

7. Thalassaemia disorders

Contents

7.1 Key points	2
What are thalassaemia disorders?	2
The carrier state	2
Who should be investigated?	3
Investigations	3
7.2 Background	4
What are the thalassaemia disorders?	4
The carrier state	5
The disease state (β -thalassaemia major)	10
Appendix 1: Haemoglobinopathies caused by structural change ...	11
7.3 Patient and further information	12
7.4 Where to refer	13

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7.1 Key points

What are the thalassaemia disorders?

- The thalassaemias are part of a group of disorders affecting haemoglobin, collectively known as haemoglobinopathies. Haemoglobinopathies are the most common blood condition worldwide and are usually found in the Mediterranean countries, the Middle East, Africa, Asia and the Indian subcontinent.
- A haemoglobin molecule comprises four globin chains (two α -globin chains and two β -globin chains) and four haem molecules. Alterations (mutations) in the genes encoding the globin chains cause haemoglobinopathies.
- Thalassaemia states are characterised by the decreased production or absence of one or more of the component chains of haemoglobin and may result in varying degrees of hypochromic, microcytic anaemia.
- α -thalassaemias are caused by decreased production of the α -globin chain. β -thalassaemias are caused by decreased or absent production of the β -globin chain.
- Other types of thalassaemia can arise from more complex rearrangements.
- Thalassaemia major is due to a complete absence of one of the types of globin chains and is medically severe disease.
- Thalassaemia minor is the carrier state and is due to reduced quantities of one globin chain type. Individuals with thalassaemia minor may have minor haematological changes, such as low red cell indices, which can be confused with iron deficiency.
- In general, the thalassaemia major states are autosomal recessive, with two gene alterations present. However the genetics are complicated.
- Other haemoglobinopathies are due to structural variations in haemoglobin and include HbS (sickle cell trait or disease), HbC and HbE (see Appendix 1). The co-existence of a haemoglobin variant and thalassaemia can be clinically significant. Some carriers may not be anaemic and have normal red cell indices. Specific haemoglobinopathy testing is required for diagnosis.

The carrier state

- Many healthy people in Australia are carriers of an altered globin gene.
- The risk of having thalassaemia minor is higher in certain ethnic groups; however, individuals with thalassaemia minor are also found in low-risk ethnic backgrounds.
- It is important to identify the thalassaemia carrier state in women of childbearing age because if she and her partner are carriers of a thalassaemia disorder and/or haemoglobin variant, they may be at risk of having a severely affected child.
- Identification of individuals with thalassaemia minor and haemoglobin variants prior to pregnancy is preferable to allow time for testing the partner and, if necessary, DNA studies.

Whenever an individual with thalassaemia minor is identified it is *essential* that the partner be also investigated. If the woman is already pregnant, testing of the baby's father is an urgent priority and should be performed in consultation with a specialist.

- If both members of the couple are carriers of a thalassaemia disorder and/or a haemoglobin variant, they have an increased risk of having a severely affected child. They *should be immediately referred to specialist services* for counselling and DNA studies.
- Prenatal diagnosis is available to couples who are at risk of having a child with severe disease, if the causative gene changes are known. The diagnosis is performed on a sample of cells collected by chorionic villus sampling (see Part 5 *Testing during pregnancy*).

Who should be investigated?

- Women considering pregnancy.
- All pregnant women.
- Partners of individuals who have suspected or confirmed thalassaemia minor or are carriers of a haemoglobin variant.
- A family history of haemoglobinopathy (thalassaemia and/or haemoglobin variant) or haemoglobinopathy carrier state.
- Personal history of unexplained anaemia.

Consider for all women of childbearing age.

Investigations

At present there is not complete consensus regarding screening for thalassaemia carrier state.

The testing regimen will depend on the clinical picture and will be influenced by pregnancy, ethnic background, consanguinity, a family history of thalassaemia and/or haemoglobin variants or carrier state and test status of the partner.

