The Hereditary Anemia's

Hereditary anaemias include disorders of the structure or synthesis of haemoglobin (Hb), deficiencies of enzymes that provide the red cell with energy or protect it from chemical damage and abnormalities of the proteins of the red cell's membrane. Inherited diseases of haemoglobin (haemoglobinopathies) are by far the most important.

The structure of human Hb changes during development (Fig. 3.1). By the 12th week of gestation, embryonic haemoglobin is replaced by fetal haemoglobin (Hb F), which is slowly replaced after birth by the adult haemoglobins, Hb A and Hb A2. Each type of haemoglobin consists of two different pairs of peptide chains; Hb A has the structure α2β2.Hb A2 has the structure α2δ2 and Hb F, α2γ2.

The haemoglobinopathies consist of structural haemoglobin variants (sickling disorders) and thalassaemias (hereditary defects of the synthesis of either the α or β globin chains).

Other anaemias with an important inherited component include Fanconi's anaemia (hypoplastic anaemia with skeletal deformities), Blackfan–Diamond anaemia (red cell aplasia) and several forms of congenital dyserythropoietic anaemia.

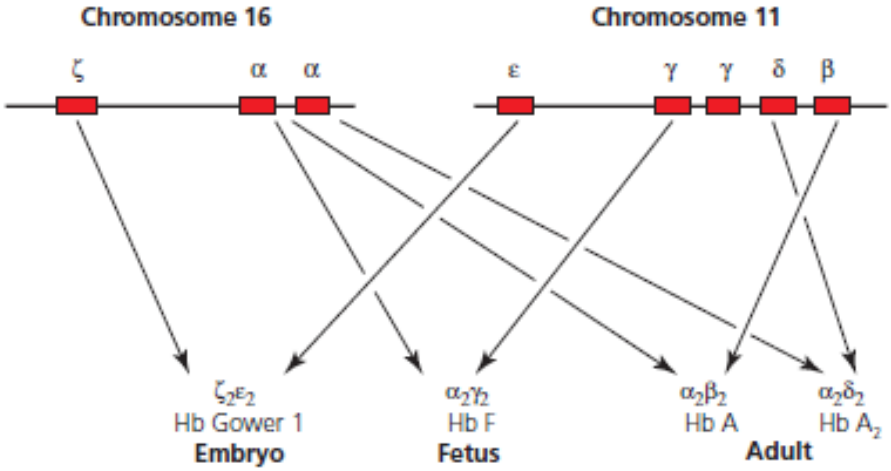


Figure 3.1 Simplified representation of the genetic control of human haemoglobin (Hb). Because α chains are shared by both fetal and adult Hb, mutations of the α globin genes affect Hb production in both fetal and adult life; diseases that are due to defective β globin production are only manifest after birth when Hb A replaces Hb F.

The Thalassaemias

Classification

The thalassaemias are classified as α or β thalassaemias, depending on which pair of globin chains is synthesized inefficiently. Rarer forms affect both β and δ chain productions: δβ thalassaemias.
Also classified to thalassemia major, thalassemia intermedia, and thalassemia minor

Inheritance

The β thalassaemias result from over 200 different mutations of the β globin genes, which reduce the output of β globin chains, either completely (β° thalassaemia) or partially (β^+thalassaemia). They are inherited in the same way as sickle cell anaemia; carrier parents have a one in four chance of having a homozygous child. The genetics of the α thalassaemias is more complicated because normal people have two α globin genes on each of their chromosomes 16. If both are lost (α^o thalassaemia) no α globin chains are made, whereas if only one of the pair is lost (α+ thalassaemia) the output of α globin chains is reduced (Fig. 3.5). Impaired α globin production leads to excess γ or β chains that form unstable and physiologically useless tetramers: γ4 (Hb Bart's) and β4 (Hb H) (Fig. 3.6). The homozygous state for α° thalassaemia results in the Hb Bart's hydrops syndrome, whereas the inheritance of α° and α^+ thalassaemia produces Hb H disease.

