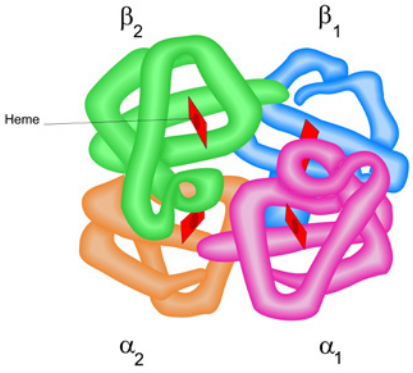
Additional information on thalassaemia

Normal haemoglobin

A normal red blood cell contains approximately 300 million haemoglobin (Hb) molecules. These molecules are made up of two parts, haem and globin. Haem contains an iron molecule that transports oxygen around the body. Globin is made up of four protein chains that are arranged in pairs. Normal adult haemoglobin has two alpha chains and two non-alpha chains. In a healthy adult the vast majority consist of two alpha (α) chains and two beta (β) chains, so each molecule contains α2β2: this is referred to as HbA or adult haemoglobin.[1]



Haemoglobin molecule showing two alpha and two beta globin chains, and their associated haem molecule.

Haemoglobinopathies such as α thalassaemia, β thalassaemia and sickle cell disease are caused by inherited abnormalities that result in either reduced production of one, or more globin chains, or production of an abnormal globin chain.

There are approximately 332,000 affected conceptions and births globally each year.[2] There are multiple types of thalassaemia, the most common ones being alpha (α) and beta (β) thalassaemia.

Alpha (α) thalassaemia

Alpha (α) thalassaemia is characterised by reduced or absent production of the α globin chains. The inheritance of α thalassaemia is complex.[1] The severity of the disease is determined by how many defective genes are inherited, as each person has four copies (alleles) of the two genes (HBA1 and HBA2) responsible for α globin production.

The most severe form of the disease occurs when all four copies of the α globin gene are defective or absent (*Hb Bart syndrome*). This usually results in death in utero, stillbirth or a baby born with *hydrops fetalis*. If a baby is diagnosed in utero as having this severe form of α thalassaemia, through early identification of carrier parents and intrauterine testing, it is possible to provide intrauterine transfusion support. After birth it is possible that the baby may survive but will continue to be transfusion dependent; however, most babies with the severe form of the disease will not survive. There are also health implications for the mother, for example hypertension during pregnancy and severe pre-eclampsia. Genetic counselling for at-risk couples aims to reduce the risk of having a severely affected baby.

When a child inherits three defective α globin genes and one normal α globin gene the condition is less severe with features of a moderate *haemolytic anaemia*. This is known as HbH disease. More severely affected patients will have a chronic transfusion requirement.

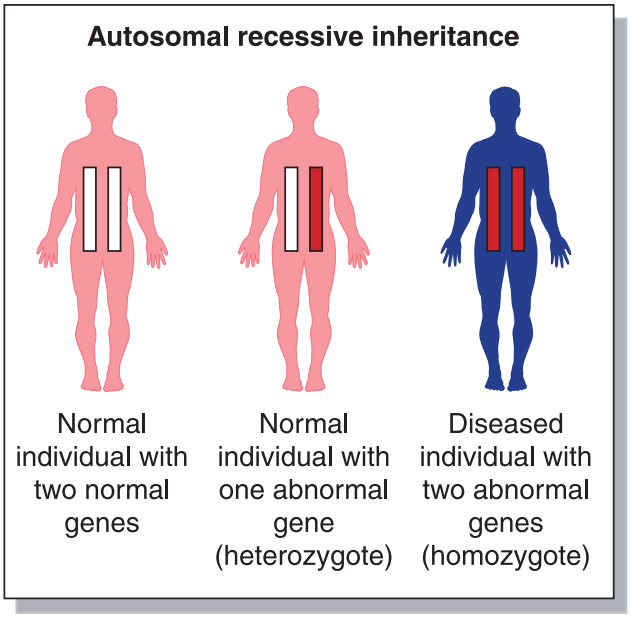
Inheritance of only one or two copies of the defective α globin gene results in what is known as a silent carrier, and is not associated with any serious clinical findings.[3] However, these patients are at risk of having affected children if the other parent also has one or two copies of the defective gene.

