



HEMOGLOBIN ELECTROPHORESIS

Types of hemoglobins:

There are hundreds of hemoglobin variants that involve genes both from the alpha and beta gene clusters. The list below touches on some of the more common and important hemoglobin variants.

Normal Hemoglobins :

- **Hemoglobin A.** This is the designation for the normal hemoglobin that exists after birth. Hemoglobin A is a tetramer with two alpha chains and two beta chains ($\alpha_2\beta_2$).
- **Hemoglobin A2.** This is a minor component of the hemoglobin found in red cells after birth and consists of two alpha chains and two delta chains ($\alpha_2\delta_2$). Hemoglobin A2 generally comprises less than 3% of the total red cell hemoglobin.
- **Hemoglobin F.** Hemoglobin F is the predominant hemoglobin during fetal development. The molecule is a tetramer of two alpha chains and two gamma chains ($\alpha_2\gamma_2$).

Clinically Significant Variant Hemoglobins:

- **Hemoglobin S.** This the predominant hemoglobin in people with sickle cell disease. The alpha chain is normal. The disease-producing mutation exists in the beta chain, giving the molecule the structure, $\alpha_2\beta^S_2$. People who have one sickle mutant gene and one normal beta gene have sickle cell trait which is benign.
- **Hemoglobin C.** Hemoglobin C results from a mutation in the beta globin gene and is the predominant hemoglobin found in people with hemoglobin C disease ($\alpha_2\beta^C_2$). Hemoglobin C disease is relatively benign, producing a mild hemolytic anemia and splenomegaly. Hemoglobin C trait is benign.
- **Hemoglobin E.** This variant results from a mutation in the hemoglobin beta chain. People with hemoglobin E disease have a mild hemolytic anemia and mild splenomegaly. Hemoglobin E trait is benign. Hemoglobin E is extremely common in S.E. Asia and in some areas equals hemoglobin A in frequency.
- **Hemoglobin Constant Spring.** Hemoglobin Constant Spring is a variant in which a mutation in the alpha globin gene produces an alpha globin chain that is abnormally long. The result is a thalassemic phenotype. (The designation Constant Spring derives from the isolation of the hemoglobin variant in a family of ethnic Chinese background from the Constant Spring district of Jamaica.)
- **Hemoglobin H.** Hemoglobin H is a tetramer composed of four beta globin chains. Hemoglobin H occurs only with extreme limitation of alpha chain availability. Hemoglobin H forms in people with three-gene alpha thalassemia as well as in people with the combination of two-gene deletion alpha thalassemia and hemoglobin Constant Spring.
- **Hemoglobin Barts.** Hemoglobin Barts develops in foetuses with four-gene deletion alpha thalassemia. During normal embryonic development, the epsilon gene of the alpha globin gene locus combines with genes from the beta globin locus to form functional hemoglobin molecules. The epsilon gene turns off at about 12 weeks, and normally the alpha gene takes over. With four-gene deletion alpha thalassemia no alpha chain is produced. The gamma chains produced during foetal development combine to form gamma chain tetramers. These molecules transport oxygen poorly. Most individuals with four-gene deletion thalassemia

and consequent hemoglobin Barts die in utero (hydrops fetalis). Compound Heterozygous Conditions

Compound heterozygous:

Occasionally someone inherits two different variant genes from the alpha globin gene cluster or two different variant genes from the beta globin gene cluster. This condition is called "compound heterozygous".

- **Hemoglobin SC disease.** Patients with hemoglobin SC disease inherit a gene for hemoglobin S from one parent, and a gene for hemoglobin C from the other. Hemoglobin C interacts with hemoglobin S to produce some of the abnormalities seen in patients with sickle cell disease. On average, patients with hemoglobin SC disease have milder symptoms than do those with sickle cell disease. This is only an average, however. Some people with hemoglobin SC disease have a condition equal in severity to that of any patient with sickle cell disease. A number other syndromes exist that involve a hemoglobin S compound heterozygous state. They are less common than hemoglobin SC disease, however. Ironically, hemoglobin SC disease is often a much more severe condition than is homozygous hemoglobin C disease. The expression of a single hemoglobin S gene normally produces no problem (i.e., sickle cell trait). The hemoglobin C molecule disturbs the red cell metabolism only slightly. However, the disturbance is enough to allow the deleterious effects of the hemoglobin S to be manifested.
- **Sickle/beta-thalassemia.** In this condition, the patient has inherited a gene for hemoglobin S from one parent and a gene for beta-thalassemia from the other. The severity of the condition is determined to a large extent by the quantity of normal hemoglobin produced by the beta-thalassemia gene. (Thalassemia genes produce normal hemoglobin, but in variably reduced amounts). If the gene produces no normal hemoglobin, β^0 -thalassemia, the condition is virtually identical to sickle cell disease. Some patients have a gene that produces a small amount of normal hemoglobin, called β^+ -thalassemia. The severity of the condition is dampened when significant quantities of normal hemoglobin are produced by the β^+ -thalassemia gene. Sickle/beta-thalassemia is the most common sickle syndrome seen in people of Mediterranean descent (Italian, Greek, Turkish). Beta-thalassemia is quite common in this region, and the sickle cell gene occurs in some sections of these countries. Hemoglobin electrophoresis of blood from a patient with sickle/ β^0 -thalassemia shows no hemoglobin A. Patients with sickle/ β^+ -thalassemia have an amount of hemoglobin A that depends of the level of function of the β^+ -thalassemia gene.
- **Hemoglobin E/beta-thalassemia.** The combination of hemoglobin E and beta-thalassemia produces a condition more severe than is seen with either hemoglobin E trait or beta-thalassemia trait. The disorder manifests as a moderately severe thalassemia that falls into the category of thalassemia intermedia. Hemoglobin E/beta-thalassemia is most common in people of S.E. Asian background.
- **Alpha thalassemia/Hemoglobin Constant Spring.** This syndrome is a compound heterozygous state of the alpha globin gene cluster. The alpha globin gene cluster on one of the two chromosomes 16 has both alpha globin genes deleted. On the other chromosome 16, the alpha gene has the Constant Spring mutation. The compound heterozygous condition produces a severe shortage of alpha globin chains. The excess beta chains associate into tetramers to form hemoglobin H.