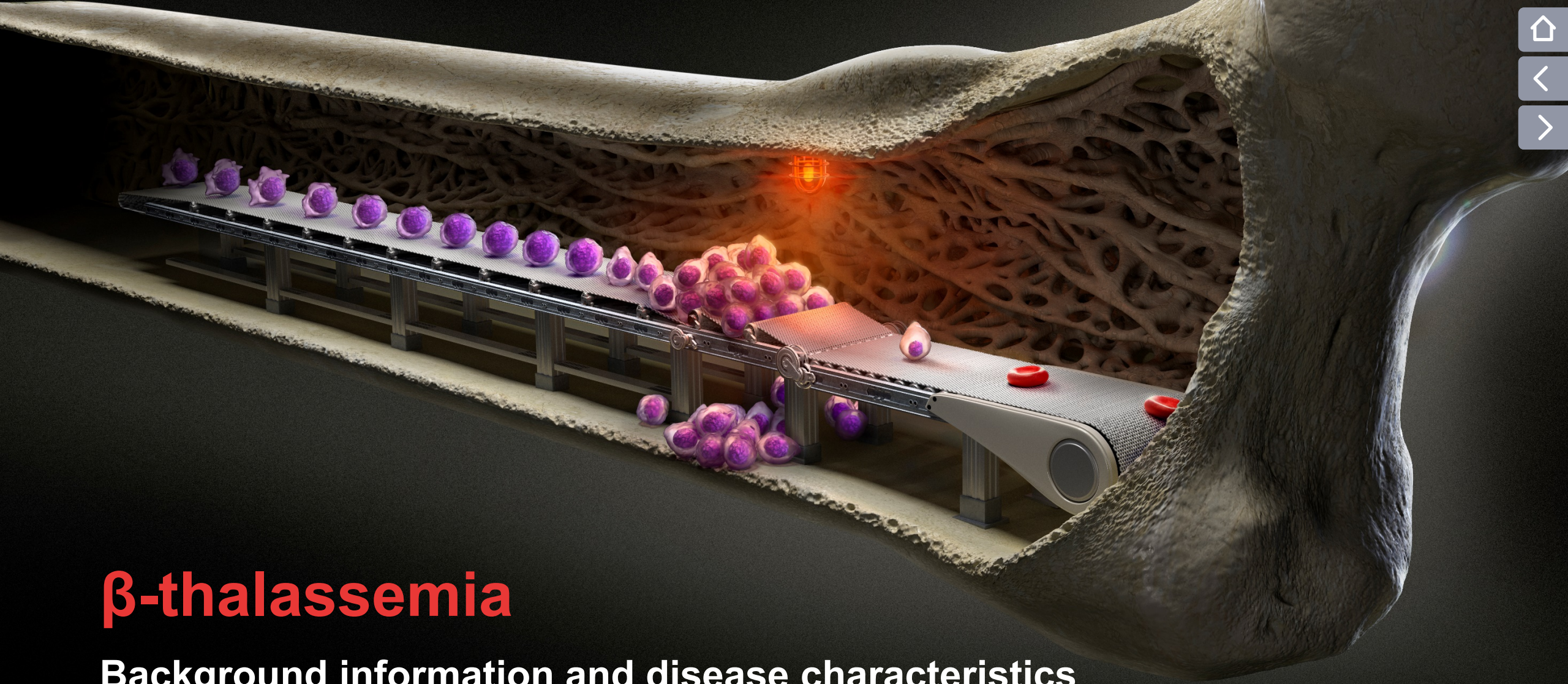


β-thalassemia

Background information and disease characteristics

Enter

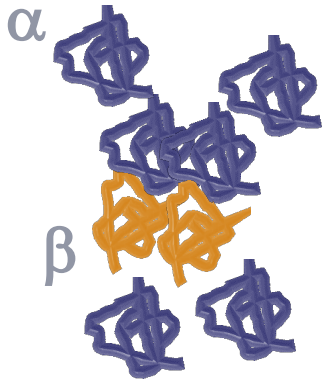
Contents

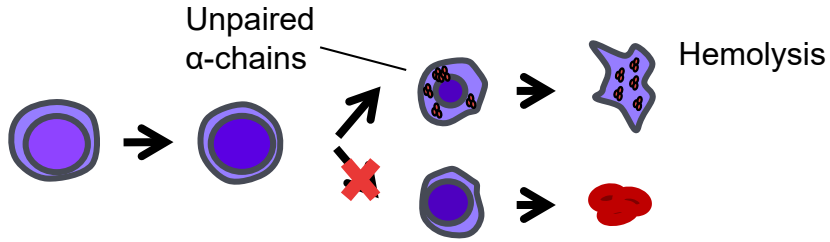
β-thalassemia

β-thalassemia is an inherited blood disorder that reduces production of hemoglobin[1]

- Characterized by reduced or absent synthesis of the β-globin chain component of hemoglobin (Hb), decreased Hb in the blood, RBC production and anemia

Defects in β-globin chain synthesis lead to reduced or absent β-chains and an excess of unpaired α-chains → Results to premature death of erythroid precursors and ineffective erythropoiesis → Reduced RBC production and anemia





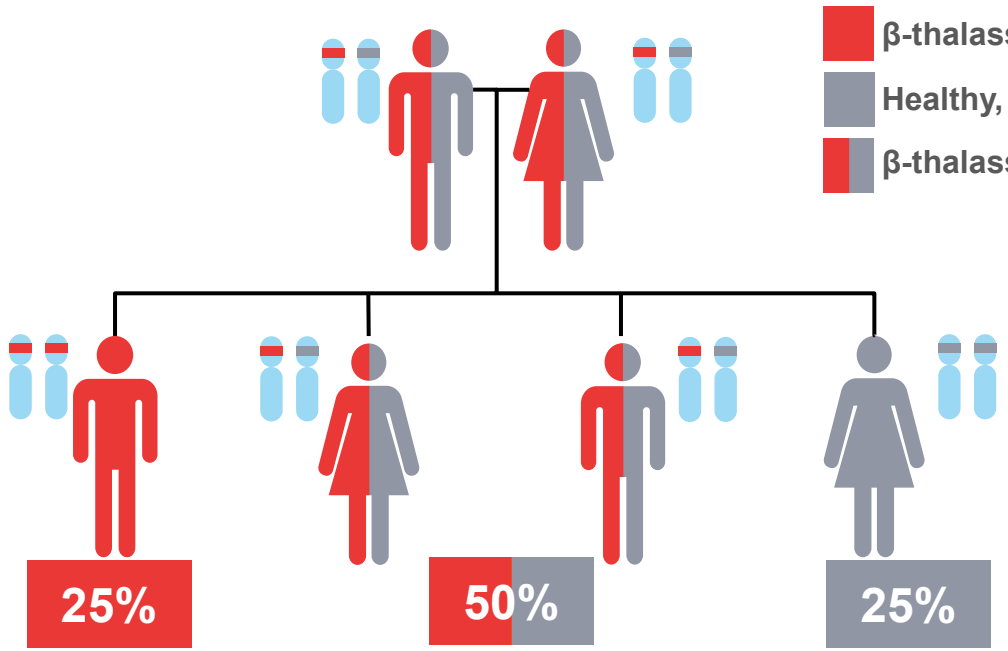
The imbalance of α- to β-globin chains in Hb contributes to impaired erythroid maturation[1]

