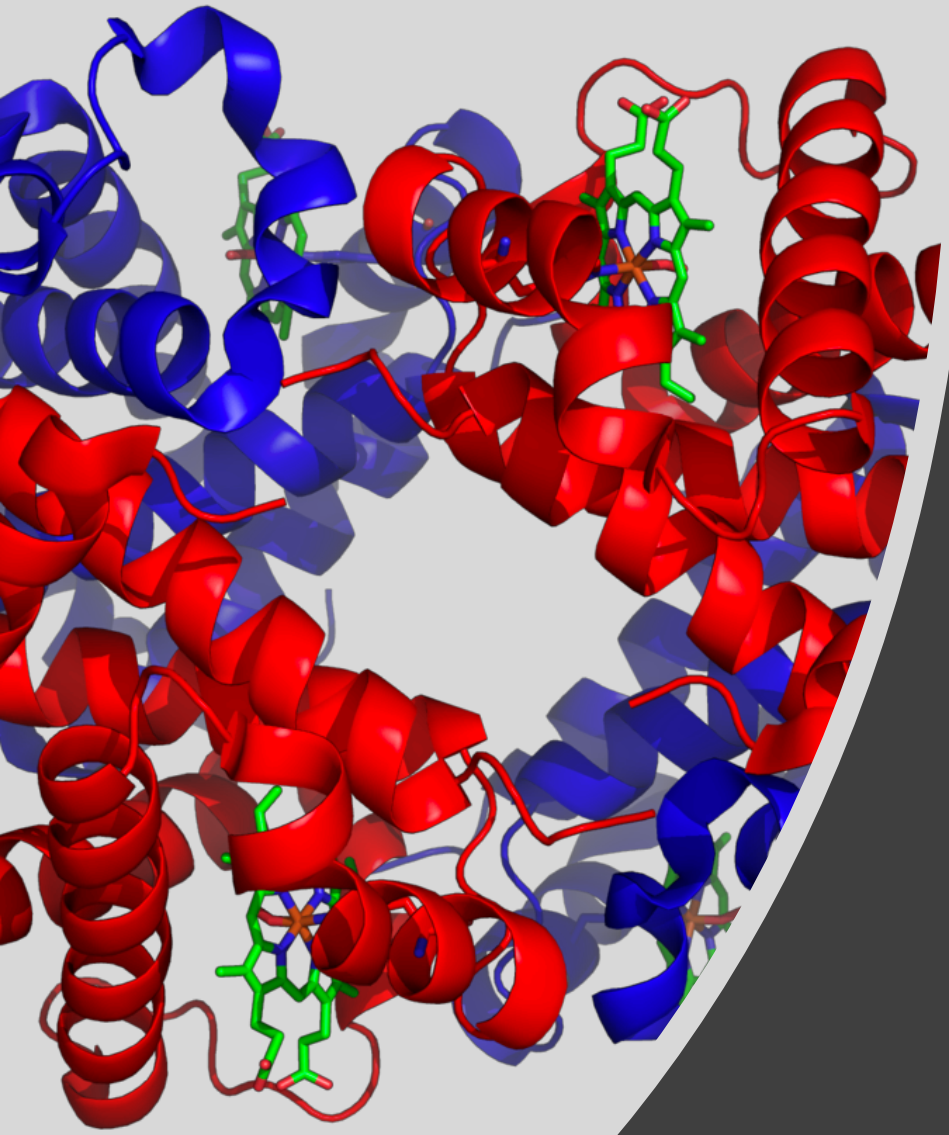
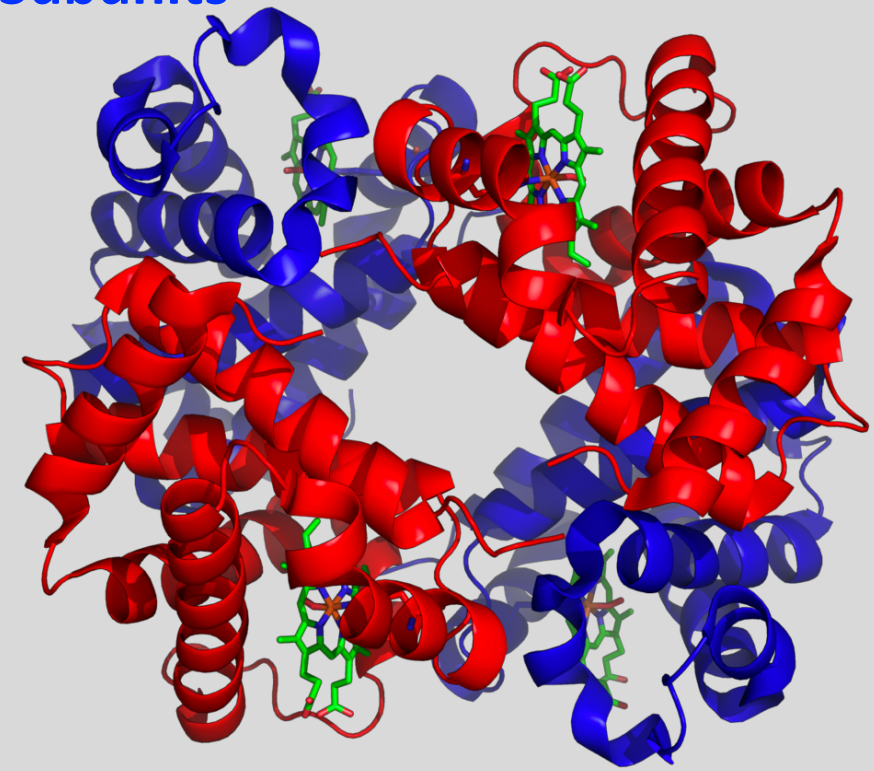