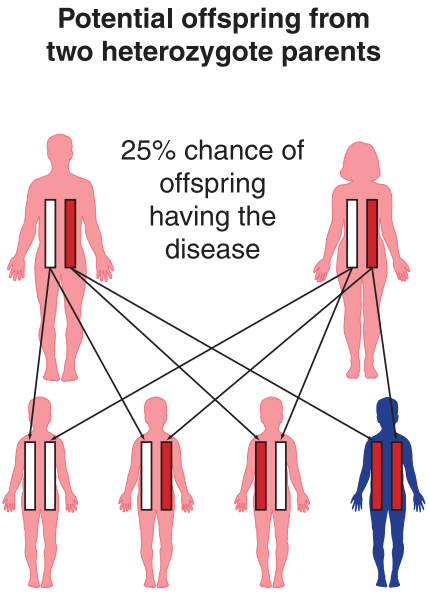
Beta (β) thalassaemia

Beta (β) thalassaemia is usually caused by mutations in the HBB gene and results in a reduction or absence of β globin chains.[4,5] It is amongst the most common *autosomal recessive* diseases in the world. [4] The disease is most common in people of Mediterranean, Asian and Middle Eastern descent [1, 4-6] with 1.5% of the world's population estimated to carry a gene for β thalassaemia.[5]

The type of β thalassaemia is dependent upon whether one or two copies of a β thalassaemia gene have been inherited (see table below). Untreated thalassaemia major, also known as Cooley's anaemia or Mediterranean anaemia, results in death in the first decade of life.[6]

The reduced or absent production of β globin chains results in an imbalance between β and α globin chains. The excessive α chains form aggregates that damage, and can subsequently destroy the red cell precursors in the bone marrow. Red cells that are released into the circulation are often destroyed in the spleen and haemolysed in the blood stream.[1] The resulting anaemia stimulates the kidneys to release erythropoietin. This increases red cell production in the bone marrow, resulting in marrow *hyperplasia*, and *extramedullary haematopoiesis*.[1]





The same β thalassaemia mutations (genotype) may have different manifestations (*phenotype*) between patients due to the effect of other factors, including alpha mutations, other globin mutations or deletions.

β globin mutations	Phenotype	Clinical features	Disease outcomes	Transfusion requirement
2 mutations inherited	β thalassaemia major	Severe anaemia Bone marrow hyperactivity Presents in infancy	Severe anaemia leads to heart failure and death in first decade of life if untreated Causes growth retardation, hepato/splenomegaly, bone deformities and cortical bone thinning due to marrow expansion and growth outside bone cavities (extramedullary haematopoiesis expansion and growth outside bone cavities (*extramedullary haematopoiesis*)	Lifelong red cell transfusion required
2 mutations inherited	β thalassaemia intermedia	Mild to moderate anaemia May produce enough haemoglobin to maintain growth and development without transfusions May present later in childhood	Variable depending upon the individual	Not usually transfusion dependent May require regular transfusions if growth fails or other complications
1 mutation	β thalassaemia minor (β thalassaemia trait)	Normal or slightly low haemoglobin	Potential for offspring to have severe form of disease if the other parent also has a thalassaemia gene	Usually nil

(3,7,8)

Thalassaemia

Effects of insufficient transfusion

Face
Facial deformity
Hypertrophy of upper maxillary bones

Spleen
Hypersplenism

Blood
Anaemia

Bone marrow expansion
Pathological fractures
Premature closure of the lower femoral epiphysis

