Mutations

Accurate DNA replication, transcription, and translation all depend on the reliable pairing of complementary bases. Errors occur, though infrequently, in all three processes—least often in DNA replication. But, the consequences of DNA errors are the most severe because only they are heritable. Mutations are heritable changes in genetic information, which may occur spontaneously or may be induced.

Mutations have different phenotypic effects phenotypically, we can understand mutations in terms of their effects on proteins and their function:

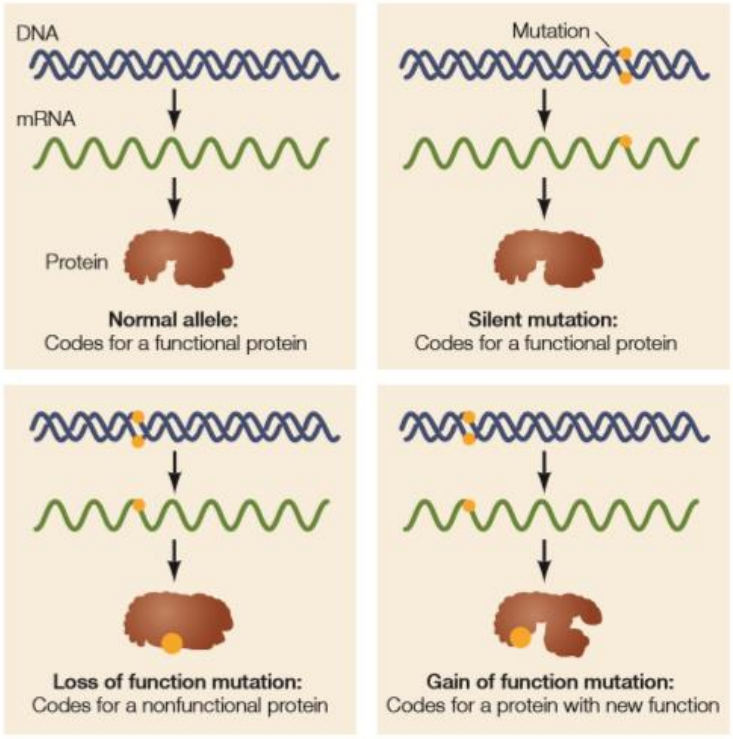

Figure 1- Mutations may or may not affect the protein phenotype. Image courtesy- Sadava et al, Life: The science of Biology, 9th edition.

All mutations are alterations in the nucleotide sequence of DNA. At the molecular level, we can divide mutations into two categories:

• **A point mutation** results from the gain, loss, or substitution of a single nucleotide. After DNA replication, the altered nucleotide becomes a mutant base pair. If a point mutation occurs within a gene (rather than in a noncoding DNA sequence), then one allele of that gene (usually dominant) becomes another allele (usually recessive).

• **Chromosomal mutations** are more extensive than point mutations. They may change the position or orientation of a DNA segment without actually removing any genetic information, or they may cause a segment of DNA to be duplicated or irretrievably lost.