1. Galanello R, Origa R. Beta-thalassemia. *Orphanet J Rare Dis* 2010 May 21;5:11

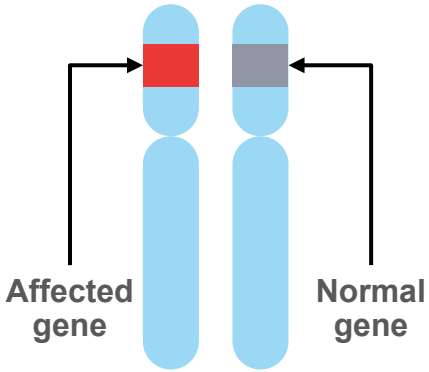
RBC: Red blood cell.

Inheritance pattern

The inheritance of β-thalassemia follows an autosomal recessive pattern[1]



Chromosome 11:
1 β-globin gene from each parent



β-globin chain synthesis is controlled by one gene on each chromosome 11

1. Galanello R, Origa R. Beta-thalassemia. *Orphanet J Rare Dis* 2010 May 21;5:11.

2007CA2000434-01E

Epidemiology: Incidence and prevalence

The total annual incidence of symptomatic individuals is 1 in 100,000[1]

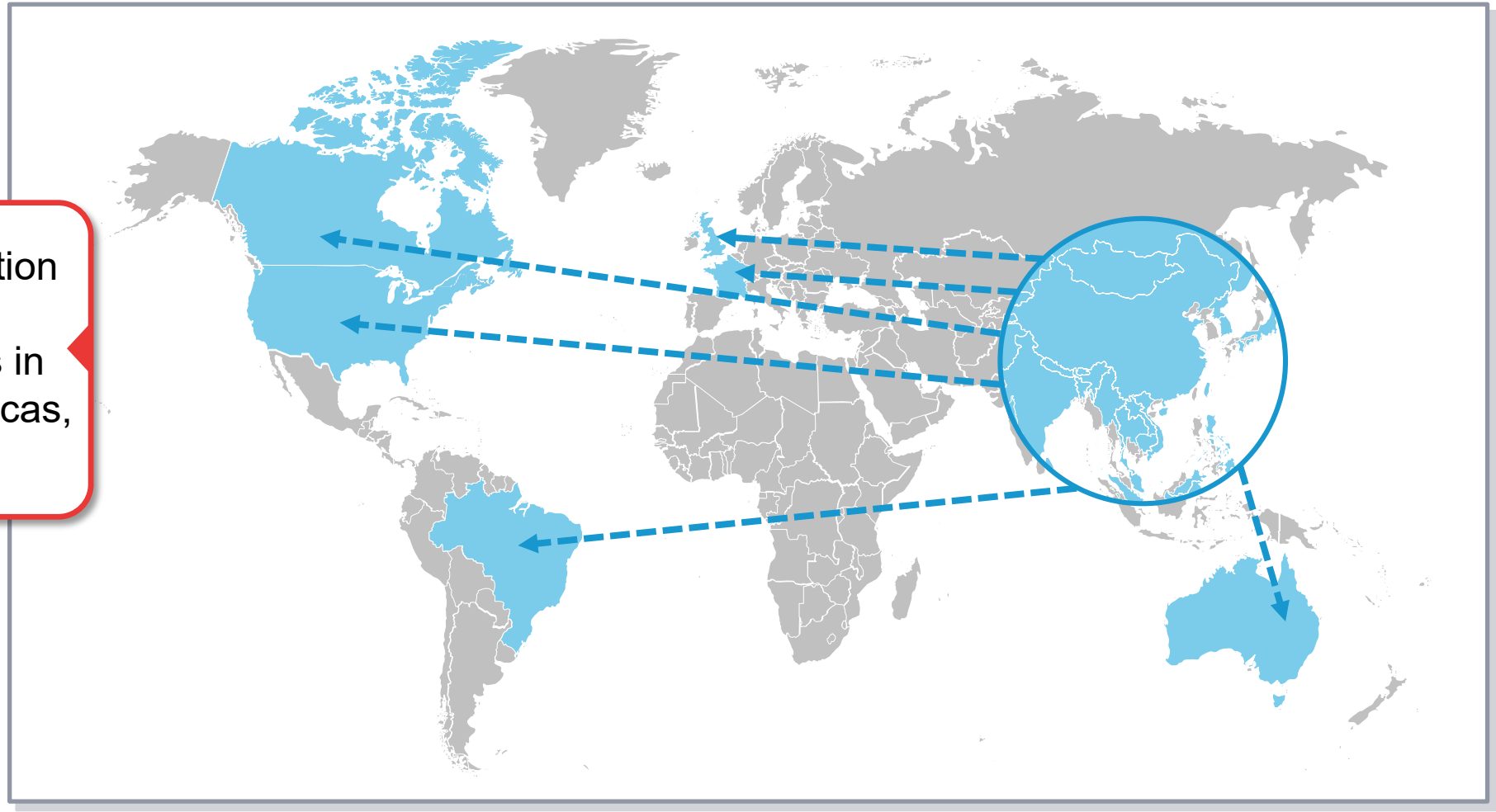
- Approximately 1.5% of the global population (80 to 90 million people) are carriers of β-thalassemia
- Around 60,000 symptomatic individuals are born annually, with the majority born in the developing world

The highest frequency of β-thalassemia carriers is in sub-Saharan Africa, the Mediterranean, Middle East, South Asia, and Southeast Asia due to the conferred resistance of carriers to severe forms of malaria[1]

1. Galanello R, Origa R. Beta-thalassemia. *Orphanet J Rare Dis* 2010 May 21;5:11.

Epidemiology: Migration

Population migration has increased prevalence rates in Europe, the Americas, and Australia[1]