β-thalassaemia

Heterozygotes for β thalassaemia are asymptomatic, have hypochromic microcytic red cells with a low mean cell haemoglobin and mean cell volume (Fig. 3.7), and have a mean Hb A2 level of about twice that of normal. **Homozygotes**, or those who have inherited a different β thalassaemia gene from both parents, usually develop severe anaemia in the first year of life. This results from a deficiency of β globin chains; excess α chains precipitate in the red cell precursors leading to their damage, either in the bone marrow or the peripheral blood. Hypertrophy of the ineffective bone marrow leads to skeletal changes, and there is variable hepatosplenomegaly.

The Hb F level is always raised. If these children are transfused, the marrow is 'switched off ', and growth and development may be normal. However, they accumulate iron and may die later from damage to the myocardium, pancreas, or liver (Fig. 3.8). They are also prone to infection and folic acid deficiency.
Milder forms of β thalassaemia (thalassaemia intermedia), although not transfusion dependent, are often associated with similar bone changes, anaemia, leg ulcers and delayed development. The most important form of β thalassaemia intermedia is Hb E β thalassaemia, which results from the inheritance of Hb E (**glutamic acid to lysine in β chain (E26)**) and a β thalassaemia gene. This condition is the commonest form of severe thalassaemia in many parts of Asia and is associated with a remarkably diverse clinical course; some patients are transfusion dependent while others may remain asymptomatic.

How are thalassemias diagnosed?

Various blood tests are used to diagnose thalassemias:

- A complete blood count (CBC)
- A reticulocyte count
- **Iron status tests** (serum iron, total iron binding capacity, percent transferrin saturation and s. Ferritin)
- **Hemoglobin electrophoresis** (Fractions of hemoglobin A, A_2, F, H, E, and other variants are measured)
- **Genetic testing**
- **Bone marrow aspirate:** Bone marrow aspirate can be differentiate β-thalassemia from sideroblastic anemia
- **Molecular analysis** for β-globin gene

Most people with thalassemia minor are diagnosed when their complete blood count (CBC) reveals mild microcytic anemia. Additional tests are needed for differential diagnosis, since microcytic anemia can also be caused by iron deficiency, lead poisoning, sideroblastic anemia, or anemia of chronic disease.

- In children, the Mentzer index (the ratio of MCV to RBC count) may help differentiate iron deficiency from thalassemia:

    1. Ratio >13 in iron deficiency
    2. Ratio <13 in thalassemia

    In patients who are β-thalassemia carriers, the RDW will be normal or slightly increased. This finding can help differentiate thalassemia minor from other microcytic hypochromic anemias such as sideroblastic anemia in which RDW values are typically very high.

    Consequently, a finding of microcytic anemia in a person with a normal RDW will commonly be caused by thalassemia, whereas microcytic anemia in a person with an elevated RDW does not suggest thalassemia but warrants further testing.