Identifying individuals with thalassaemia minor is usually a multistep process, with results of FBE, ferritin studies and clinical features influencing decisions regarding haemoglobinopathy testing¹ and DNA analysis. For specific advice, contact a service with expertise in screening for thalassaemia and haemoglobin variants.

- It is considered good practice to investigate all women of childbearing age with FBE and ferritin. Ferritin is ordered because iron deficiency can interfere with the techniques used to test for thalassaemia minor.
- **Haemoglobinopathy testing may be performed when there is a clinical suspicion of carrier state such as:**
 - ✦ Reduced red cell indices (MCV < 80fL or MCH < 27pg) and normal ferritin.
 - ✦ An ethnic background suggestive of increased risk.
 - ✦ A family history of haemoglobinopathy (thalassaemia and/or haemoglobin variant) or haemoglobinopathy carrier state.
 - ✦ Partners of individuals who have thalassaemia minor or are carriers of a haemoglobin variant.

¹ Haemoglobin testing refers to the identification and/or quantification of haemoglobin molecules. As different techniques (for example, haemoglobin electrophoresis and high-performance liquid chromatography) are used by different laboratories, a generic term has been applied.

7.2 Background

What are the thalassaemia disorders?

The thalassaemias are, collectively, one of the most common inherited blood disorders worldwide and often seen in many populations including those of Mediterranean background and people from the Middle East, Africa, Asia and the Indian subcontinent. Thalassaemia is caused by the altered rate of production of haemoglobin chains. A consequence of this imbalance is ineffective erythropoiesis, decreased red blood cell survival and, depending on severity, possible anaemia and an expanded blood volume.

As a number of different genes encode the haemoglobin chains, the thalassaemias are genetically heterogenous. Beta (β) thalassaemia and Alpha (α) thalassaemia are the most common types.

The decreased production of α - or β -globin chains usually results in low or borderline red cell indices. Investigations of haemoglobin composition and quantity can assist in diagnosis of thalassaemia and thalassaemia carriers.

Other haemoglobinopathies are caused by structural variations in the haemoglobin chain and include HbS (sickle cell trait or disease), HbC and HbE, with other significant abnormalities listed in Appendix 1. These haemoglobin variants can co-exist with thalassaemia mutations to produce major thalassaemia syndromes. HbE is the most common haemoglobin abnormality in Southeast Asia, and affects up to 30% of people in some areas.

α -thalassaemia

- α -thalassaemia is most commonly seen in individuals of Asian origin but occurs in many other ethnic groups.
- α -thalassaemia is caused by decreased or absent production of the α -globin chains.
- There are two identical genes encoding α -globin chains. Each individual inherits two copies of these two genes from each parent – a total of four copies altogether.
- α -thalassaemia major is most commonly caused by *deletion of all four copies* and results in *Hydrops Fetalis*, causing early fetal or neonatal death. In addition, the mother of an affected fetus is at risk of severe early pre-eclampsia, ante partum or post partum haemorrhage, and pre-term delivery.
- *Haemoglobin H disease* is caused by deletion of three copies of the α -globin genes. This is an intermediate form of α -thalassaemia, which varies in severity. HbH disease can cause life long anaemia of mild to moderate degree and rarely requires transfusion support. Medical management may be required.
- Individuals with α -thalassaemia minor have *one or two* copies of the α -globin genes deleted. This is not usually a medical condition; however, haemoglobin is often in the low end of the normal range and MCV and MCH may be reduced.
- In general, α -thalassaemia major is inherited in an autosomal recessive manner; however; the genetics is complex.

Couples who are both carriers of α -thalassaemia should be referred to a specialist service for information about their risk of having an affected pregnancy.

β -thalassaemia

β -thalassaemia is caused by reduced or absent production of the β -globin chain of haemoglobin molecule.

There is one gene encoding the β -globin chain. Each individual has two copies of this gene, one from each parent.