1. Galanello R, Origa R. Beta-thalassemia. *Orphanet J Rare Dis* 2010 May 21;5:11.

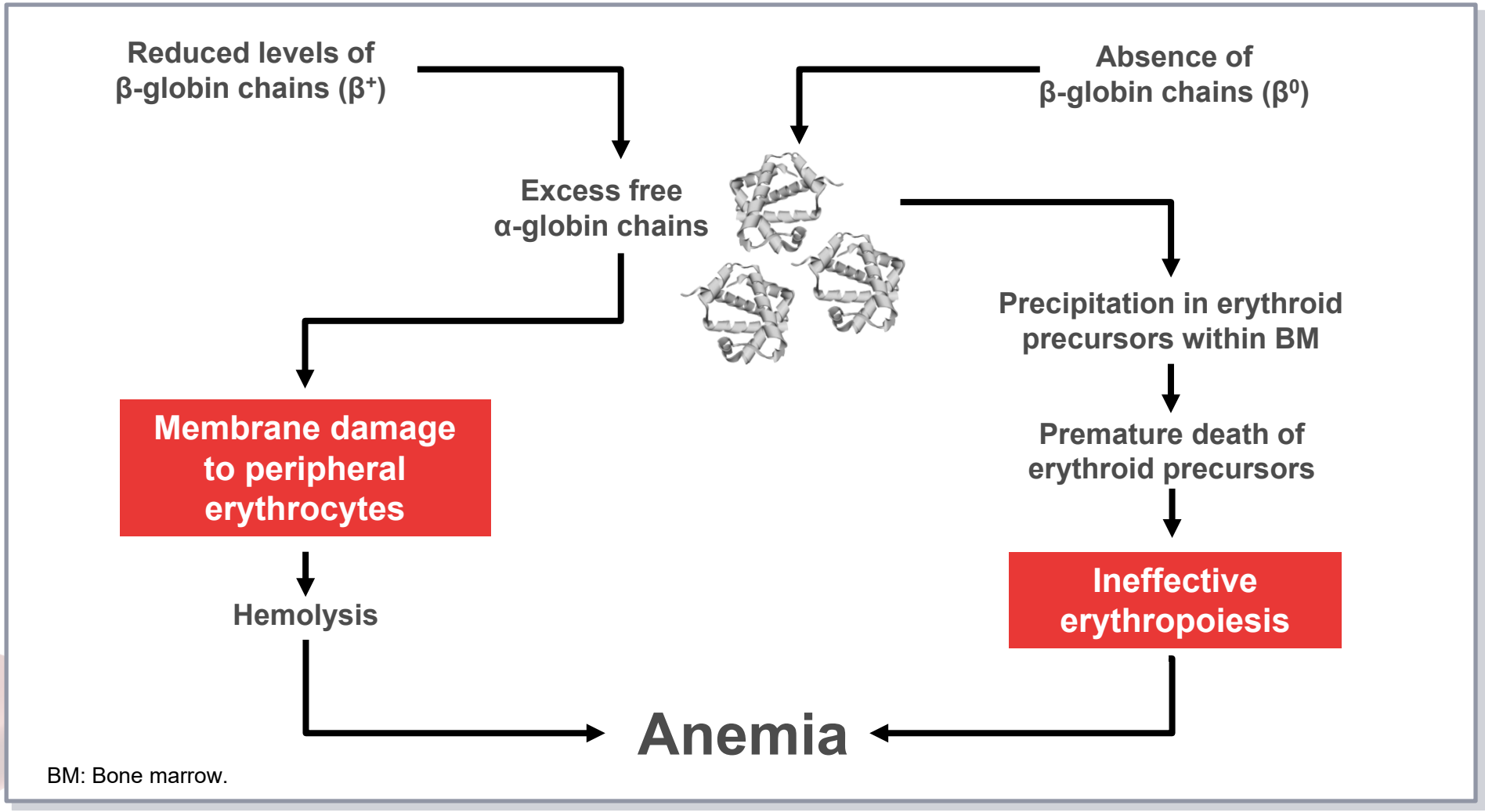
Epidemiology: Ethnic groups at increased risk

The geographic distribution of ethnic populations in Canada at increased risk for thalassemia[1]

Regions of Origin	Thalassemia
Africa	↑
Mediterranean region e.g., Sardinia, Corsica, Sicily, Italy, Spain, Portugal, Greece, Cyprus, Turkey, Egypt, Algeria, Libya, Tunisia, Morocco, Malta	↑
Middle East e.g., Iran, Iraq, Syria, Jordan, Saudi Arabia and other Arabian peninsula countries, Qatar, Lebanon, Palestine, Israel (both Arabs and Sephardic Jews affected), Kuwait	↑
Southeast Asia e.g., India, Afghanistan, Pakistan, Indonesia, Bangladesh, Thailand, Myanmar	↑
Western Pacific region e.g., China, Vietnam, Philippines, Malaysia, Cambodia, Laos	↑
Caribbean countries	↑
South American countries	↑

1. Langlois S, Ford JC, Chitayat D *et al*. Carrier screening for thalassemia and hemoglobinopathies in Canada. *J Obstet Gynaecol Can* 2008;30:950-959.

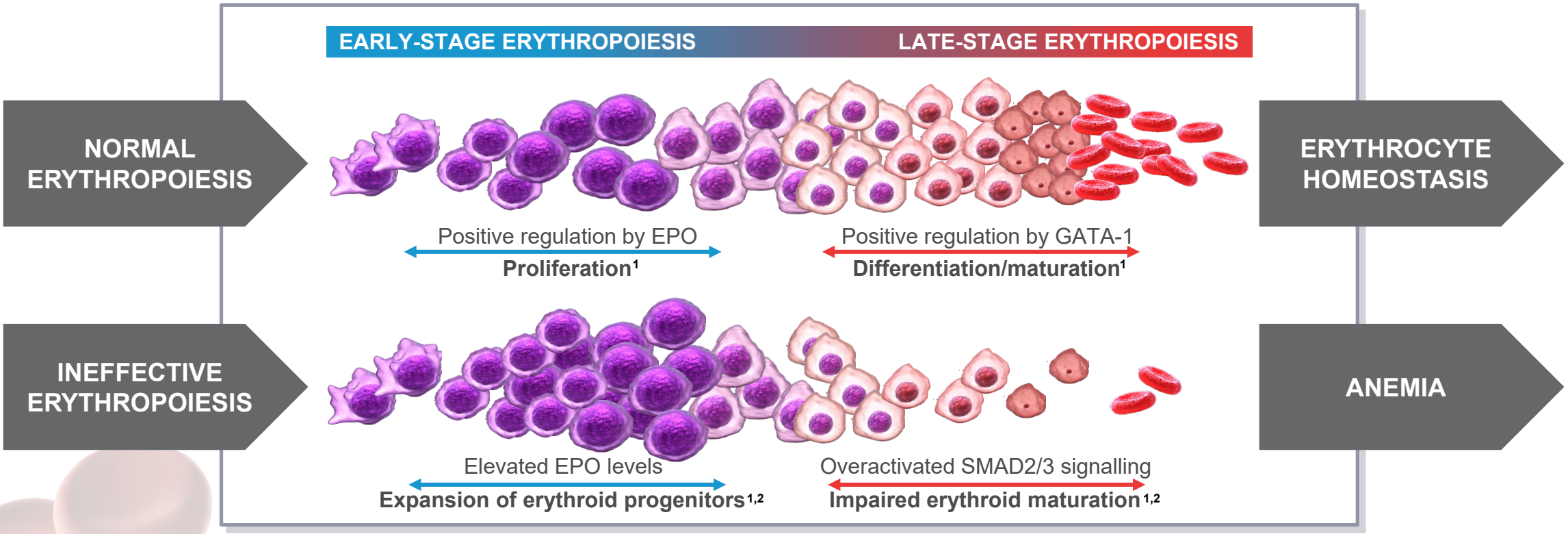
Ineffective erythropoiesis in β-thalassemia[1]



