Hemoglobin variants

Hemoglobin variants are mutant forms of hemoglobin in a population (usually of humans), caused by variations in genetics. Some well-known hemoglobin variants such as sickle-cell anemia are responsible for diseases, and are considered hemoglobinopathies. Other variants cause no detectable pathology, and are thus considered non-pathological variants.

Some normal hemoglobin types are; Hemoglobin A (Hb A), which is 95-98% of hemoglobin found in adults, Hemoglobin A2 (Hb A2), which is 2-3% of hemoglobin found in adults, and Hemoglobin F (Hb F), which is found in adults up to 2.5% and is the primary hemoglobin that is produced by the fetus during pregnancy.

Hemoglobin variants occur when there are genetic changes in specific genes, or globins, that cause changes or alterations in the amino acid. They could affect the structure, behavior, the production rate, and/or the stability of that specific gene. Usually there are four genes that code for alpha globin and two genes that code for beta globin. If the genes for alpha chains is mutated, the most common condition that occurs is alpha thalassemia, which causes a decrease in production of that gene. The level of severity of alpha thalassemia is determined by the number of genes that are affected.

Along with lengthy list of common hemoglobin variants, there are some variants that are less common. These variants are considered silent, which means that they have no signs or symptoms. They usually affect the functionality and/or the stability of the hemoglobin molecule. With most of these variants are mutations in the alpha globin gene that result in an abnormally long alpha chain and an unstable hemoglobin molecules.

Hemoglobin A (HbA) is the most common type of hemoglobin variants found in human. This type of hemoglobin is normal in structure and function. Among adult humans nearly 95%-98% reports HbA variant of hemoglobin. This type of hemoglobin contains two alpha and two beta chins. **Hemoglobin A2** is a other type of normal hemoglobin. Nearly

2-3% adults reports this type of hemoglobin. This type of hemoglobin contains two alpha and two delta chins.

Other normal hemoglobin is **HbF**. This type of hemoglobin contains two alpha and two gamma chain. Hemoglobin F is the primary hemoglobin produced by the fetus. The hemoglobin transports oxygen efficiently in a low oxygen environment. The hemoglobin production stops at birth and decreases to adult levels by the age of one or two. The levels can be normal to increased in beta thalassemia. Hemoglobin F frequently increases in individuals with sickle cell anemia and sickle cell-beta thalassemia. Individuals with sickle cell and increase of Hb F have a milder case of the disease. There are situations where the Hb F is increased. This rare condition is called Hereditary Persistence of Fetal Hemoglobin (HPFH).

Of these three normal hemoglobin types HbF dominates until 3weeks of age and afterwords HbA dominates throughout the life.

Hemoglobin H (HbH) increases the affinity for oxygen. This means that it holds onto the oxygen instead of releasing it into tissue and cells. Hb H usually occurs in some alpha thalassemia and is composed of four beta globin (protein) chains. This variant is usually produced in response to a severe shortage of alpha chains, and usually cause beta chains to function abnormally.

Hemoglobin S (HbS) is responsible for sickle cell anemia disease. As a result of this abnormal mutation a abnormal variant of hemoglobin is produced which leads to the disease sickle cell anemia. In this case in beta globins chain, 6^{th} number amino acid is changed (from glutamic acid to valine) due to single nucleotide mutation.

Hemoglobin C (HbC) is an abnormal hemoglobin in which like HbS, in the 6^{th} position glutamic acid is changed, but this time with a lysine. Most people do not have symptoms. It can cause a mild to moderate enlargement of the spleen, splenomegaly, as well as hemolytic anemia (which is the form of anemia due to abnormal breakdown of red blood

cells prematurely). Too much hemoglobin C can reduce the number and size of red blood cells in the body, causing mild anemia.

Hemoglobin E (HbE) is is an abnormal hemoglobin with a single point mutation in the β chain. At position 26 there is a change in the amino acid, from glutamic acid to lysine. Hemoglobin E is very common among people of Southeast Asian, Northeast Indian, Sri Lankan and Bangladeshi descent.

The βE mutation affects β-gene expression creating an alternate splicing site in the mRNA at codons 25-27 of the β-globin gene. Through this mechanism, there is a mild deficiency in normal β mRNA and production of small amounts of anomalous β mRNA. The reduced synthesis of β chain may cause β-thalassemia. Also, this hemoglobin variant has a weak union between α- and β-globin, causing instability when there is a high amount of oxidant. HbE can be detected on electrophoresis.

People with **hemoglobin D (HbD)** trait have slightly more hemoglobin A than hemoglobin D. People with Hemoglobin D trait do not have health problems related to having the trait. People with hemoglobin D trait do not have Hemoglobin D disease or sickle cell disease. They cannot develop these diseases later in life. Hemoglobin helps red blood cells carry oxygen from the lungs to other parts of the body. Normal red blood cells have hemoglobin A. People with hemoglobin D trait have red blood cells that have normal hemoglobin A and an abnormal hemoglobin. The abnormal hemoglobin is called hemoglobin D. Among the seven known types of Hemoglobin D, only Hemoglobin D Punjab can cause a serious hemoglobin disorder. While Hemoglobin D can be detected without a DNA test, one is needed to ascertain that a person who carries Hemoglobin D carries hemoglobin D-Punjab.

A single mutation in the HBB gene is called Hemoglobin D Trait. There is no clinical disease detected, however children of affected individuals have increased risk of having Hemoglobin D Disease.