- *β -thalassaemia major* is caused by alterations in both copies of the β -globin gene, resulting in virtually no functional β -globin being produced. This is a severe medical condition requiring frequent transfusion and iron chelation therapy.
- *β -thalassaemia minor* is caused by an alteration in one copy of the β -globin gene. While this is not a serious medical condition, it manifests as reduced red cell indices and elevated concentrations of HbA₂² and can be mistaken for iron deficiency.
- β -thalassaemia major is an autosomal recessive condition. Carriers have a 50% chance of passing the altered β -globin gene to their children. Couples who are both carriers have a 25% (one in four) chance of having an affected child. This risk applies for every pregnancy of that partnership.
- Co-inheritance of β -thalassaemia minor and a haemoglobin variant (for example, Hb Lepore, HbC or HbE) may result in a form β -thalassaemia major (see Appendix 1). This is known as compound heterozygosity, as the two types of gene changes are different.

Couples who are both carriers of β -thalassaemia and/or a haemoglobin variant should be referred to a specialist service for information about their risk of having an affected pregnancy.

The carrier state

It is important to identify carriers of thalassaemias and haemoglobin variants in order to offer couples who are both carriers information about their risk of having a child severely affected by thalassaemia and, where possible, prenatal diagnosis.

The best time to identify carriers is prior to pregnancy.

Who is at increased risk?

The carrier state is common.

Individuals at increased risk of being a carrier of thalassaemia include:

- An individual with an MCH less than 27pg and/or MCV less than 80fL.
- Individuals from ethnic groups with a high prevalence of thalassaemia (see figure 1)
 - ✦ Mediterranean countries
 - ✦ Middle East
 - ✦ The Indian subcontinent
 - ✦ Southern China
 - ✦ Southeast Asia.

It is not always possible to assume ethnicity from country of birth or surname. More information can be obtained by asking patients where their parents or grandparents were born. Some other haemoglobin variants (for example, HbS) also have a higher prevalence in Africa.

- Individuals with a family history of thalassaemia major and/or thalassaemia minor.
- A history of severe pre-eclampsia in association with early fetal death.

² HbA₂ is a normal variant of haemoglobin and composed of two α -globin and two δ -globin chains ($\alpha_2\delta_2$). It usually represents 2 to 3.5% of normal total adult haemoglobin.

Figure 1. Countries of origin of the thalassaemia disorders



Adapted from Weatherall, DJ, Clegg JB, Hicks, DR & Wood, WG 1995, 'The haemoglobinopathies', in *The metabolic basis of inherited disease*, eds CR Scriver et al., McGraw Hill.

Who should be investigated?

- Women considering pregnancy.
- All pregnant women.
- Partners of individuals who have thalassaemia minor or are carriers of a haemoglobin variant. This is an urgent priority if the woman is pregnant. Carrier states of haemoglobin variants may be clinically and haematologically silent, with normal red cell indices. For this reason, *all* partners of patients with confirmed thalassaemia minor or abnormal haemoglobins should have definitive haemoglobinopathy testing.
- A family history of haemoglobinopathy (thalassaemia and/or haemoglobin variant) or haemoglobinopathy carrier state.
- Persistent abnormality of red cell indices.

Consider testing for all women of childbearing age.

Investigations

Specialist services can provide advice regarding appropriate testing. See Where to refer.

- It is considered good practice to investigate *all women of childbearing age* with FBE and ferritin.
- Investigation for the thalassaemia carrier state is usually a multistep process, with results of FBE, Ferritin studies and clinical picture influencing decisions regarding haemoglobinopathy testing and DNA analysis.
- All indications for investigation should be given, including pregnancy, gestation, ethnicity and family history, to assist the laboratory in interpreting test results.

FBE and ferritin

FBE and ferritin identify women requiring further investigation but not all carriers of α -thalassaemia and β -thalassaemia will be identified. For example, carriers of α -thalassaemia with a one-gene deletion will usually have borderline to normal red cell indices. Carriers of other haemoglobinopathies (for example, sickle cell, HbE, HbC) may not be detected by these simple tests and haemoglobinopathy testing (see below) should be considered.