1. Cappellini MD, Cohen A, Porter J, *et al*. Guidelines for the management of TD thalassemia. 3rd edition. Nicosia (CY): thalassemia International Federation. 2014. Accessed September 2020.

Ineffective erythropoiesis (IE)

IE is characterized by the proliferation of erythroid progenitors, increased apoptosis of erythroblasts and impaired maturation[1]



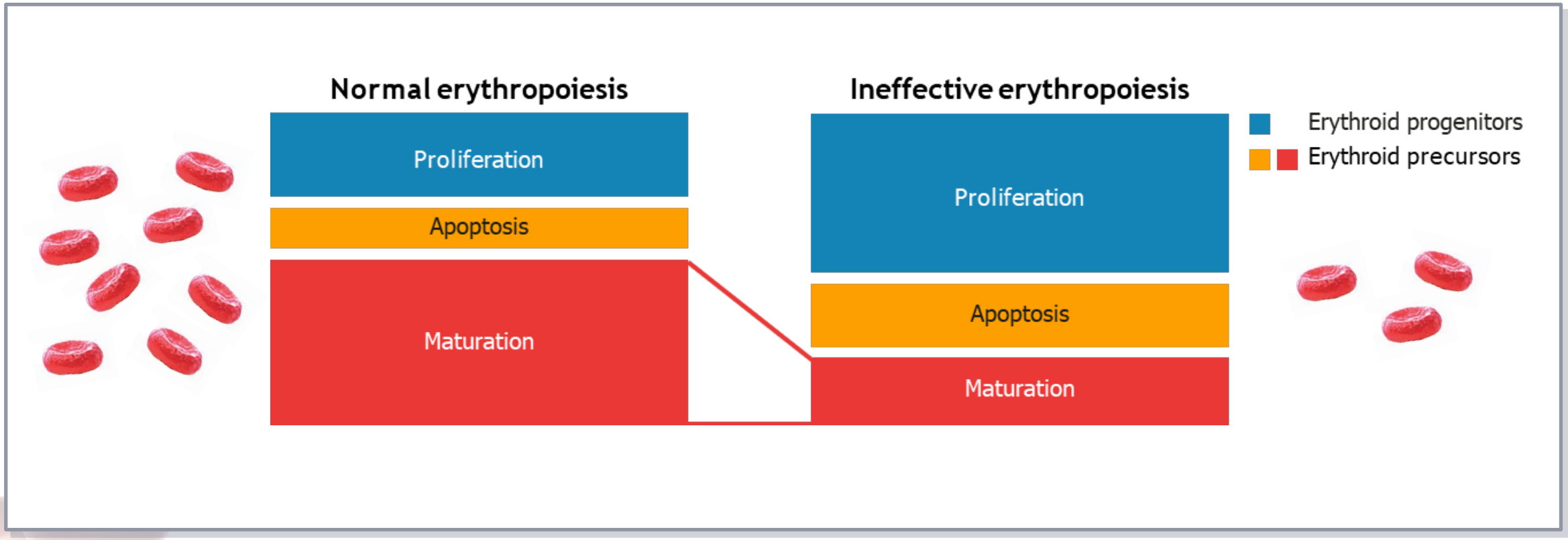
EPO: Erythropoietin.

1. Oikonomidou PR, Rivella S. What can we learn from ineffective erythropoiesis in thalassemia? *Blood Rev* 2018;32:130-143.
2. Valent P, Büsche G, Theurl I, *et al*. Normal and pathological erythropoiesis in adults: from gene regulation to targeted treatment concepts. *Haematologica* 2018;103:1593-1603.

2007CA2000434-01E

Characteristics of IE

IE is an ongoing pathological state where increased erythroid proliferation is unable to restore red blood cell counts[1,2]