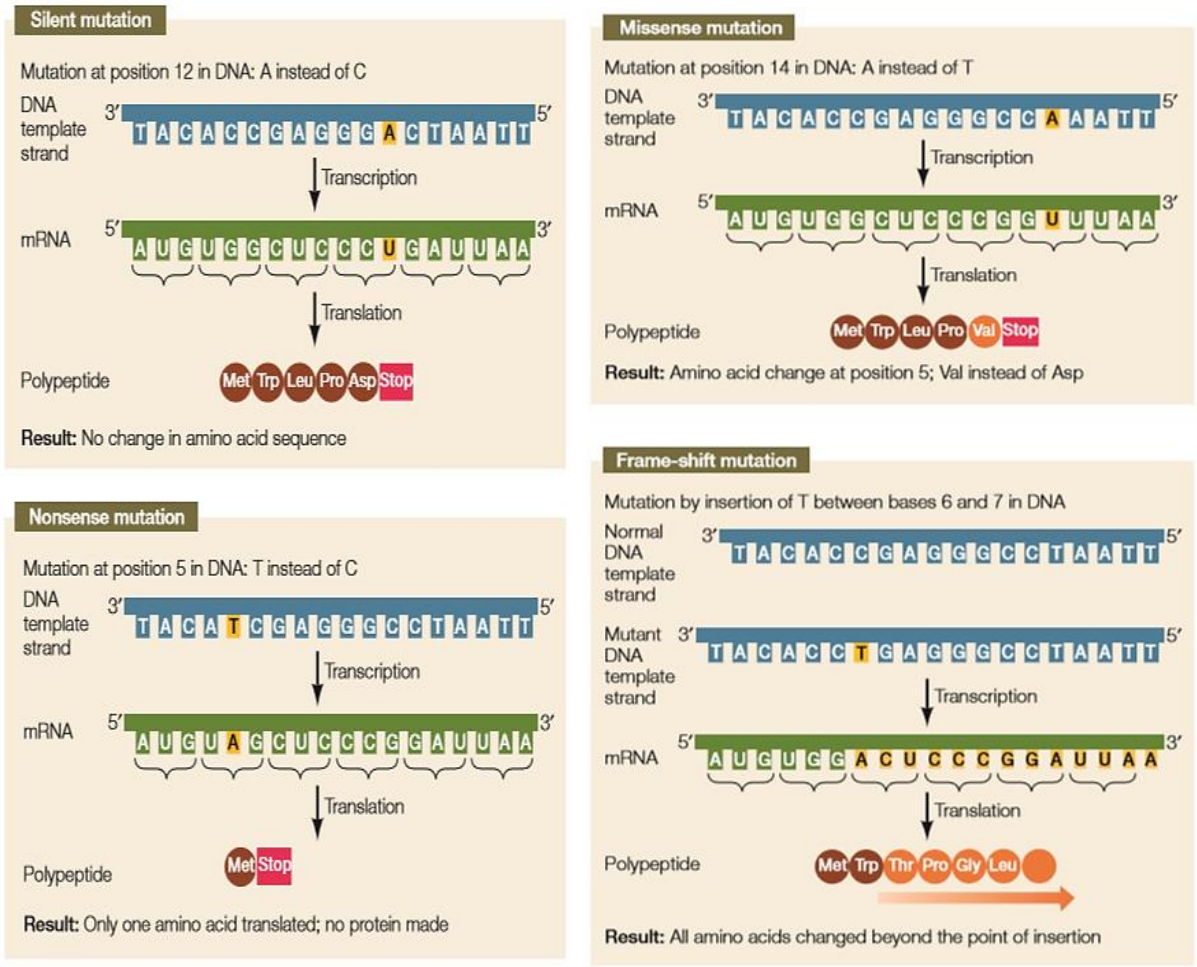

Figure 2- Point mutations. Image courtesy- Sadava et al, Life: The science of Biology, 9th edition.

Changes in single nucleotides are not the most dramatic changes that can occur in the genetic material. Whole DNA molecules can break and rejoin, grossly disrupting the sequence of genetic information. There are four types of such chromosomal mutations: deletions, duplications, inversions and translocations. These mutations can be caused by severe damage to chromosomes resulting from mutagens or by drastic errors in chromosome replication.