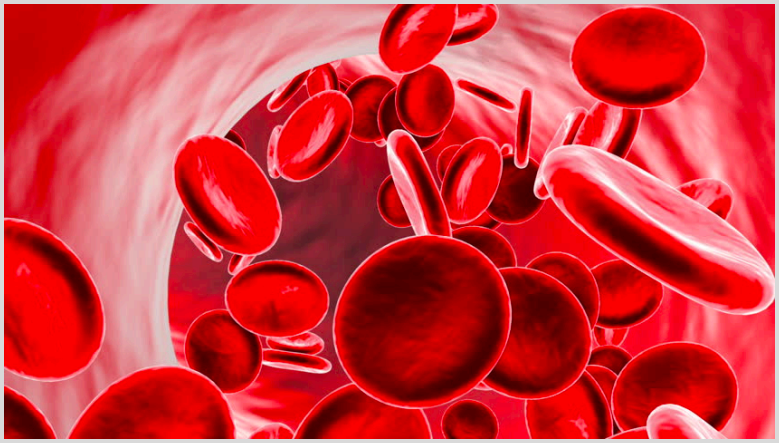
Week 5- Case of Study

Genetic anemia and beta hemoglobin (beta globin)

What is hemoglobin?

Protein that contains a metal iron co-factor





Transports oxygen in the red blood cells (Erythrocytes).