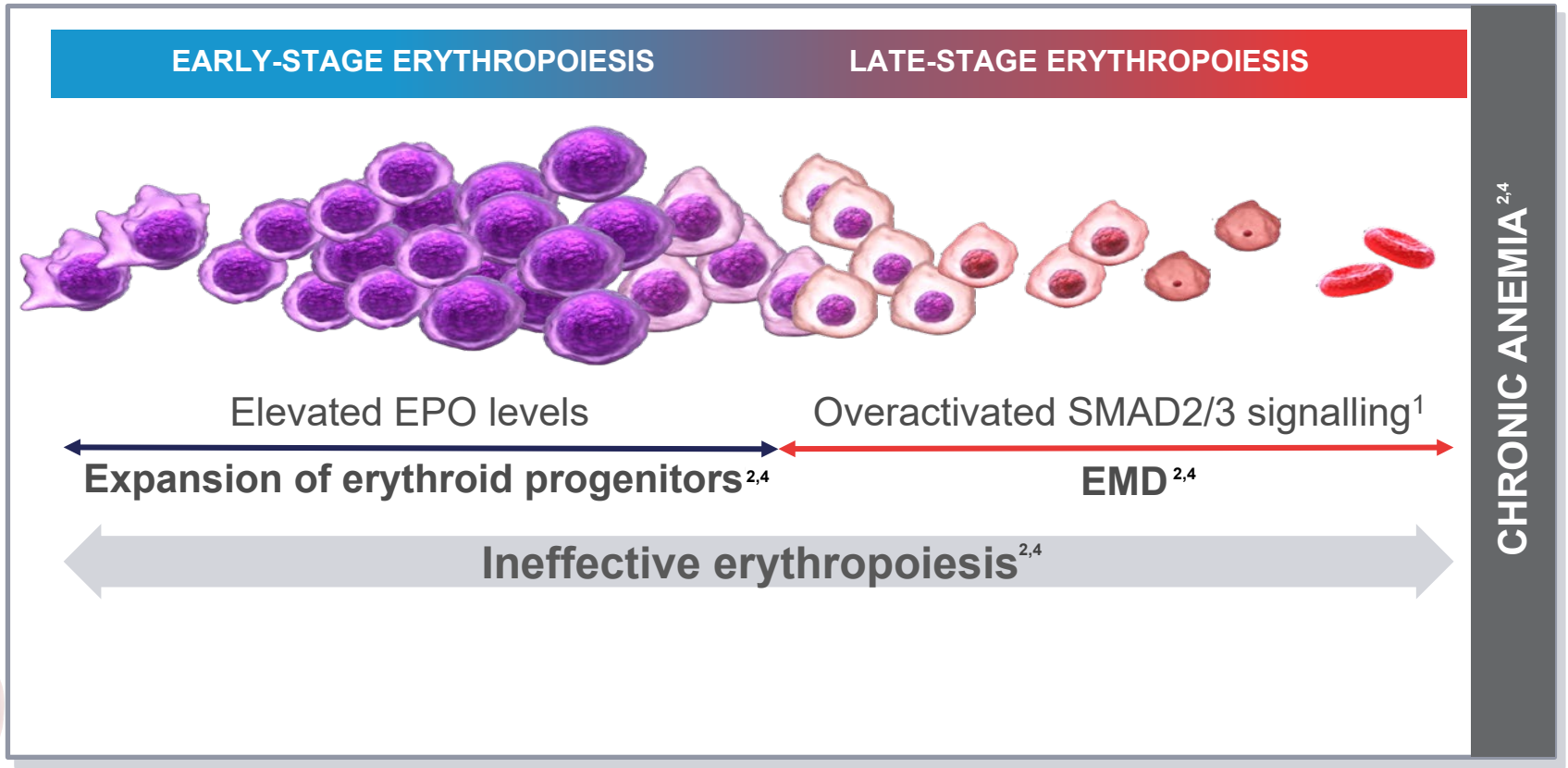


1. Camaschella C, Nai A. Ineffective erythropoiesis and regulation of iron status in iron loading anaemias. *Br J Haematol* 2016;172:512-523.
2. Liang R, Ghaffari S. Advances in understanding the mechanisms of erythropoiesis in homeostasis and disease. *Br J Haematol* 2016;174:661-673.

Erythroid maturation defects (EMDs)

EMDs form the underlying mechanism of ineffective erythropoiesis[1]

These defects occur in late-stage erythropoiesis and contribute to IE and chronic anemia observed in β-thalassemia[1-3]



1. Liang R, Ghaffari S. Advances in understanding the mechanisms of erythropoiesis in homeostasis and disease. *Br J Haematol* 2016;174:661-673.
2. Valent P, Büsche G, Theurl I, *et al*. Normal and pathological erythropoiesis in adults: from gene regulation to targeted treatment concepts. *Haematologica* 2018;103:1593-1603.
3. Koury MJ. Abnormal erythropoiesis and the pathophysiology of chronic anemia. *Blood Rev* 2014;28:49-66.
4. Oikonomidou PR, Rivella S. What can we learn from ineffective erythropoiesis in thalassemia? *Blood Rev* 2018;32:130-143.

2007CA2000434-01E

EMDs: Dysregulation of TGF-β signalling

Overactivated TGF-β superfamily signalling via SMAD2/3 contributes to impaired erythroid maturation in select hematologic diseases[1,2]

Elevated levels of select TGF-β superfamily ligands lead to increased activation of the SMAD2/3 signalling pathway via the ActRII receptor[4]

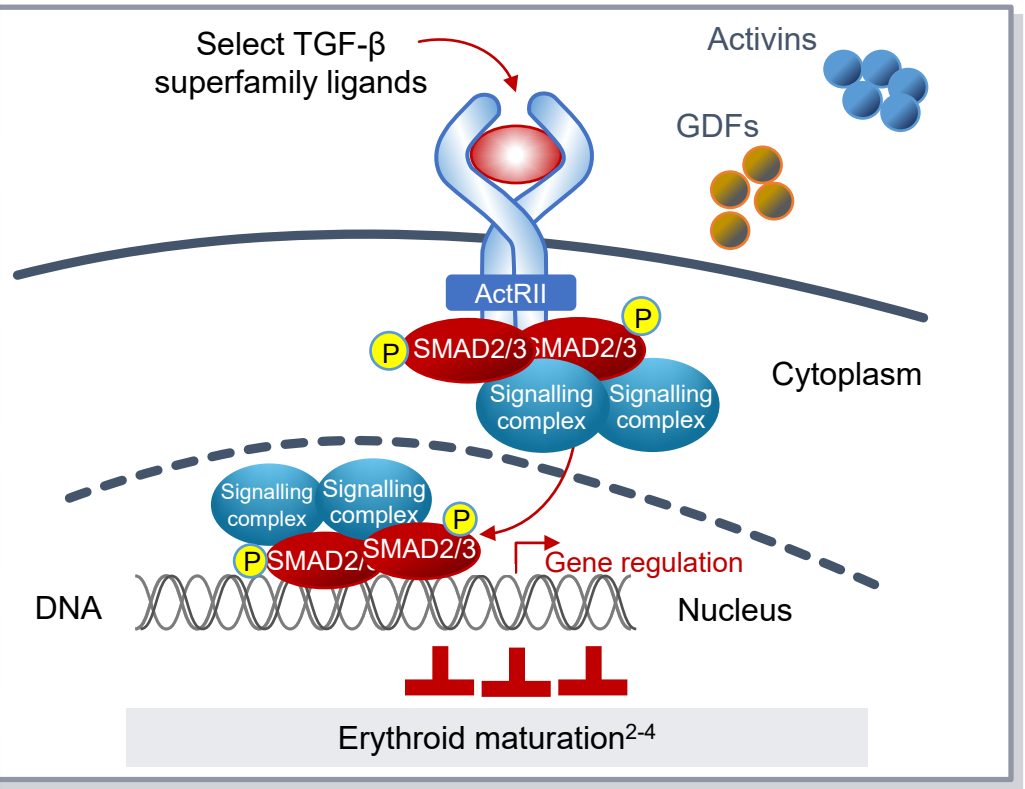
Increased phosphorylation of SMAD2/3 and translocation of signalling complexes into the nucleus[2]

SMAD2/3 signalling complexes negatively regulate late-stage differentiation of erythroblasts

Impaired maturation of erythroblasts into terminally-differentiated erythrocytes[2]

Fewer mature erythrocytes released into the bloodstream[2,5]

IE and chronic anemia[6]



TGF: Transforming growth factor.
GDF: Growth differentiation factor.
DNA: Deoxyribonucleic acid.