Ferritin is ordered to identify iron deficiency. Iron deficiency may mask thalassaemia carrier status. If the woman is not pregnant, FBE should be repeated when iron stores are replete. If the woman is pregnant, her partner should be investigated before iron stores are corrected. If the partner is shown to have thalassaemia minor or carry a haemoglobin variant, DNA studies on both partners may be appropriate.

Possible results

The majority of β -thalassaemia carriers and individuals with two or three copies of the α -globin gene deleted will have:

- MCV < 80fL
- MCH < 27pg
- Hb may be slightly low or normal.

Interpretation of results

Interpretation of results may be assisted by a haematologist.

Table 1. Interpretation of results

MCH (pg)	Ferritin	Interpretation
> 27	Normal	Thalassaemia unlikely
	Low	Reduced iron stores or iron deficiency, thalassaemia unlikely
< 27	Normal	Suspect thalassaemia
	Low	Iron deficiency Thalassaemia may coexist

Haemoglobinopathy testing

- Haemoglobinopathy testing determines the types, quantity and proportions of haemoglobin in the blood. Techniques for this may include haemoglobin electrophoresis and HPLC³ analysis. Blood films and HbH preparations identify HbH inclusions found in HbH disease and sometimes in α -thalassaemia minor.
- If a thalassaemia screen is requested, a haemoglobinopathy screen should also be requested to adequately investigate for thalassaemia and haemoglobin variant carrier states.
- Ideally, haemoglobinopathy testing should be performed six months after iron replacement and when iron stores are replete, however testing should not be delayed if the woman is pregnant. If the woman is pregnant and has low red cell indices, her partner should be investigated. Consult a haematologist or thalassaemia service for advice.
- Ideally, haemoglobinopathy testing should be performed after FBE and ferritin investigations. However, in some situations, haemoglobinopathy testing should be performed concurrently with FBE/ferritin.

These include:

- ✦ Pregnant woman with low red cell indices. In this case, the father of the baby should also be tested.
- ✦ Pregnant woman from high-risk ethnic backgrounds.
- ✦ Partners of individuals with thalassaemia minor or who carry a haemoglobin variant.
- ✦ A family history of haemoglobinopathy (thalassaemia and/or haemoglobin variant) or haemoglobinopathy carrier state.
- ✦ Consanguinity.

³ High-pressure liquid chromatography.

- **Consideration could be given to concurrent haemoglobinopathy testing in:**
 - ✦ Non-pregnant woman from high-risk ethnic background.
 - ✦ Non-pregnant woman with a family history suggestive of a thalassaemia or haemoglobin variant.

Table 2. Indications for haemoglobinopathy testing

Indications for Hb/opathy testing	Non pregnant	Pregnant
Low red cell indices	Perform, if ferritin normal	Perform
High-risk ethnic background	Consider	Perform
Family history thalassaemia	Consider	Perform
Partner is thalassaemia carrier	Perform	Perform
Relatives are thalassaemia carriers	Perform	Perform

Interpretation of results

A haematologist or thalassaemia service should be consulted for assistance in interpreting haemoglobinopathy testing results, as interpretation is influenced by the clinical picture.

- β -thalassaemia minor is characterised by the presence of increased HbA₂, but this can be masked in some circumstances, such as low iron stores.
- α -thalassaemia carrier states are characterised by low red cell indices, with normal HPLC and/or haemoglobin electrophoresis results. Individuals of a three-gene deletion and sometimes two-gene deletions may be identified by an HbH preparation⁴; however, a normal HbH preparation does not exclude α -thalassaemia, especially one- and two-gene deletion forms. Definitive identification of carriers with one- and two-gene deletions requires DNA testing.