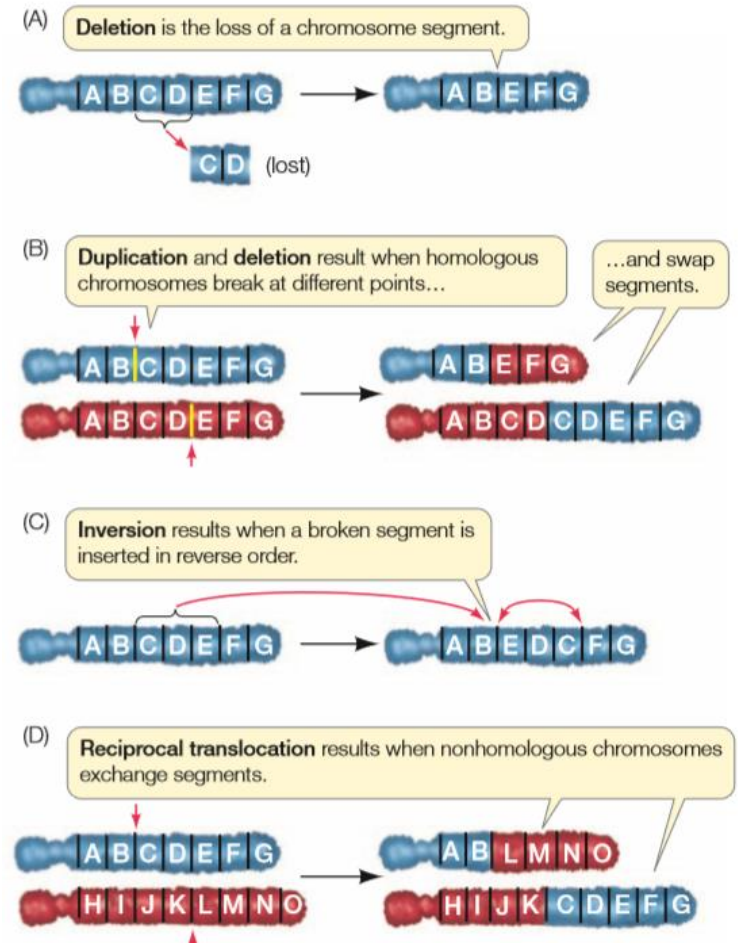

Figure 3- Chromosomal Mutations Chromosomes may break during replication, and parts of chromosomes may then rejoin incorrectly. The letters on these chromosome illustrations represent large segments of the chromosomes. Each segment may include anywhere from zero to hundreds or thousands of genes. . Image courtesy- Sadava et al, Life: The science of Biology, 9th edition.

Effects of mutation:

Mutations provide the scope for evolution: A mutation in somatic cells may benefit the organism immediately. Second, a mutation in germ line cells may have no immediate selective advantage to the organism but may cause a phenotypic change in offspring. If the environment changes in a later generation, that mutation may be advantageous and thus selected for under these conditions.

Germ line and somatic mutations can be harmful: Mutations in germ line cells that get carried to the next generation are often deleterious, especially if the offspring are homozygous for a harmful recessive allele. In their extreme form, such mutations produce phenotypes that are lethal. Lethal mutations can kill an organism during early development, or the organism may die before maturity and reproduction.

Sickle cell anemia:

The protein in red blood cells (RBCs) that transports oxygen from the lung to metabolically active tissues, like muscle, where it is needed. The discovery of haemoglobin S (HbS) by Linus Pauling and colleagues in 1949 was the first demonstration that the production of an abnormal protein could be the cause of a genetic disorder. In 1956, Vernon Ingram identified the abnormality in the amino acid sequence of the β-globin chain (β6Glu→Val). This abnormality resulted in the normal concave cells gaining a sickled appearance.

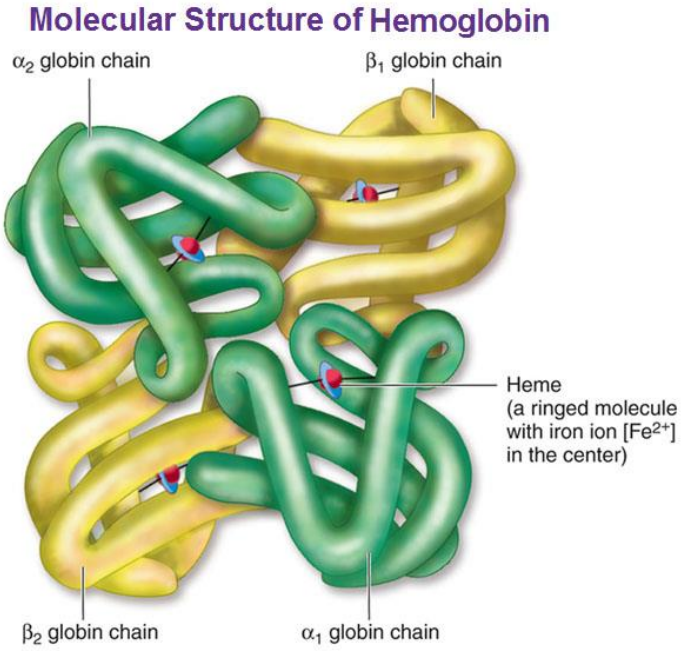

Figure 4- The structure of hemoglobin protein in the RBCs. Sickle cell anemia id produced due to mutation event in the beta chain of hemoglobin.

