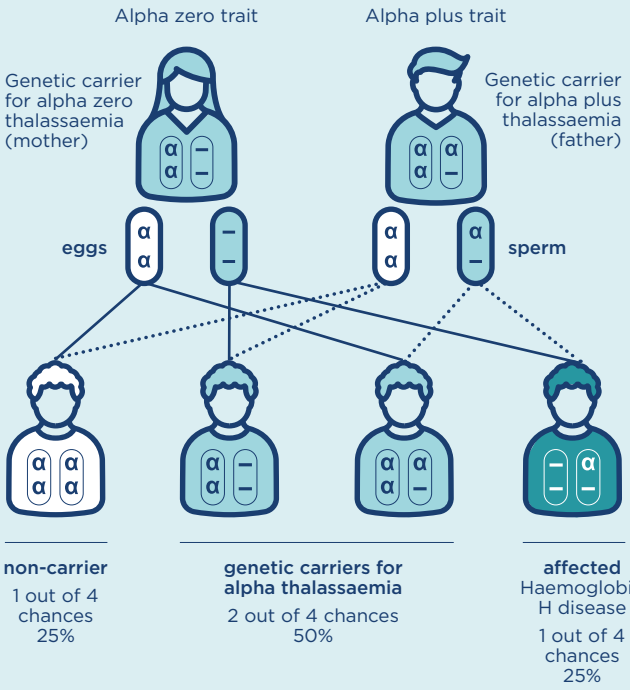


Figure 43.3:
Autosomal recessive inheritance where parent is a carrier of two non-working alpha globin gene on one of their copies of chromosome 16 (alpha zero trait) and the other parent is a carrier of one non-working alpha globin gene on one of their copies of chromosome 16 (alpha plust trait). There is one chance in four of having a child with a mild form of alpha thalassaemia, Haemoglobin H disease. The non-working 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 in 4 (25%) chance that they will have a child who inherits both copies of the recessive gene variant from their parents. In this case, reduced working protein will be made and their child will have Haemoglobin H disease
- 1 in 4 (25%) chance that their child will inherit both copies of the working gene and will not have alpha thalassaemia and is not a genetic carrier
- 1 in 2 (50%) chance that their child will inherit the recessive gene variant and the working copy of the gene from the parents and they will be an unaffected genetic carrier for alpha thalassaemia, just like either parent.

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 variants, one on each chromosome.

As there are still two working copies of the alpha globin gene, enough haemoglobin protein is made 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, the baby will not have alpha thalassaemia.