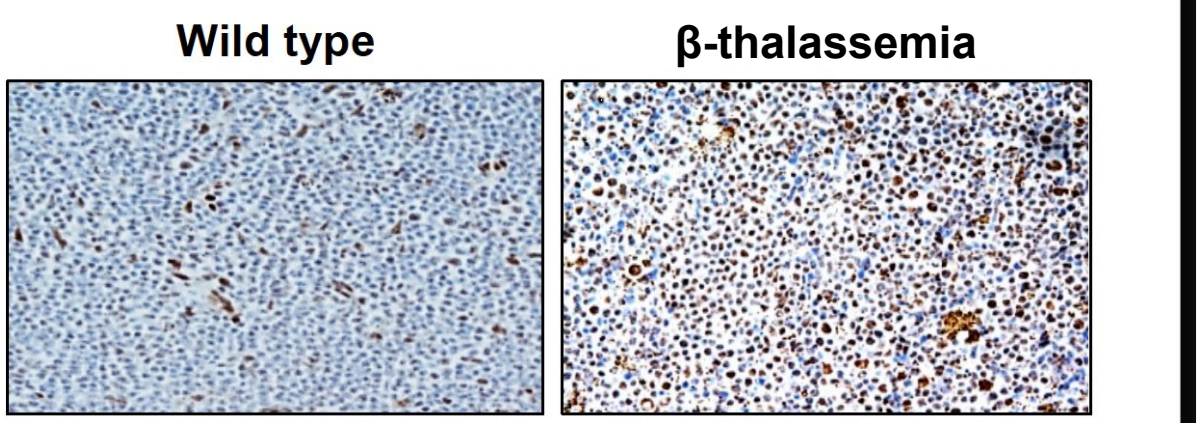
1. Torres LDS, Okumura JV, da Silva DG, *et al*. Plasma levels of TGF-β1 in homeostasis of the inflammation in sickle cell disease. *Cytokine* 2016;80:18-25.
2. Zhou L, Nguyen AN, Sohal D, *et al*. Inhibition of the TGF-beta receptor I kinase promotes hematopoiesis in MDS. *Blood* 2008;112:3434-3443.
3. Suragani RN, Cadena SM, Cawley SM, *et al*. Transforming growth factor-beta superfamily ligand trap ACE-536 corrects anemia by promoting late-stage erythropoiesis. *Nat Med* 2014;20:408-414.
4. Oikonomidou PR, Rivella S. What can we learn from ineffective erythropoiesis in thalassemia? *Blood Rev* 2018;32:130-143.
5. Camaschella C, Nai A. Ineffective erythropoiesis and regulation of iron status in iron loading anaemias. *Br J Haematol* 2016;172:512-523.
6. Liang R, Ghaffari S. Advances in understanding the mechanisms of erythropoiesis in homeostasis and disease. *Br J Haematol* 2016;174:661-673.

2007CA2000434-01E

EMDs: Dysregulation of TGF-β signalling

Increased TGF-β superfamily signalling via SMAD2/3 is commonly observed in β-thalassemia[1]

IN MICE



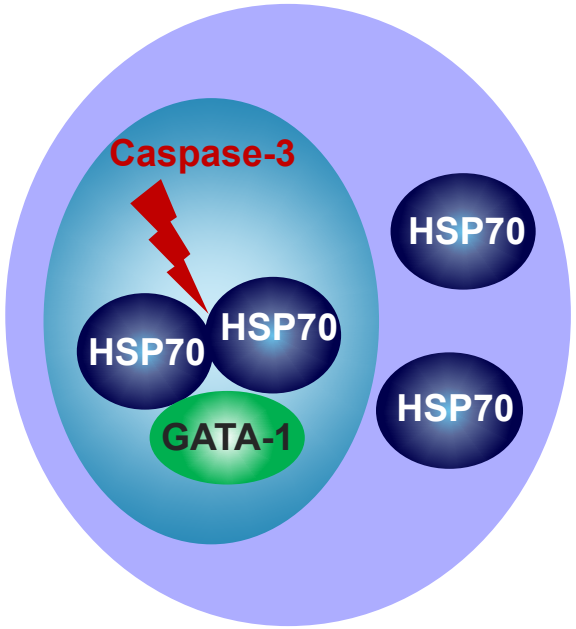
Phosphorylated SMAD2/3 immunostaining (brown) in spleen sections[1]

1.Suragani RN, Cawley SM, Li S, *et al.* Modified activin receptor IIB ligand trap mitigates ineffective erythropoiesis and disease complications in murine b-thalassemia. *Blood* 2014;123(25):3864-72.

EMDs: GATA-1 degradation

Low levels of GATA-1 contribute to EMDs and IE and are commonly seen in β-thalassemia[1]

NORMAL ERYTHROPOIESIS

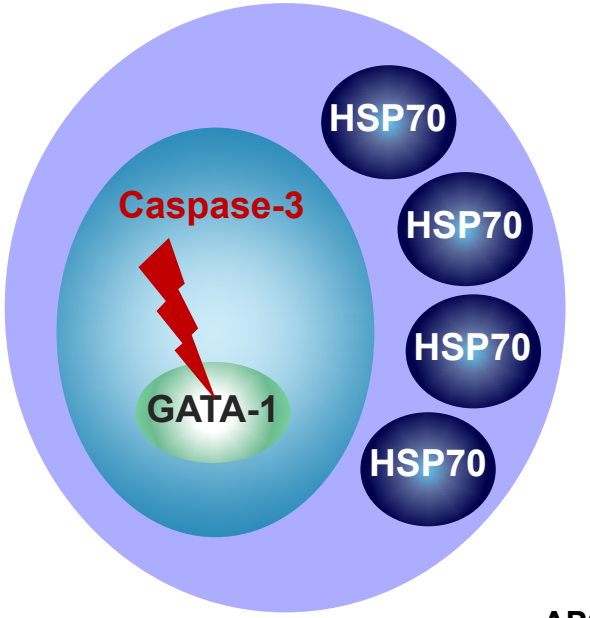


Healthy adult: HSP70 translocates into the nucleus and **protects GATA-1** from cleavage by caspase-3[1]

GATA-1 available to induce differentiation and maturation of erythroid progenitors[1]

MATURATION

EMD



β-thalassemia: HSP70 is sequestered in the cytoplasm by α-globin chains[1]

GATA-1 is cleaved by caspase-3 and is not available to exert anti-apoptotic effects or induce differentiation and maturation[1]

