Molecular Basis and Genetic Modifiers of Thalassemia

Sachith Mettananda, MBBS, MD, DPhil[a,b], Douglas R. Higgs, FMedSci, FRS[a,c,*]

KEYWORDS

• Thalassemia • Globin genes • Hemoglobin • Gene regulation • Phenotype-genotype • Genetic modifiers • α-Globin

KEY POINTS

- Defective synthesis of α-globin caused by more than 120 deletional and nondeletional mutations in the α-globin genes and their regulatory elements are known to cause α-thalassemia.
- More than 250 mutations in and around the β-globin gene that affect multiple stages of gene expression cause β-thalassemia.
- In β-thalassemia, because of the absence of β-globin, unpaired α-globin chains precipitate in red blood cells and their precursors to cause hemolysis and ineffective erythropoiesis, leading to anemia.
- The clinical severity of β-thalassemia may be ameliorated via polymorphisms in the *Xmn1-HBG2* region, the *HBS1L-MY*B intergenic region, the *BCL11A* enhancer, and mutations in *KLF1*, all of which upregulate γ-globin.
- The clinical severity of β-thalassemia may also be ameliorated by coinheritance of α-thalassemia, which reduces the excess α-globin chains.

INTRODUCTION

Thalassemia is one of the most common monogenic disorders in the world.[1] It is estimated that nearly 70,000 children with various forms of thalassemia are born each year.[2] Thalassemia is particularly common in the traditional thalassemia belt, which extends from the Mediterranean region through sub-Saharan Africa and the Middle East to South and Southeast Asia.[3] The high prevalence of thalassemia

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[a] Molecular Hematology Unit, Medical Research Council (MRC), Weatherall Institute of Molecular Medicine, University of Oxford, John Radcliffe Hospital, Headington, Oxford OX3 9DS, UK; [b] Department of Paediatrics, Faculty of Medicine, University of Kelaniya, Thalagolla Road, Ragama 11010, Sri Lanka; [c] National Institute for Health Research, Oxford Biomedical Research Centre, Blood Theme, Oxford University Hospitals, Headington, Oxford OX3 9DU, UK
* Corresponding author.
E-mail address: doug.higgs@imm.ox.ac.uk

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in these regions has been attributed to the selective advantage of carriers of thalassemia mutations against *Plasmodium falciparum* malaria, because prevalence of both conditions shows considerable overlap.[4] However, because of population migration, thalassemia has become an important health problem in most developed countries including the United Kingdom, Canada, and the United States.[5]

Most commonly the molecular defects that cause thalassemia lie within the human globin genes, which encode for α- and β-globin polypeptide chains of hemoglobin. Two α- and two β-globin chains, each conjugated with a heme moiety that is an iron-containing porphyrin derivative, form adult hemoglobin (hemoglobin A [HbA]), the specialized oxygen carrier molecule in human red blood cells (RBC).[6] Molecular defects in thalassemia lead to reduced or absent production of one of the globin chains with relative excess of the other; reduced or absent production of β-globin chains results in β-thalassemia, whereas defective synthesis of α-globin leads to α-thalassemia.

HUMAN α- AND β-GLOBIN GENE LOCI

The globin genes are possibly the most extensively studied and characterized gene loci in the human genome. The α- and β-globin gene loci are located in two different chromosomes. The human α-globin gene cluster is located on the short arm of chromosome 16 (16p13.3) close (∼150 kilobase [kb]) to the telomere. In this 135-kb segment, globin genes are arranged in the order in which they are expressed during development: telomere-ζ-μ-α_2-α_1-centromere (Fig. 1).[7] Similarly, several β-like globin genes are located in the order of their expression during development

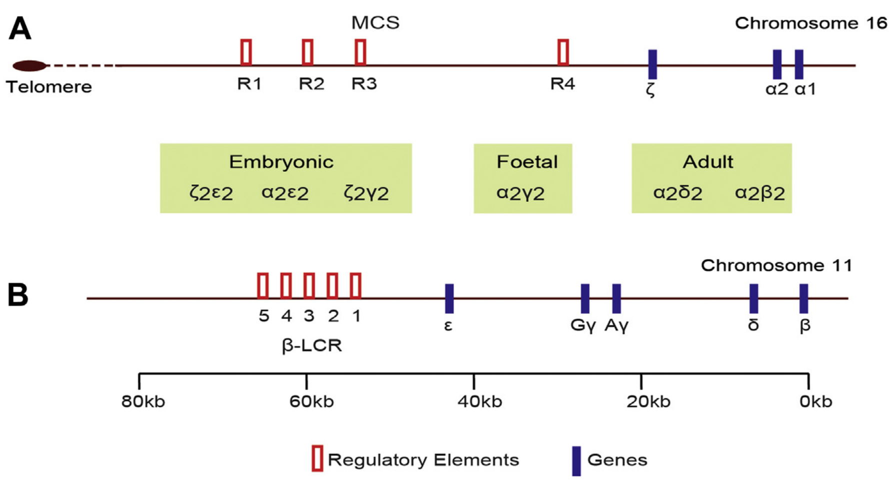

Fig. 1. Schematic diagram of α- and β-globin gene clusters and the types of hemoglobin produced at each developmental stage. Genes are arranged along the chromosome in the order in which they are expressed during development: (*A*) in the α-cluster ζ (embryonic) and α (embryonic, fetal, and adult); (*B*) in the β-cluster ε (embryonic), γ (fetal), and δ and β (adult). The four upstream regulatory elements of the α-locus are known as multispecies conserved sequences (MCS-) R1 to R4, whereas the five regulatory elements of the β-locus are collectively referred to as β-locus control region (β-LCR). (*Modified from* Mettananda S, Gibbons RJ, Higgs DR. alpha-Globin as a molecular target in the treatment of beta-thalassemia. Blood 2015;125(24):3695; with permission.)