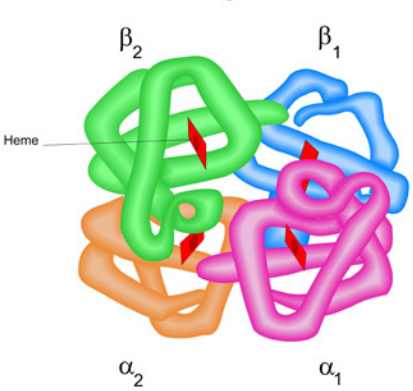
Additional information on sickle cell disease

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]

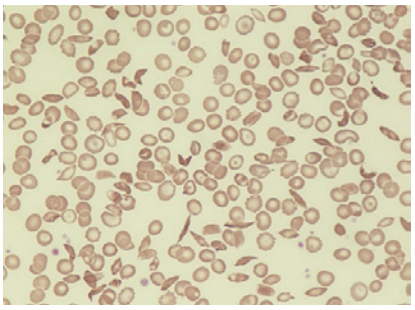
Haemoglobinopathies such as α thalassaemia, β thalassaemia and sickle cell disease are caused by inherited abnormalities that result in reduced production of one or more globin chains or production of an abnormal globin chain.



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

Pathophysiology of sickle cell disease

In sickle cell disease a mutation of the β globin chain results in the production of sickle Hb molecules (HbS). Red cells containing HbS are less elastic than normal red cells and have a characteristic sickle shape. At times of low oxygen tension, when the oxygen is released from haemoglobin, the HbS molecules clump together (*polymerise)* [2] into long fibres that damage the red cell membrane; cause the characteristic sickle shape, and are more rigid and sticky.[3] Unlike normal red cells the sickle cells are unable to deform as they pass through capillaries. This results in blockage of vessels, which if not reversed, results in tissue death.



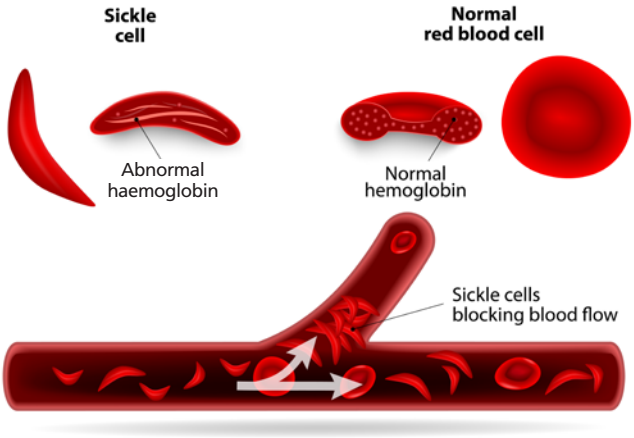
Blood film showing sickle shaped red cells in a patient with sickle cell disease.

Clinical manifestation of sickle cell disease

There are two main pathological processes that occur with sickle cell disease:

- Premature destruction (haemolysis) that results in anaemia. Sickle cells have a shortened life span.[2]
- Blockage of capillaries and small vessels causing tissue *ischaemia*, vaso-occlusion and reperfusion injury.[4-6]

Vaso-occlusion occurs when the sickled red cells and white cells adhere to the lining of the small blood vessels and occlude circulation.[4,6] This can result in painful episodes of ischaemia and infarction, known as “crises”, and chronic damage eg avascular necrosis of the hip and renal failure. Further damage can occur to organs and blood vessels when the blood flow is restored to the micro-circulation and is known as reperfusion injury.[4]