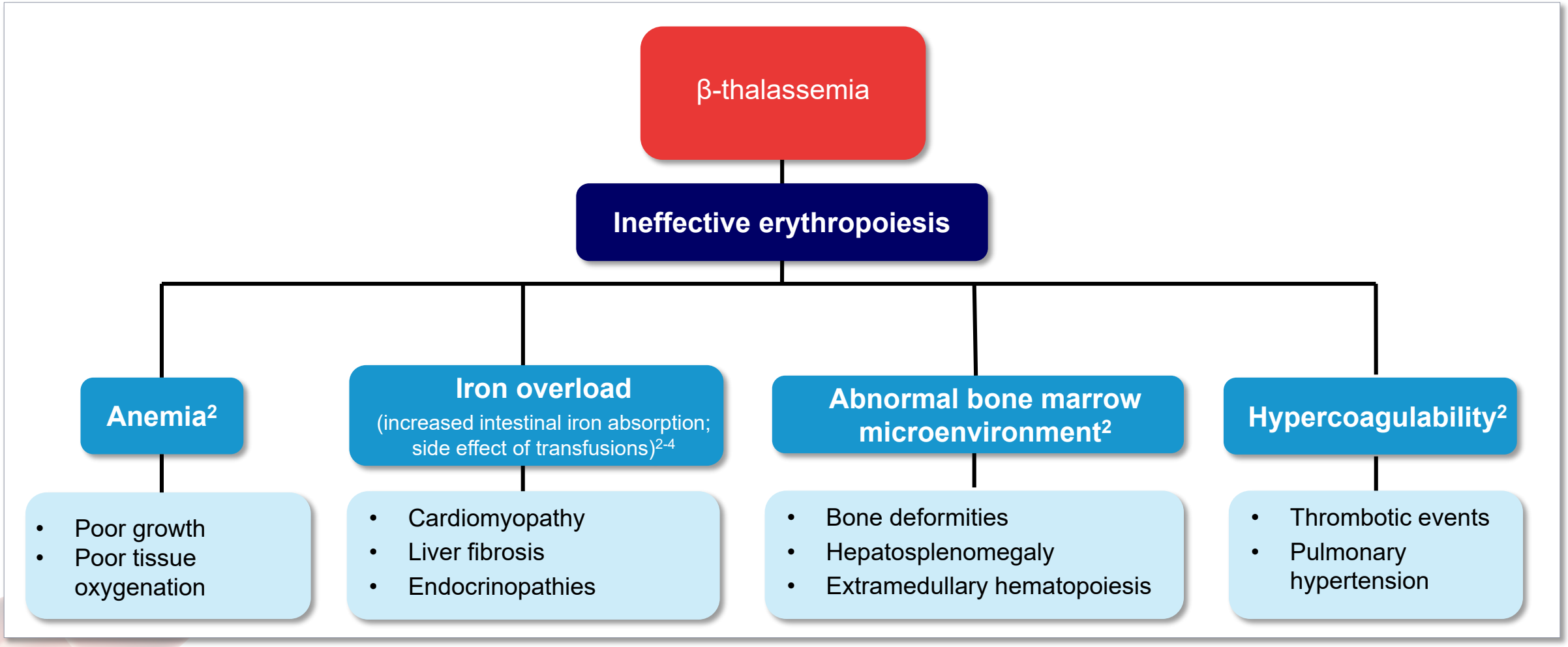
APOPTOSIS/MATURATION ARREST

HSP: Heat shock protein.

1. Valent P, Büsche G, Theurl I, *et al*. Normal and pathological erythropoiesis in adults: from gene regulation to targeted treatment concepts. *Haematologica* 2018;103:1593-1603.

Implications of IE

IE may contribute to a range of symptoms and complications in patients with β-thalassemia[1]



1. Camaschella C, Nai A. Ineffective erythropoiesis and regulation of iron status in iron loading anaemias. *Br J Haematol* 2016;172:512-523.
2. Sleiman J, Tarhini A, Bou-Fakhredin R, *et al*. Non-transfusion-dependent thalassemia: An update on complications and management. *Int J Mol Sci* 2018;19: 182.
3. Gattermann N. Iron overload in myelodysplastic syndromes (MDS). *Int J Hematol* 2018;107:55-63.
4. Munoz M, Villar I, Garcia-Erce JA. An update on iron physiology. *World J Gastroenterol* 2009;15:4617-4626.

2007CA2000434-01E

Anemia is an underlying condition of β-thalassemia

Anemia is characterized by the shortage of functional hemoglobin or RBCs that reduces oxygen delivery to tissues[1]

Ineffective erythropoiesis (IE) is a pathological state that results in low RBC count and contributes to anemia[1,2]

Anemia results in lower RBC count[1,2]

Number of circulating RBCs

Hb levels	Hematocrit levels
• According to the WHO, Hb levels <120 g/L in women or <130 g/L in men are indicative of anemia	• Percentage volume of packed RBCs in a blood specimen

This condition may develop into chronic, severe anemia, which is frequently observed in a range of hematological disorders, often as a result of ineffective erythropoiesis.[3]

1. Kassebaum NJ. The global burden of anemia. *Hematol Oncol Clin N Am* 2016;30:247-308.
2. Smith RE. The clinical and economic burden of anemia. *Am J Manag Care* 2010;16:S59-S66.
3. Oikonomidou PR, Rivella S. What can we learn from ineffective erythropoiesis in thalassemia? *Blood Rev* 2018;32:130-143.

WHO: World Health Organization.
RBC: Red blood cell.

2007CA2000434-01E

Classification per disease severity

Patients are grouped into 1 of 3 major forms of β-thalassemia based on disease severity[1]

β-thalassemia major[1,2]

- Severe form of disease, symptoms are usually seen within the first 2 years of life
- Absence of adult hemoglobin (HbA)
- Cardiac complications are the cause of the deaths in 71% of the patients with β-thalassemia major

β-thalassemia intermedia[1,2]

- Diagnosed later in childhood
- Decreased production in HbA levels
- Mild/moderate anemia
- Milder clinical presentation than β-thalassemia major

β-thalassemia carrier/minor[1]

- Mild or asymptomatic microcytic/hypochromic anemia
- There are no important clinical effects (as sufficiently stable Hb levels are produced)

1. Galanello R, Origa R. Beta-thalassemia. *Orphanet J Rare Dis* 2010 May 21;5:11.
2. Cao A, Galanello R. Beta-thalassemia. *Genet Med* 2010;12:61-76.