Makes up about 96% of the red blood cells

Diseases affecting hemoglobin synthesis and function

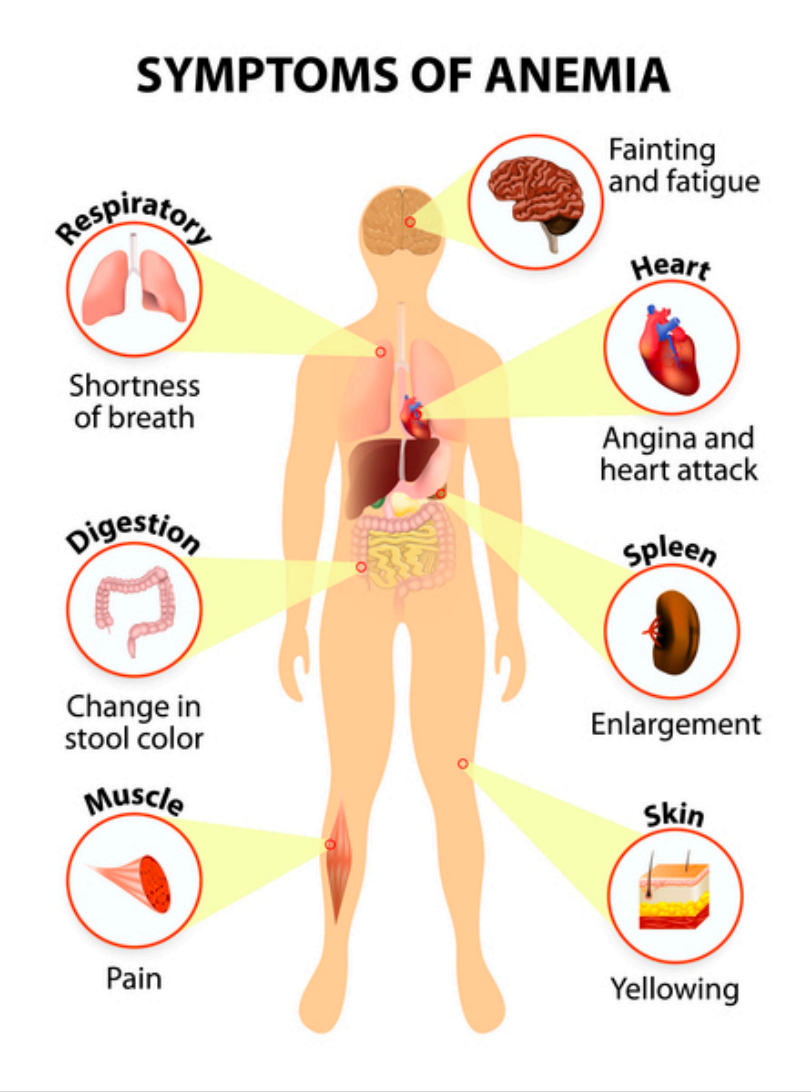
More than 1000 naturally occurring human hemoglobin variants with single amino acid substitutions throughout the molecule have been discovered.

Types of Mutations:

1. Impair Globin Subunit Production

2. Produce structurally abnormal globin proteins (Hb variants)

MOST COMMON: Missense mutations (single a.a. substitutions)



(Thom et al., 2013. Hemoglobin Variants: Biochemical Properties and Clinical Correlates)

