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The Hospital Physician Hematology Board Review Manual is a study guide for fellows and practicing physicians preparing for board examinations in hematology. Each manual reviews a topic essential to the current practice of hematology.

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Hemoglobinopathies

Series Editor:
Eric D. Jacobsen, MD
Instructor in Medicine, Harvard Medical School; Attending Physician, Dana-Farber Cancer Institute, Boston, MA

Contributors:
Katharine Batt, MD, MSc
Fellow in Hematology/Oncology, Mount Sinai Hospital New York, NY

Thomas Reske, MD
Fellow in Hematology/Oncology, Boston University Medical Center, Boston, MA

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Cover Illustration by Kathryn K. Johnson
Hemoglobinopathies

Katharine Batt, MD, MSc, and Thomas Reske, MD

INTRODUCTION

Hemoglobin is a tetrameric protein composed of 2 pairs of globin chains (4 globin polypeptides) complexed with 4 heme groups. Each globin chain, or subunit, is associated with a heme group in its center. Globin chains are designated as α, β, γ, and δ and are classified as α chain or non–α chain. The dominant form of adult hemoglobin is hemoglobin A (HbA), which is made up of 2 α chains and 2 β chains.

α-Globin genes are encoded on chromosome 16, and the γ, δ- and β-globin genes are encoded on chromosome 11. Each individual carries a linked pair of α-globin genes: 2 from the paternal chromosome and 2 from the maternal chromosome. The synthesis and structure of the different globin chains is under tight genetic control, resulting in a 1.00 (± 0.05) ratio of α to non–α chains. Defects in these genes can cause the abnormal production of hemoglobin and anemias, disorders called hemoglobinopathies. These genetic defects can result in structural defects in the hemoglobin molecule, diminished production of the hemoglobin subunits, or abnormal association of subunits. Hemoglobinopathies can be qualitative (abnormal hemoglobin as in sickle cell disease), quantitative (anemia as in thalassemia), or both (sickle cell disease with concurrent thalassemia). Most hemoglobinopathies are not clinically apparent, while others produce abnormal laboratory findings and a few cause serious disease.

Structural defects in the hemoglobin molecule often occur because of mutations in either the α or β subunit chains, but mutations can also appear in the δ and γ chains. The most common clinically encountered qualitative mutation in the United States is hemoglobin S (HbS), a hemoglobinopathy characterized by an amino acid substitution at position 6 on the β chain, resulting in structurally abnormal sickle-shaped hemoglobin.

Mutations that cause diminished production of 1 of the 2 subunits of hemoglobin result in disorders called “thalassemias.” Mutations can affect any step in the pathway of globin gene expression, including transcription, pre-mRNA splicing, mRNA translation, mRNA stability, post-translational assembly, and stability of globin polypeptides. The 1.00 ratio of α to non–α chains is not maintained, and there is decreased production of total hemoglobin. Those hemoglobin molecules that are produced are structurally normal. Thalassemias are referred to by the deficient subunit: α-thalassemia or β-thalassemia. While the production of normal hemoglobin requires the linking of an α subunit with a β subunit to produce 1 of 2 dimers, in the case of an extreme lack of potential subunit partners, like subunits will abnormally associate. In the case of severe α-thalassemia, the α-globin subunits associate into groups of 4 (tetramers). In severe β thalassemia, α subunits do not self-associate and are rapidly degraded. The amount of affected globin determines the clinical picture and is epoymic for the phenotypes thalassemia minor, thalassemia intermedia, and thalassemia major.

CLASSIFICATION

Hemoglobinopathies have no universal classification. By convention, hemoglobinopathies are classified according to the qualitative nature of the resultant hemoglobin (ie, sickle cell disease) and the quantitative amount of hemoglobin produced (ie, thalassemia).

The first attempt at classification dates back to the 1950s, when sickle cell hemoglobin was found to migrate differently from normal hemoglobin in an electric field, implying a different ionic charge. Hemoglobin A, or HbA, referred to normal adult hemoglobin, and hemoglobin S, or HbS, referred to sickle hemoglobin. Fetuses were known to have alkali-resistant hemoglobin, which is referred to as hemoglobin F (HbF). Inherited methemoglobinemia had been described by some Japanese investigators, so M was reserved for such hemoglobin variants. The next variant described was hemoglobin C (HbC), which has 2 more positive charges per tetramer than HbS and therefore migrates more slowly at alkaline pH. Hemoglobins D and G (the latter α variants) migrate in a fashion very similar to HbS. Hemoglobin J and hemoglobin I have 2 and 4 charges per tetramer electronegative to HbA, respectively, and thus migrate faster than HbA. As the discovery of variants continued, it became clear that the alphabet would be exceeded.