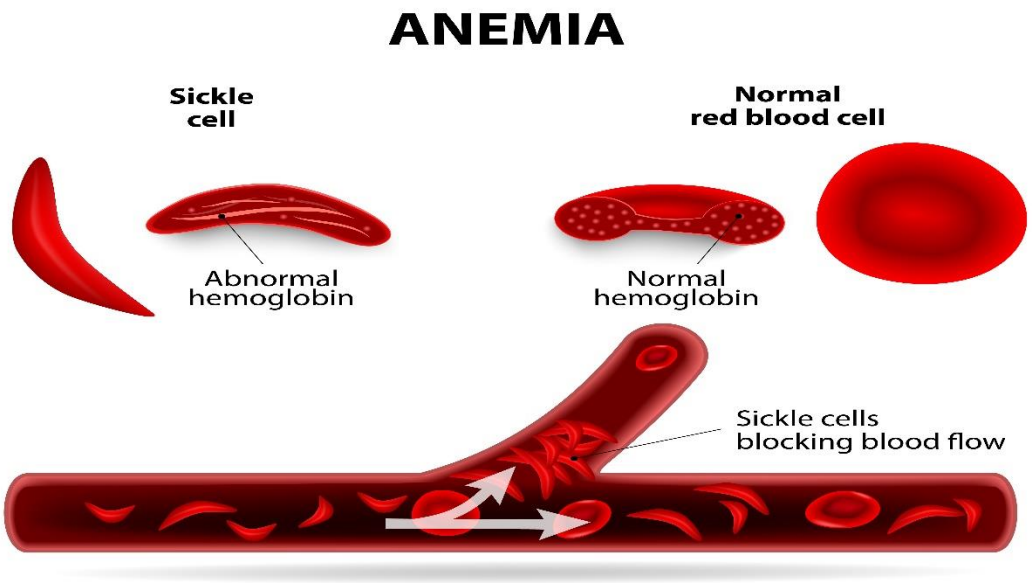

Figure 5- The abnormal cells of RBC as seen in Sickle cell Disease (SCD) compared with the normal RBCs. The sickle shape of the abnormal cells obstructs the blood flow and causes blood blockage in the thin capillaries causing extreme pain.

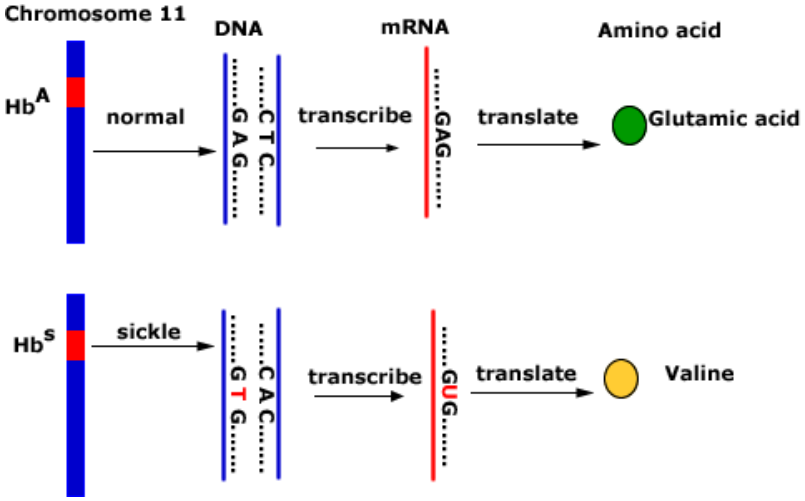

Figure 6- The gene for the beta chain of hemoglobin in normal RBCs codes for glutamic acid, which is hydrophilic in nature. The mutation in the gene coding for beta chain changes the codon on the mRNA to code for valine instead of glutamic acid. Valine is hydrophobic in nature.