Sickled-Cell Anemia

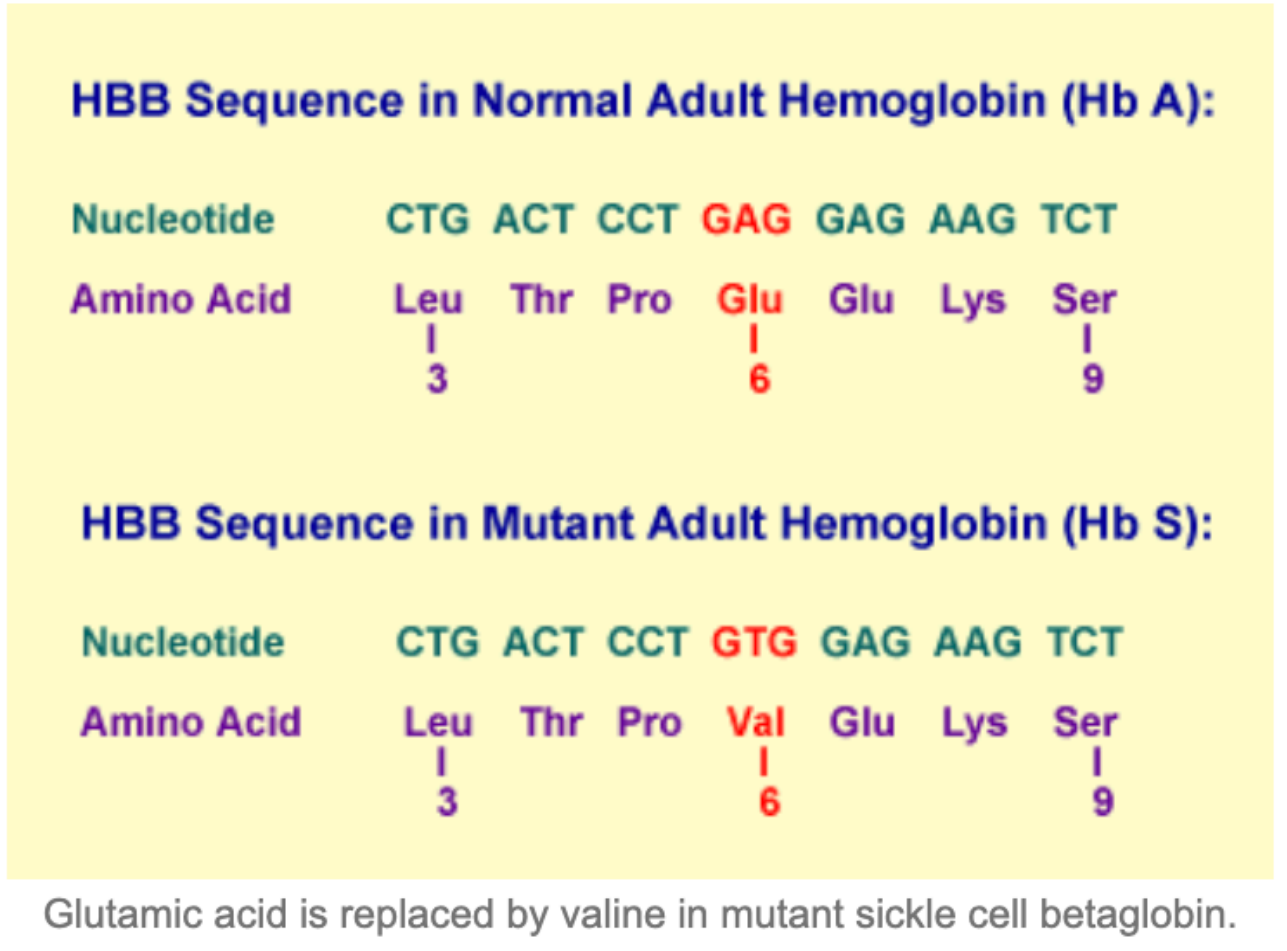
Hereditary disease that destroys red blood cells by causing them to take on a rigid “sickle” shape.

Symptoms of chronic anemia:

Fatigue, pale skin, and shortness of breath, susceptibility to infection, jaundice and other eye problems, delayed growth, and episodic crises of severe pain in the abdomen, bones, or muscles.

Sickled-Cell Anemia

A single nucleotide change (MUTATION) alters only one amino acid in the beta protein chain, but the results are devastating.



Glutamic acid is replaced by valine in mutant sickle cell betaglobin.

Sickled-Cell Anemia

Sickle cell anemia occurs mainly in persons of African descent.
1 in 12 blacks worldwide carries the sickle cell trait
1 in 400 has sickle cell anemia.