Clinical presentation: Symptoms and complications

Cardiovascular[1,2]

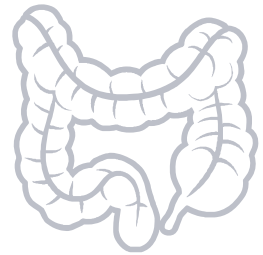
- Cardiac siderosis
- Pulmonary hypertension
- Silent cerebral ischemia
- Venous thrombosis
- Extramedullary hematopoietic pseudotumor
- Cardiac failure

Hepatic[1,2]

- Hepatic failure
- Fibrosis
- Cirrhosis
- Cancer
- Jaundice
- Chronic viral hepatitis

Digestive[1]

- Gallstones
- Abdominal swelling



Skeletal[1,2]

- Osteoporosis
- Facial abnormalities

Endocrine[2]

- Hypothyroidism
- Hypoparathyroidism
- Hypogonadism
- Diabetes mellitus
- Poor growth

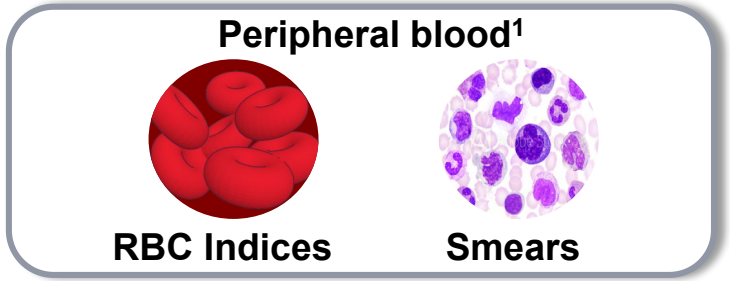
Other[1]

- Cytopenias (including microcytic anemia)
- Splenomegaly
- Leg ulcers
- Diarrhea
- Fevers, pale skin, irritability

1. Galanello R, Origa R. Beta-thalassemia. *Orphanet J Rare Dis* 2010 May 21;5:11.
2. Cao A, Galanello R. Beta-thalassemia. *Genet Med* 2010;12:61-76.

Diagnosis

Hematological and molecular diagnostic methods are used to diagnose β-thalassemia



Diagnostic approaches to β-thalassemia

Hemoglobin assessments[1]	• Qualitative and quantitative Hb assessment identifies the amount and type of Hb present in order to determine the disease severity
Cell morphology[1]	• RBC changes and features: microcytosis, hypochromia, anisocytosis, poikilocytosis, nucleated RBC (erythroblasts), increased reticulocytes, basophilic stippling
Genotype-phenotype correlation[2]	• The extent of α- and β-globin chain imbalance is the main determinant of clinical severity in β-thalassemia
Mutational analysis[1,2]	• Commonly occurring mutations of the β-globin gene are detected by PCR-based methods

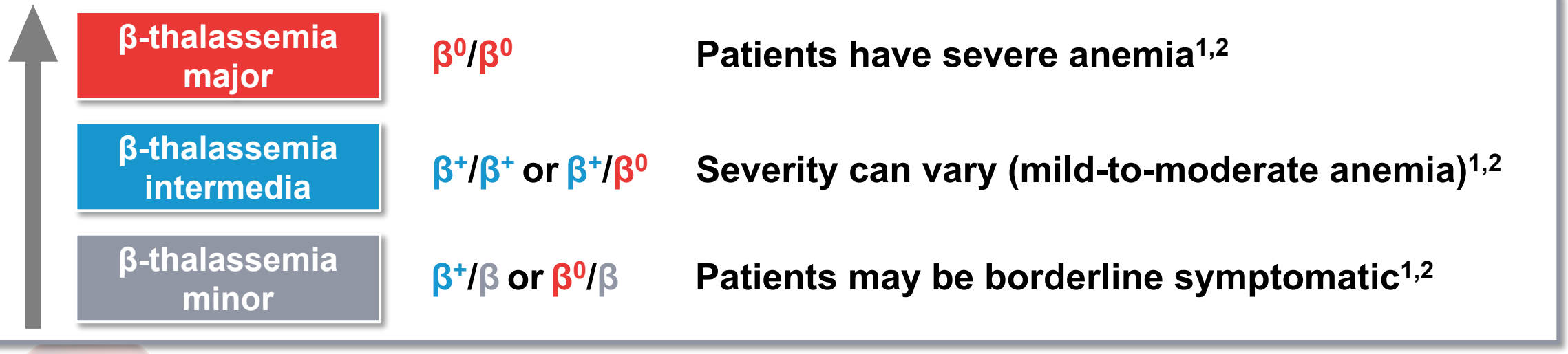
1. Galanello R, Origa R. Beta-thalassemia. *Orphanet J Rare Dis* 2010 May 21;5:11.
2. Cappellini MD, Cohen A, Porter J, *et al*. Guidelines for the management of TD thalassemia. 3rd edition. Nicosia (CY): thalassemia International Federation. 2014. Accessed September 2020.

RBC: Red blood cell.
PCR: Polymerase chain reaction

Mutations

Severity of β-thalassemia is influenced by the mutational status of the β-globin gene

- Over 200 disease-causing mutations in the β-globin gene have been documented[1]
  - **β^0 – severe mutations** that result in a complete absence of β-globin
  - **β+ – mild promoter mutations** that cause a slight reduction in β-globin chain synthesis
  - **β – no mutation**



1. Cappellini MD, Cohen A, Porter J, *et al*. Guidelines for the management of TD thalassemia. 3rd edition. Nicosia (CY): thalassemia International Federation. 2014. Accessed September 2020.
2. Galanello R, Origa R. Beta-thalassemia. *Orphanet J Rare Dis* 2010 May 21;5:11.

Summary

β-thalassemia is an inherited blood disorder that reduces Hb production[1]

- Characterized by reduced or absent synthesis of the Hb β-globin chain, decreased Hb in the blood, ineffective erythropoiesis, reduced RBC production, and anemia
- β-thalassemia follows an autosomal inheritance recessive pattern

  Annual global incidence
  - » ~1 in 100,000[1]

    and
  - » ~1.5% of global population are carriers[1]

Patients are classified according to disease severity (major, intermedia, minor)[1,2]

- Symptoms vary depending on disease severity, but many are related to chronic anemia
- Disease severity is also influenced by the mutational status of the β-globin gene

Anemia is mainly driven by ineffective erythropoiesis (IE) and may lead to life-threatening outcomes in β-thalassemia.[3-6]

1. Galanello R, Origa R. Beta-thalassemia. *Orphanet J Rare Dis* 2010 May 21;5:11.
2. Cappellini MD, Cohen A, Porter J, *et al*. Guidelines for the management of TD thalassemia. 3rd edition. Nicosia (CY): thalassemia International Federation. 2014. Accessed September 2020.
3. Kassebaum NJ. The global burden of anemia. *Hematol Oncol Clin N Am* 2016;30:247-308.
4. Malcovati L, Della Porta MG, Strupp C, *et al*. Impact of the degree of anemia on the outcome of patients with myelodysplastic syndrome and its integration into the WHO classification-based Prognostic Scoring System (WPSS). *Haematologica* 2011;96:1433-1440.
5. Camaschella C, Nai A. Ineffective erythropoiesis and regulation of iron status in iron loading anaemias. *Br J Haematol* 2016;172:512-523.
6. Liang R, Ghaffari S. Advances in understanding the mechanisms of erythropoiesis in homeostasis and disease. *Br J Haematol* 2016;174:661-673.

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RBC: Red blood cell.