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

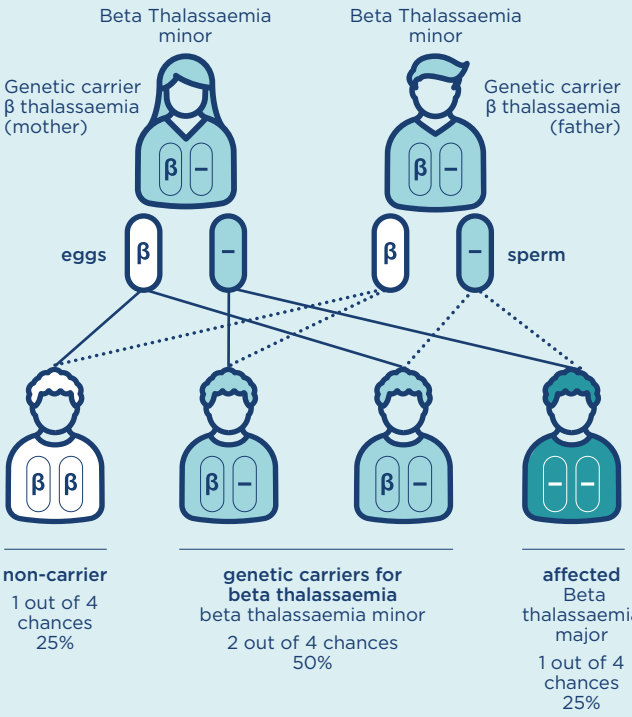
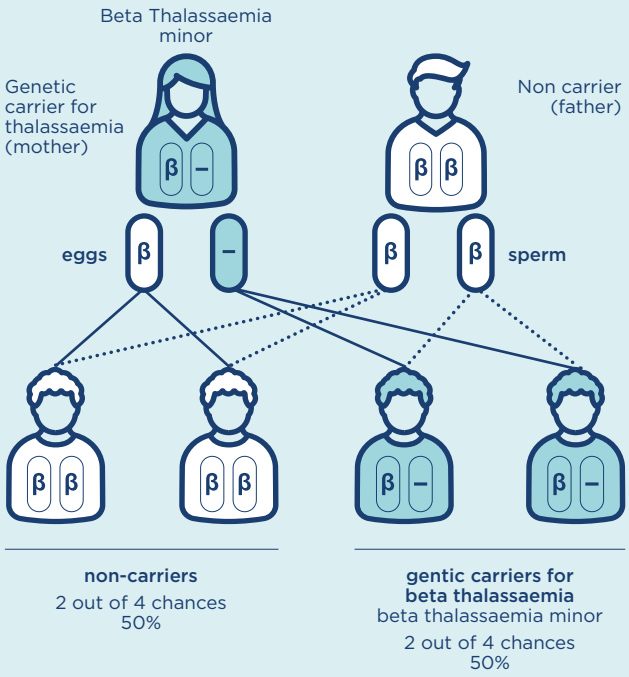


Figure 43.5:
Where only one parent is a carrier of the non-working beta globin gene copy on chromosome 11, there is no chance of having a child with beta thalassaemia major. The non-working haemoglobin beta chain gene copy is represented by a minus sign (-); the working copy by 'β'.



For Beta Thalassaemia:

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

- 1 in 4 (25%) chance that they will have a child who inherits both copies of the recessive gene variant from their parents. In this case, no working gene product will be made and their child will have beta thalassaemia
- 1 in 4 (25%) chance that their child will inherit both copies of the working gene and will not have beta thalassaemia and is not a genetic carrier
- 1 in 2 (50%) chance that their child will inherit the recessive gene variant and the working copy of the gene from the parents and they 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 with beta thalassaemia

- 1 in 2 (50%) chance that they will have a child who inherits both copies of the working gene from their parents. In this case, the child will not have beta thalassaemia
- 1 in 2 (50%) chance that their child will inherit the recessive gene variant and the working copy of the gene from the parents and they 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 variants 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. These are both variants of the beta globin chain.

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 talk about the possible outcomes with your health care practitioner based on you and your partner's genetic carrier status.

IS THERE ANY TESTING AVAILABLE FOR THALASSAEMIA?

People 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 found on these blood tests alone. Genetic testing of the alpha globin genes or beta globin gene may confirm a diagnosis of thalassaemia or genetic carrier status of a person.

Testing for genetic carrier status

When a person is found to be 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 by specialised blood tests through your family doctor, or genetic testing may be offered if the gene variants have been identified in your family.

Planning a pregnancy

For couples who are both known genetic carriers for thalassaemia, testing may be available during a pregnancy. This will work out whether the baby will be unaffected, have thalassaemia or is a genetic carrier for thalassaemia.

Genetic testing in a pregnancy for thalassaemia is optional and should be talked about in full with your doctor, midwife or genetic counsellor. It may also be possible to have pre-implantation genetic diagnosis (PGD) to look for thalasseamia in an embryo made using in vitro fertilisation (IVF).

Reproductive genetic carrier screening is also available for couples who are planning pregnancy, or are in early pregnancy. This may include genetic screening for thalassaemia amongst other recessive genetic conditions.

When planning a family, options for testing are best talked about and considered before pregnancy.

More support and information is available for individuals and families through support organisations including Genetic Alliance Australia.