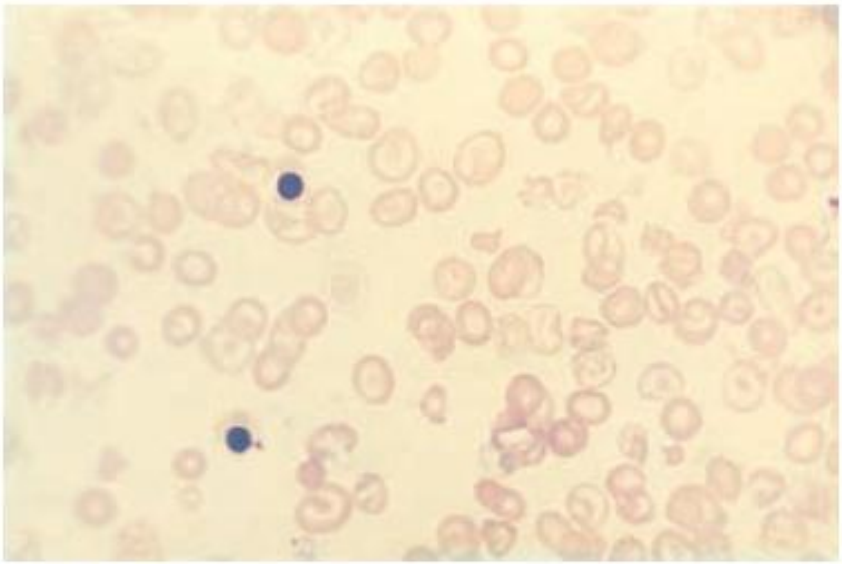
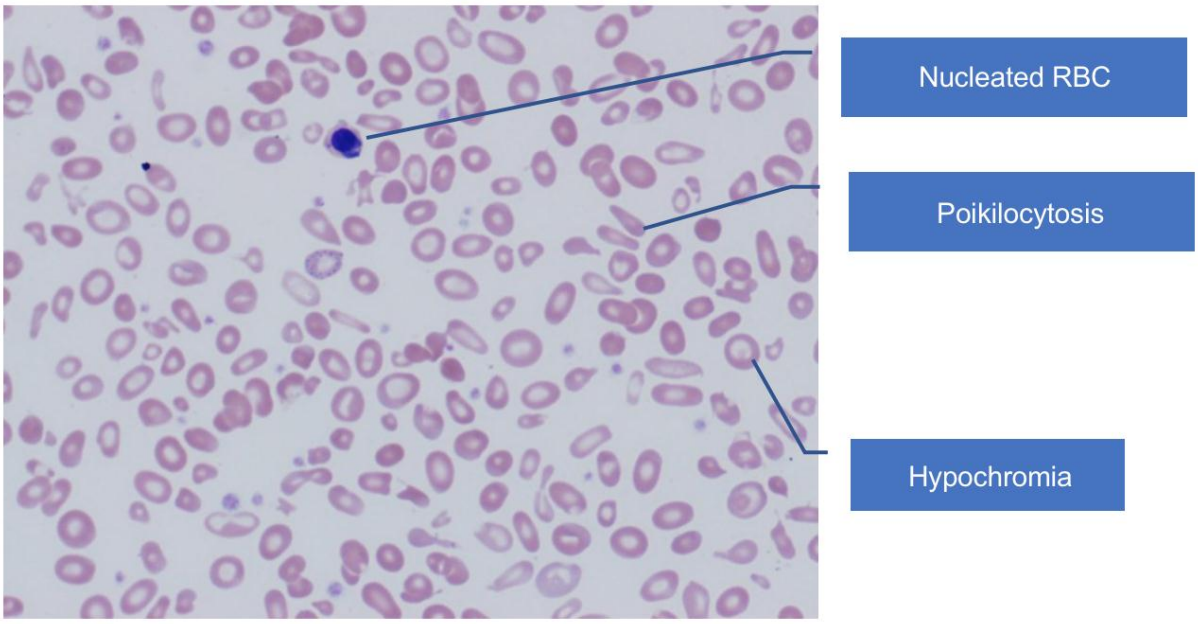


Figure 3.7 Peripheral blood film in homozygous β thalassaemia showing pronounced hypochromia and anisocytosis with nucleated red blood cells.



Peripheral bloodsmear from thalassemia intermedia patient, showing anisopoikilocytosis (variation of cell size and shape), a nucleated red cell, and basophilic stippling.

βThalassaemia trait (heterozygous carrier)	**β-Thalassaemia major (homozygous β thalassaemia)**
Are asymptomatic • Mild hypochromic microcytic anaemia • Haemoglobin 9.0–11.0 g/dL • Mean cell volume 5.0–7.0 g/dL • Mean corpuscular haemoglobin 20–22 pg • No clinical features, patients asymptomatic • Occasional symptomatic anaemia in pregnancy • Often diagnosed on routine blood count • Raised Hb A2 level	• Severe anaemia (Hb less than 9.0 g/dL) **Blood film** • Anisopoikilocytosis • Hypochromic red cells • Target cells • Basophilic stippling • Nucleated red cells •Moderately raised reticulocyte count • Infants are well at birth but develop anaemia in first few months of life when switch occurs from γ to β globin chains • Progressive splenomegaly; iron loading; susceptibility to infection

α thalassaemias

The Hb Bart's hydrops fetalis syndrome is characterized by the stillbirth of a severely oedematous (hydropic) fetus in the second half of pregnancy. Hb H disease is associated with a moderately severe haemolytic anaemia. The carrier states for α^o thalassaemia and the homozygous state for α^+ thalassaemia result in a mild hypochromic anaemia with normal Hb A2 levels. They can only be distinguished with certainty by DNA analysis in a specialized laboratory.