Table 3. Interpretation of haemoglobinopathy testing results

MCH(pg)	Ferritin	Haemoglobinopathy testing results	Interpretation
< 27	Normal	HbA ₂ increased	β -thalassaemia carrier
		HbA ₂ normal HbH present	α -thalassaemia carrier
		Normal	Possible α -thalassaemia carrier. DNA testing indicated
	low	normal	Iron deficiency Thalassaemia may coexist If woman is pregnant, seek advice about further investigations

⁴ HbH preparations are performed on blood films, and identify the HbH inclusions formed by excess β -globin chains.

DNA testing

Patients requiring DNA testing should be referred to specialist services.

Indications for DNA testing

- Possible α -thalassaemia carrier (low-borderline MCV or MCH, normal ferritin and normal haemoglobin).
- Proven β -thalassaemia carrier, and partner is also a carrier of thalassaemia or haemoglobinopathy.
- DNA testing of couples who are both carriers is necessary for prenatal diagnosis to be available. Testing can be time consuming and, if possible, couples should be referred prior to pregnancy.

Management of carriers

Carriers of β -thalassaemia should have folic acid (5 mg) daily throughout all pregnancies. Carriers of β -thalassaemia must not have long-term iron treatment to attempt to cure microcytosis, unless they are also iron deficient.

Education

Carriers do not develop thalassaemia major. Discuss testing of other family members. Family members can be referred to specialist services for testing and counselling.

Partner testing

Where a thalassaemia carrier state is identified it is essential that the partner be investigated. Testing the partner is an urgent priority if the woman is already pregnant.

Referral

- If both members of the couple are found to be carriers of a thalassaemia or haemoglobin variant, they should be immediately referred to specialist services for information regarding their risk of having a child with thalassaemia, and to discuss the need for DNA studies. Some combinations of thalassaemia and haemoglobin variants can result in a clinically affected child.
- Pregnant couples at risk of having a child with a major thalassaemia syndrome should be urgently referred to a specialist service for counselling and possible prenatal diagnosis.
- Genetic counselling is available from specialist services.

Prenatal diagnosis

- **Prenatal diagnosis is available to couples where:**
 - ✦ There is a significant risk of having a child affected by thalassaemia or other haemoglobinopathy (for example, sickle cell disease).
and
 - ✦ The causative gene alterations carried by the parents are known.
- Due to the time-consuming nature of DNA testing to identify causative gene changes, it is important that, wherever possible, DNA studies are carried out pre-pregnancy.
- Prenatal diagnosis is performed on a sample collected by chorionic villus sampling (see Part 5 *Testing during pregnancy*). This is usually performed in the first trimester but, under certain circumstances, may be performed in the second trimester.

The disease state (β -thalassaemia major)

Clinical features

The common clinical features of β -thalassaemia major manifest after birth, usually within six to 12 months and include:

- Pallor
- Lethargy
- Poor appetite
- Developmental delay
- Failure to thrive
- Irritability, difficulty settling.

Splenomegaly, growth failure with bone changes, fractures and leg ulcers also develop during childhood.

Investigations

- FBE usually shows significant anaemia, microcytosis, hypochromia and abnormal red cell morphology, including target cells. Nucleated red blood cells are usually present.
- Haemoglobinopathy testing to determine HbF⁵ and HbA2 levels is usually diagnostic of β -thalassaemia. Affected children over the age of six months usually have markedly elevated levels of HbF and elevated HbA2
- Compound heterozygous states result in a variety of abnormalities on haemoglobinopathy testing. Contact a haematologist for advice.

Treatment and management

- Treatment and management is performed by specialist services.
- Patients require regular blood transfusions every three to four weeks for their whole life.
- Excess iron is eliminated from the body by iron-chelating agents (desferrioxamine), administered overnight by pump.
- A 'no added iron' diet is recommended.
- The majority of complications associated with β -thalassaemia major are due to iron build up, despite chelation therapy, or marrow expansion.
- Splenectomy may be performed because of enlargement. These patients require the same immunisation as other children and prompt treatment of infections.
- Bone marrow transplantation may cure β -thalassaemia major but has a significant risk of complications and mortality.
- The life expectancy of well-treated, compliant patients is not known but is likely to be normal or near normal.