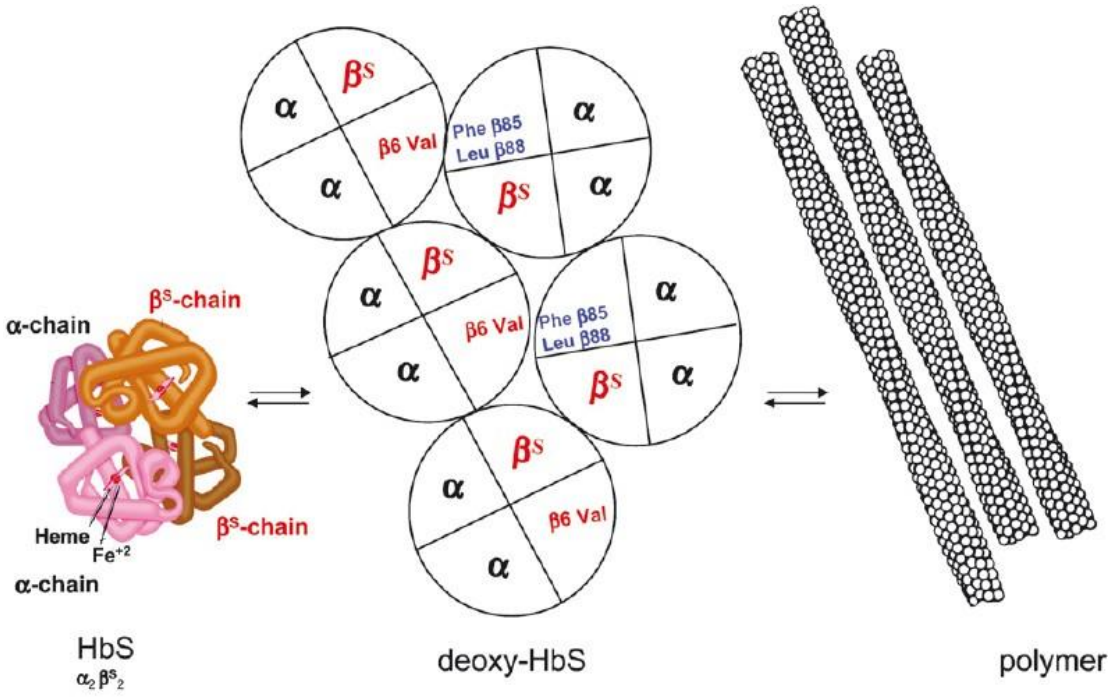

Figure 7- Basic pathophysiological mechanism of sickle cell disease: the polymerization of deoxy-HbS. The replacement of a glutamic acid by a valine residue at position 6 in the β-globin polypeptide chain characterizes the abnormal haemoglobin of SCD: HbS. The presence of hydrophobic valine in the beta chain acts as a hydrophobic pocket to which the other hydrophobic residues (phenylalanine and leucine) in the beta chain bind. At low oxygen pressure, deoxy-HbS polymerises and gets organised in long polymer fibres that deform, stiffen, and weaken the red blood cell

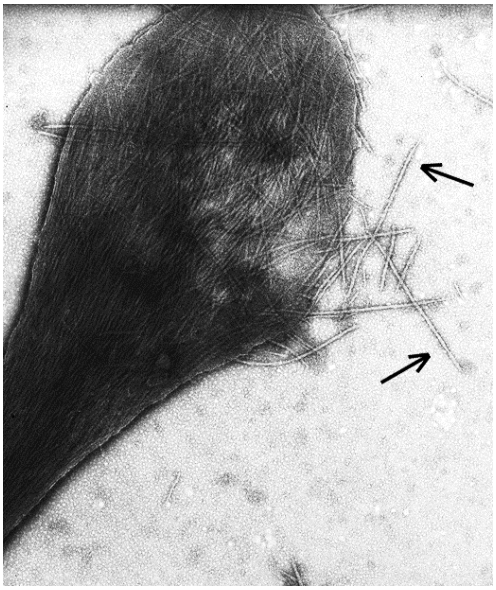

Figure 8- The beta fibers in a sickle cell are rigid and cause the normally concave shaped cells to deform into a sickle shape.

Inheritance of sickle cell anemia

The character of having a sickle cell is recessively inherited and follows the Mendelian pattern of inheritance for a recessive train. The normal cell phenotype is dominant.

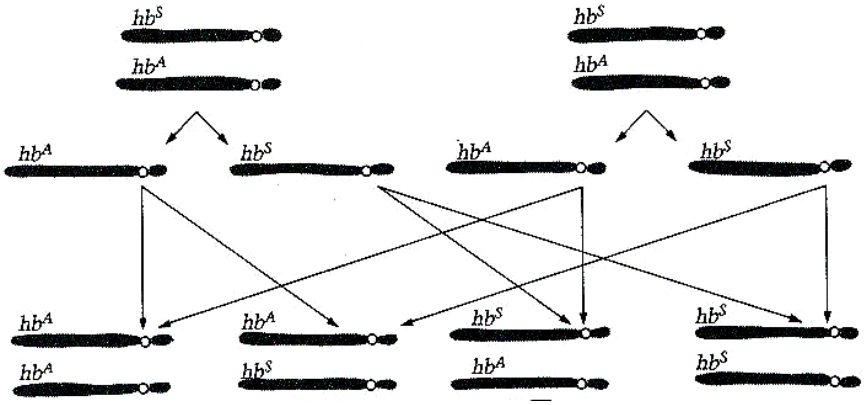

Figure 9- Inheritance of sickle cell disease. hb^A stands for normal RBC gene and hb^S stands for sickle shaped RBC gene. The recessive trait of a RBC being sickle shaped is not expressed phenotypically in a heterozygous individual. The phenotype of a sickle cell is expressed in a homozygous recessive individual. Thus the trait follows Mendelian inheritance pattern for a recessive character.

