Sickle Cell Disease

Chapter 1 Beta-Globin Gene Cluster

Approximately 15% of DNA represents the structural genes for the embryonic, fetal, and adult beta-like subunits of human hemoglobin within the human beta-globin gene cluster. The remainder of the DNA are intervening and flanking sequences. Non-coding DNA contains sequences that regulate gene expression, gene switching, and recombination. Most of the genetic variation in the human beta cluster is noncoding DNA. The beta-globin cluster sequences that regulate recombination is nonuniform. Variability is due to recombination as well as sampling variation of a limited number of haplotypes and evolutionary accidents. Nonuniformity of recombination is generally expected. Recurrent mutations, gene migrations, and gene conversion are contributory factors of increased recombination in the beta-globin gene.[1]

Chapter 2 Beta-Globin Variant & Inheritance

Sickle Cell Disease is one of the most common genetic diseases and it refers to a collection of autosomal recessive genetic disorders, the Hb S variant of the beta-globin gene.[2,3] It is recognized as a major public health problem by international agencies.[2] Sickle cell disease stems from a variant of the beta-globin gene called sickle hemoglobin (Hb S). Inherited autosomal recessive genes are required for disease expression. This is either two copies of Hb S or one copy of Hb S plus another beta-globin variant (such as Hb C). Individuals who are Hb S carriers are protected from malaria infection. This genetic protection is presumed to have evolved out of necessity and led to the high frequency of Hb S in individuals of African and Mediterranean ancestry where malaria is prevalent.[3]

The sickle cell disorders vary in severity from symptomless sickle cell trait to the dangerous state of sickle cell anemia. Even diagnoses vary in severity from a short life span to undiagnosed until late in life.[4] Individuals who are carriers of Sickle Cell Trait have one copy of the sickle variant and one copy of the normal beta-globin gene (Hb AS), which produces a mixture of sickle hemoglobin and normal hemoglobin.[3] Patients with more severe anemia may have lower blood viscosity and that may ameliorate the severity of vaso-occlusion. An association with a higher hematocrit may indicate increased disease severity. A low percentage of dense cells, a high degree of cell deformability, and a low percentage of irreversibly sickled cells are all conditions associated with high pain rates.[5]

Chapter 3 Sickling

The hemoglobin in people with sickle cell disease polymerizes in red blood cells when it becomes deoxygenated. The red blood cells then change shape from a biconcave disc to a sickled shape. The sickled cells have a propensity to adhere to the blood vessel walls. This can lead to clogged blood vessels, obstruction of blood flow, and inefficiency in delivering oxygen to organs and tissues. These sickled cells are susceptible to hemolysis, which leads to chronic anemia. Chronic anemia is a moderate risk factor for morbidity in individuals with sickle cell disease. A viral infection can lead to a temporary reduction in red blood cell production and cause life-threatening anemia, called aplastic crisis.[3]