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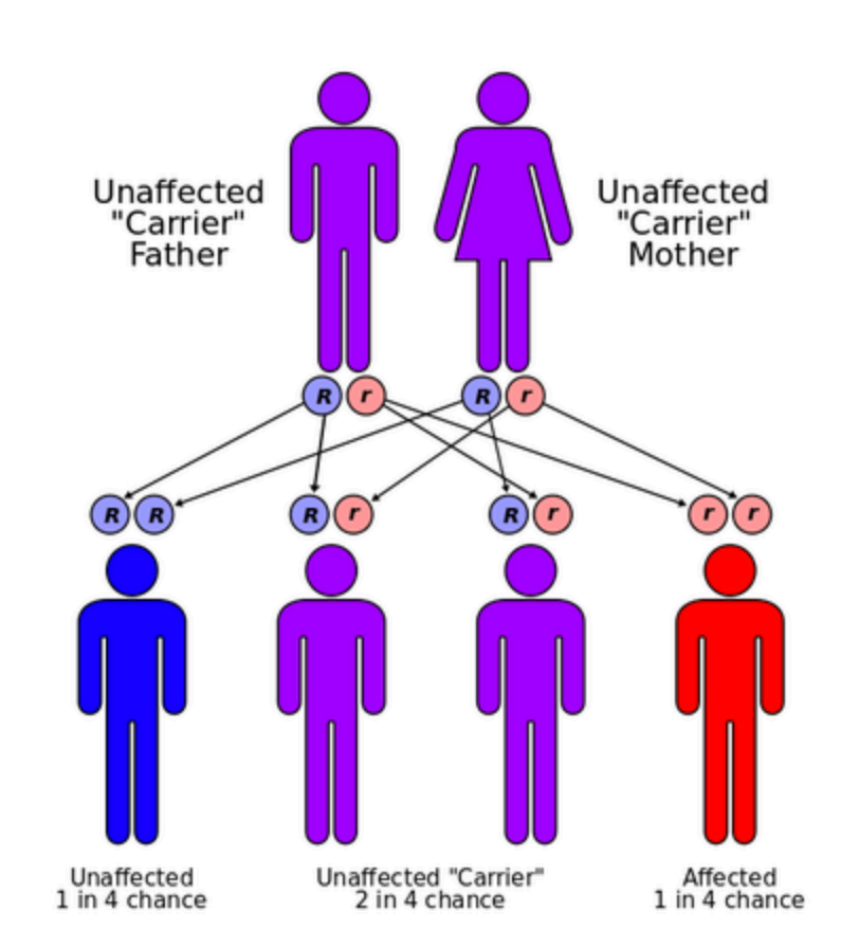
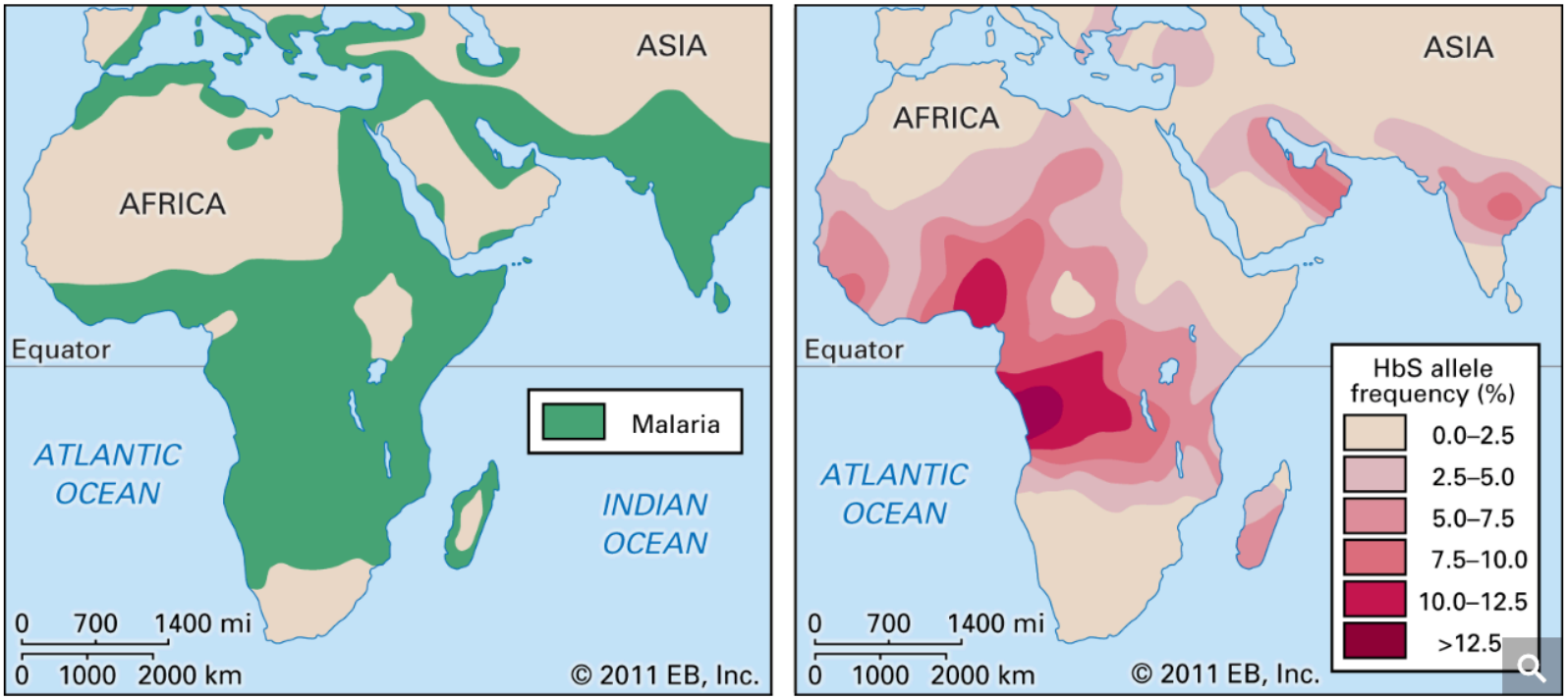