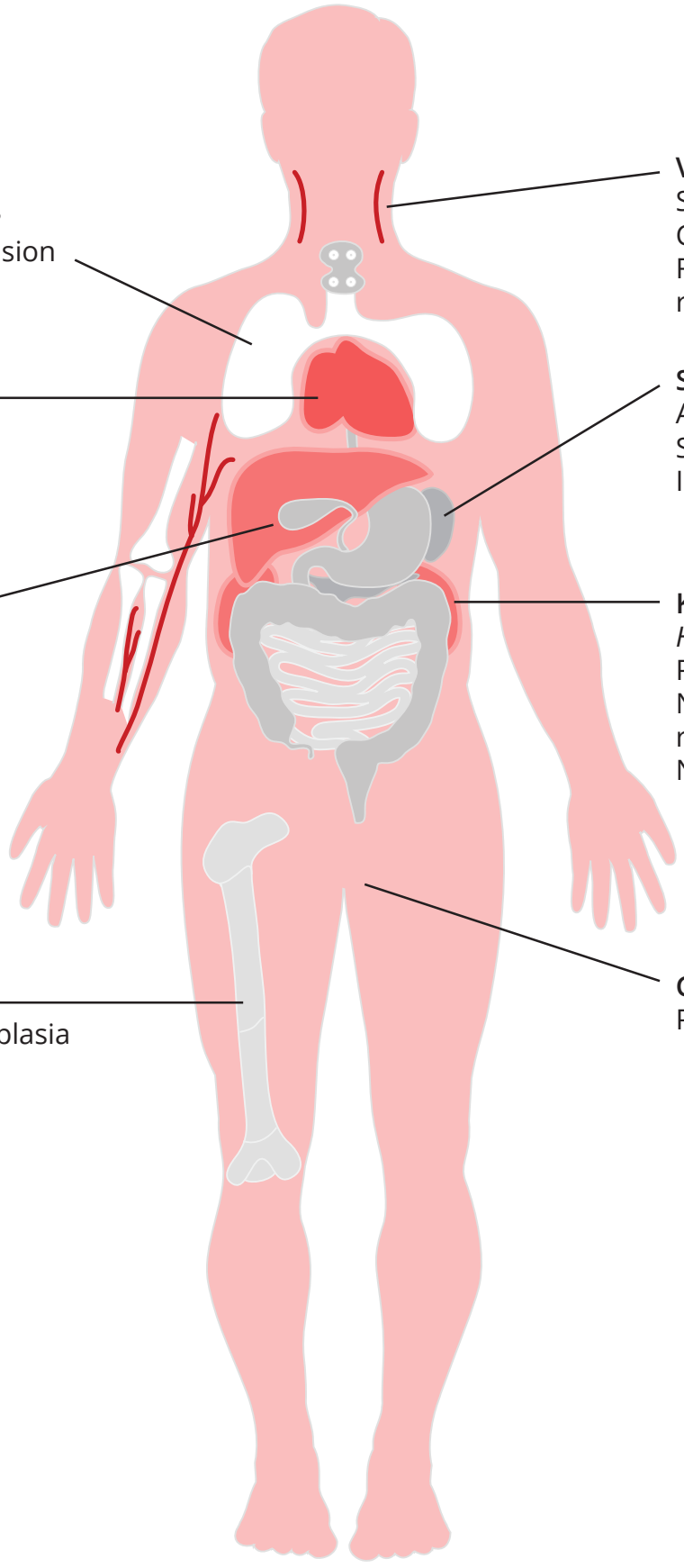


Genetics

Sickle cell disease is an *autosomal recessive disease*. There are three different inheritance patterns that can determine the severity of disease.

β globin mutations	Phenotype	Disease outcomes	Transfusion requirement
2 copies HbS gene (HbSS)	Sickle cell disease (or anaemia) Homozygous sickle cell disease	Chronic *haemolytic anaemia* Vaso-occlusive episodes - acute chest syndrome, acute pain crisis Clinical or silent stroke Frequent infections Avascular necrosis Other: chronic pain, eye vessel damage, gallstones, pulmonary hypertension, leg ulcers, liver and kidney complications	Potential for lifelong red cell transfusion requirement
1 copy HbS gene	Sickle cell trait	Often asymptomatic	Nil
1 copy HbS gene and 1 other β globin mutation eg β thalassaemia	No normal haemoglobin-sickle beta zero thalassaemia Reduced amounts of normal haemoglobin-sickle beta plus thalassaemia	Highly variable depending upon the second β globin mutation	Potential for lifelong transfusion requirement

Clinical Manifestations of Sickle Cell Disease



Lung
Acute chest syndrome
Pulmonary hypertension
Ongoing fibrosis

Heart
Cardiomyopathy
Premature coronary artery disease

Gall bladder
Gall stones

Bones/Joints
Bone marrow hyperplasia
Avascular necrosis
Dactilytis
Osteomyelitis
Aplastic crisis

Vascular
Stroke
Cerebral artery damage
Retinal artery occlusion/ retinopathy

Spleen
Autosplenectomy
Splenic sequestration
Impaired immunity

Kidney
Hyposthenuria
Papillary necrosis
Nephrotic syndrome/ renal failure
Nephropathy

Genitals
Priapism

This diagram has been taken from "A guide for the haemoglobinopathy nurse", page 80, with the permission of Thalassemia International Federation [2]

Glossary terms

Acute chest syndrome	Vaso-occlusive crisis of the pulmonary blood vessels. Can result in hypoxia.
Haemolytic anaemia	Anaemia that occurs as a result of abnormal red cell breakdown (haemolysis).
Polymers	Large molecules, or macromolecules, composed of a large number of repeating subunits.
Ischaemia	Inadequate blood supply to an organ or tissue.
Infarction	Obstruction of blood supply resulting in localised tissue death.
Avascular necrosis	Death of bone tissue caused by lack of blood supply. Can result in bone collapse.
Phenotype	The physical expression of a particular trait, according to the individual's genetic makeup.

References

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