Effects of iron overload

Pituitary gland
Affects growth, sex organs, adrenal glands, thyroid

Thyroid and Parathyroid glands
Hypoparathyroidism leading to hypocalcaemia

Heart
Cardiac failure

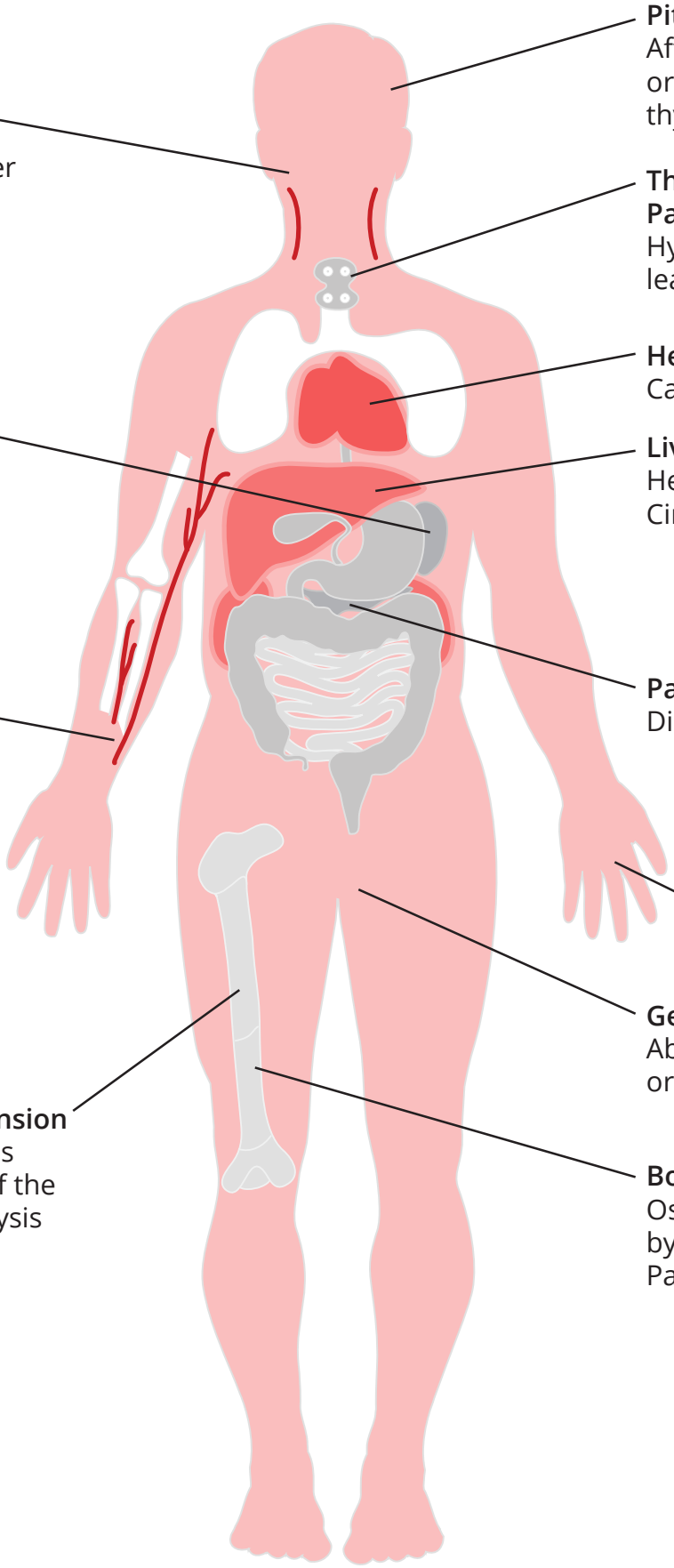
Liver
Hepatomegaly
Cirrhosis

Pancreas
Diabetes

Skin
Pigmentation

Genitals
Abnormal development or function

Bone and joints
Osteoporosis (caused by hypoparathyroidism)
Pain



This diagram has been adapted from the website *http://thalassaemia.org.cy/about-haemoglobin-disorders/beta-thalassaemia/management* with permission from Thalassaemia International Federation.

Glossary terms

Hb Bart Syndrome	A condition in which there is abnormal haemoglobin production leading to excess fluid build-up in the body before birth. Additional symptoms include anaemia, enlarged liver and spleen, heart defects and urinary system/genital abnormalities.
Hydrops Fetalis	Accumulation of fluid or oedema in the fetus or newborn in two or more body areas. Causes include severe anaemia, cardiac abnormalities, intrauterine infections, twin pregnancies and chromosomal abnormalities. Often results in death before or after birth.
Haemolytic anaemia	Anaemia that occurs as a result of abnormal red cell breakdown (haemolysis).
Autosomal recessive	An inheritance pattern that often requires two copies of an abnormal gene to be inherited for the disease to occur. In some cases where there are multiple defective genes per chromosome, more copies of the affected gene must be inherited.
Hyperplasia	Enlargement of tissues or organs as a result of increased rate of cellular reproduction.
Extramedullary haematopoiesis	The production of blood cells outside the bone marrow space to supplement decreased production or increased destruction of blood cells. More common sites include the mediastinum, liver and spleen.
Phenotype	The physical expression of a particular trait, according to the individual's genetic makeup.

References

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