⁵ HbF refers to fetal haemoglobin, a normal variant in fetal development that persists in small amounts postnatally.

It is composed of two α -globin and two γ -globin chains ($\alpha_2\gamma_2$) and usually represents less than 1% of normal total adult haemoglobin.

Appendix 1:

Haemoglobinopathies caused by structural change

Based on Bowden, DK 2001, 'Screening for thalassaemia', *Australian Prescriber*, 24:120.

- Whereas the thalassaemias are caused by a deficiency in the quantity of globin chains, other haemoglobinopathies are caused by structural variations in the globin chain.
- Individuals from certain ethnic backgrounds have increased risk of carrying a globin chain gene alteration causing a structural variant.
- Only a small number of variants capable of causing severe disease in the homozygote or in compound heterozygotes are encountered in Australia. These include HbS (sickle cell), HbC, HbD, HbE, HbO and HbLepore.
- Testing for haemoglobin variants requires haemoglobinopathy testing as it is common for no other haematological abnormality to be present.
- Partners should have FBE and haemoglobinopathy testing to investigate carrier status for β -thalassaemia and/or haemoglobin variants.

Examples of disease-causing states

Haemoglobin types	Disease status
Homozygous HbS	Sickle cell disease
HbS/ β -thalassaemia	Sickle cell disease
HbS/HbC disease	Sickle cell disease
HbS/HbD	Sickle cell disease of variable severity
Homozygous HbE	Behaves as a mild β -thalassaemia mutation
HbE/ β -thalassaemia	Mild to severe disease equivalent to β -thalassaemia
HbC/ β -thalassaemia	Sickle cell disease (mild to severe, depending on causative mutations)
Homozygous Hb Lepore	β -thalassaemia intermedia (a moderate disease state)
Hb Lepore/ β -thalassaemia	β -thalassaemia major
Hb Lepore/HbS	Sickle cell disease of variable severity

7.3 Patient and further information

Community education

The Thalassaemia Society of Victoria
333 Waverley Road, Mount Waverley 3149
Call: (03) 9888-2211
Fax: (03) 9888-2150
Email: thal.office@bigpond.com

Websites

Better Health Channel: <http://www.betterhealth.vic.gov.au>
Relevant topic: Thalassaemia is an inherited blood disorder

Further reading

Berdoukas, V 1997, 'Haemoglobinopathies: how much should the GP know?', *Modern Medicine of Australia*, March, 126–34.

Bowden, DK 2001, 'Screening for thalassaemia', *Australian Prescriber*, 24:120–23.

7.4 Where to refer

All individuals are advised to get tested prior to commencing a family. Free testing is available from:

Medical Therapy Unit
Monash Medical Centre
Clayton Road, Clayton 3168
Call: (03) 9594 2756
Head of Unit: Associate Professor Don Bowden
Clinical Nurse: Mrs Libby Reid

Thalassaemia Clinic
Royal Women's Hospital
Grattan Street, Carlton 3053
Call: (03) 9344 2121

If a high-risk couple is already pregnant, further services for prenatal diagnosis and counselling are available from:

Genetic Health Services Victoria
Royal Children's Hospital
Flemington Road, Parkville 3052
Call: (03) 8341 6270

Genetic Counsellor
Mercy Hospital for Women
Clarendon Street, East Melbourne 3002
Call: (03) 9270 2394

Genetic Health Services Victoria
Monash Medical Centre
Clayton Road, Clayton
Call: (03) 9594 2026
Head of Unit: Dr Agnes Bankier

Genetic Counsellor
Royal Women's Hospital
132 Grattan Street, Carlton 3052
Call: (03) 9344 2121

Albury/Wodonga
Genetic Counsellor
195 Melbourne Road, Wodonga 3690
Call: (02) 6056 0451

Services in regional Victoria include Bendigo, Ballarat, Geelong, Mildura, Sale, Shepparton, Traralgon and Warrnambool. Contact Genetic Health Services on (03) 83416224 to arrange an appointment.