The sickle cell eventually bursts and dies. Under low oxygen conditions (high altitude or after rigorous exercise), a heterozygous individual for the sickle cell trait, RBCs start showing the sickled phenotype. These heterozygous individuals realize oxygen scarcity in their cells under such conditions as the sickling of cells reduces the oxygen carrying capacity of RBCs.

Sickle cell and resistance to malaria:

The reduced oxygen carrying capacity gives the heterozygous individual protection against malaria. Malaria pathogen completes a part of its early life cycle in the RBCs. The early stages of the malaria pathogen's development requires oxygen to complete its life cycle. Since in the heterozygous individuals the RBCs have a low capacity to carry oxygen, the malaria pathogen is not able to survive. Thus, the heterozygous and homozygous recessive individuals are protected from malaria.

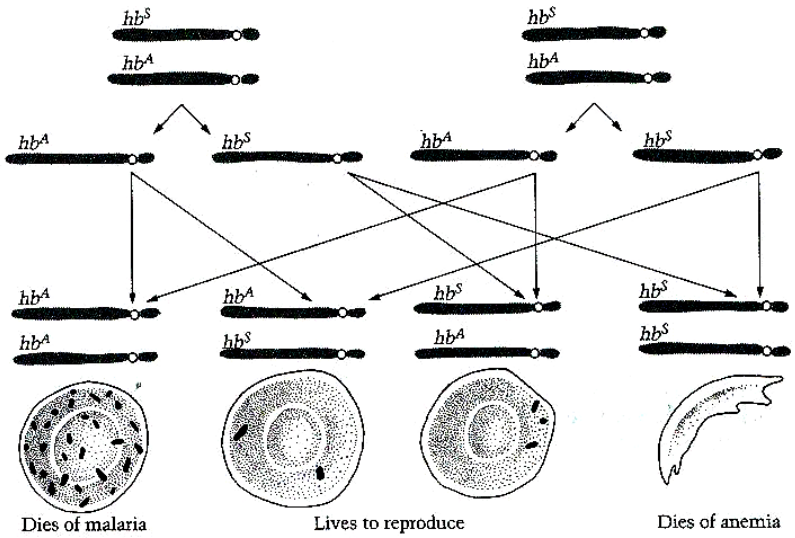

Figure 10- SCD and malaria resistance.

Evolution to protect against death by malaria:

In certain areas, where malaria is found to be indigenous, the sickle cell trait is found to arise more. Thus, hinting that the process of evolution may have used the sickle cell trait as a protection against malaria, in these regions.

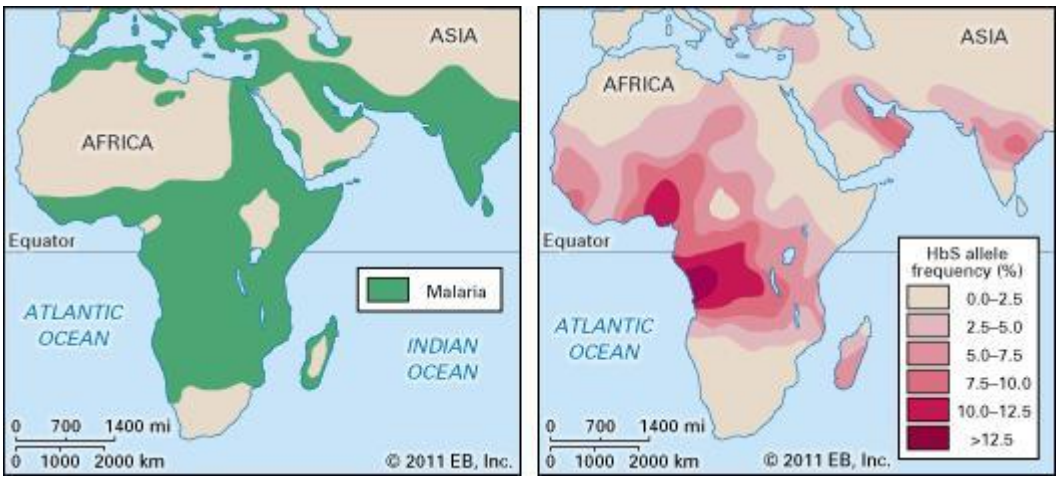

Figure 11-Geographic distribution of malaria and the appearance of sickle cell trait.