If both parents have the sickle cell trait, the chances are 1 in 4 that a child born to them will develop sickle cell anemia

Sickled-Cell Anemia and Malaria



malaria and sickle cell anemia, distribution of

The distribution of malaria and the distribution of sickle cell anemia overlap in areas of Africa, southern Asia, and the Mediterranean. The persistence of the HbS gene, which causes sickle cell anemia, has been explained by the fact that heterozygous persons are resistant to malaria.

Encyclopædia Britannica, Inc.

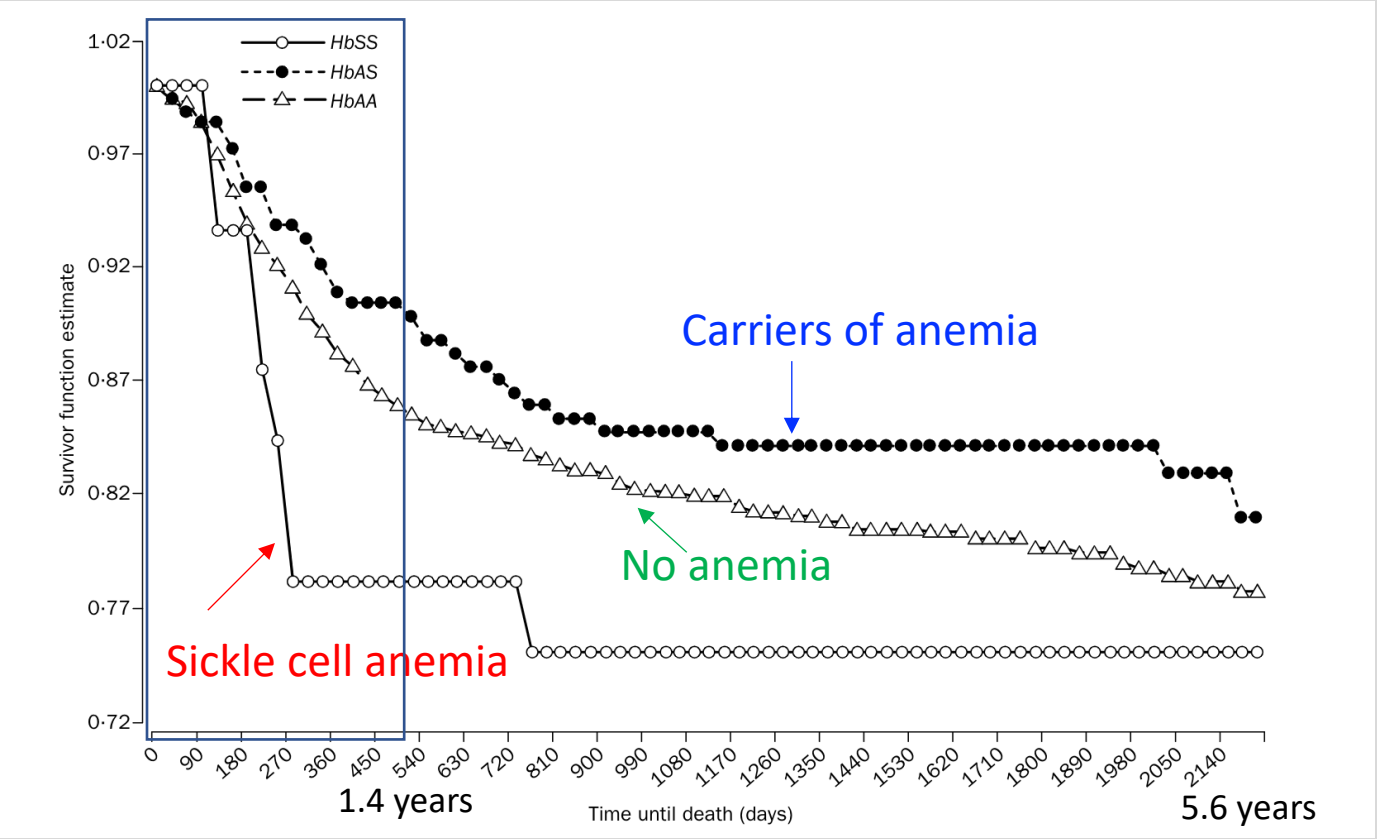
People with Sickle cell anemia are resistant to Malaria.