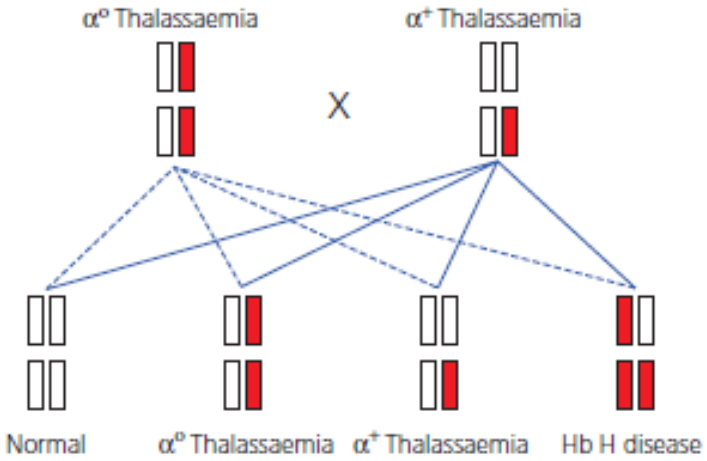


Figure 3.5 Inheritance of Hb disease (open boxes represent normal α globin genes and red boxes deleted α globin genes).

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α thalassaemia			
−α/αα, one α gene deleted	−α/−α or αα/− −, two α genes deleted	− −/−α, three α genes deleted	− −/− −, four α genes deleted
• Asymptomatic • Majority show reduced (MCV) and (MCH)	• Hb is normal or slightly reduced • Reduced MCV and MCH • No symptoms	Hb H disease • Chronic haemolytic anaemia • Reduced α chain production with formation of β4 tetramers (β4 is termed Hb H)	Hb Bart's hydrops • No α chains produced • Mainly γ, forms tetramers (γ4, termed Hb Bart's) • Intrauterine death or stillborn at 25–40

		• Hb H is unstable and precipitates in older red cells • Hb is 7.0–11.0 g/dL, although may be lower • Reduced MCV and MCH • **Clinical features**: jaundice, hepatosplenomegaly, leg ulcers, gallstones, folate deficiency	weeks or dies soon after birth αα/αα represents two α globin genes inherited from each parent. Changes due to α thalassaemia are present from birth, unlike in β thalassaemia

Prevention and treatment of thalassemia

1. As β thalassaemia is easily identified in heterozygotes, pregnant women of appropriate racial groups should be screened; if a woman is found to be a carrier, her partner should be tested and the couple counseled.
2. Prenatal diagnosis by chorionic villus sampling can be carried out between the ninth and 13th weeks of pregnancy.
3. Babies with β thalassaemia major should be observed very carefully regarding growth, activity and steady-state haemoglobin level.
4. When it is certain that they require regular transfusion, they should be given washed red cell transfusions at monthly intervals; it is vital that the blood is screened for human immunodeficiency virus/acquired immunodeficiency syndrome, hepatitis B and C viruses and, in some countries, malaria.
5. To prevent iron overload, overnight infusions of desferrioxamine together with vitamin C should be started, and the patient's serum ferritin, or better, hepatic iron concentrations, should be monitored; complications of desferrioxamine include infections with *Yersinia* spp., retinal and acoustic nerve damage and reduction in growth associated with calcification of the vertebral discs.

6. The place of the oral chelating agent **deferiprone** is still under evaluation and it causes neutropenia and variably severe arthritis, recent work suggests that it may be more effective in re-moving iron from the heart than desferrioxamine.
7. In β thalassaemia and Hb H disease, progressive splenomegaly or increasing blood requirements, or both, indicate that splenectomy may be beneficial. Patients who undergo splenectomy should be vaccinated against *S. pneumoniae*, *H. influenzae* and *N. meningitidis* preoperatively, and should receive a maintenance dose of oral penicillin indefinitely.