When the red cells are invaded by the malarial parasite, the red cell adhere to blood vessel walls, become deoxygenated, assume the sickle shape, and then are destroyed, the parasite will be destroyed with them.

Sickled-Cell Anemia and Malaria

What about carriers of the mutated gene?

The carriers have higher survival during the period from 2 to 16 months of age



The high frequency of the gene for sickle cell in malaria endemic regions is thought to be due to a selective advantage against malaria mortality

Protective Effects of the Sickle Cell Gene Against Malaria Morbidity and Mortality. Terlouw et al. Lancet 2002; 359:1311-1312.

Using programing to automatically detect mutations

Missense mutations – Sickle Cell Anemia

Table 1: Single-Base Mutation Associated with Sickle-Cell Anemia

Sequence for Wild-Type Hemoglobin												
ATG	GTG	CAC	CTG	ACT	CCT	GAG	GAG	AAG	TCT	GCC	GTT	ACT
Start	Val	His	Leu	Thr	Pro	Glu	Glu	Lys	Ser	Ala	Val	Thr
Sequence for Mutant (Sickle-Cell) Hemoglobin												
ATG	GTG	CAC	CTG	ACT	CCT	GTG	GAG	AAG	TCT	GCC	GTT	ACT
Start	Val	His	Leu	Thr	Pro	Val	Glu	Lys	Ser	Ala	Val	Thr

0 1 2 3 4 5 6 7 8 9 10 11 12

Silent Mutations

Person 1: ['AUG', 'GUG', 'CAC', 'CUG', 'ACU', 'CCU', 'GAG', 'GAG', 'AAG', 'UCU', 'GCC']
Person 2: ['AUG', 'GUG', 'CAC', 'CUG', 'ACU', 'CCU', 'GAG', 'GAG', 'AAG', 'UCU', 'GCG'] → Ala
Person 3: ['AUG', 'GUG', 'CAC', 'CUG', 'ACU', 'CCU', 'GUG', 'GAG', 'AAG', 'UCU', 'GCC']

A change in the sequence of DNA nucleotide, without a subsequent change in the amino acid or the function of the overall protein.

"silent" mutation.