Sickle Cell Hemoglobin and Malaria

Natural Selection in Human Populations

Function of Hemoglobin

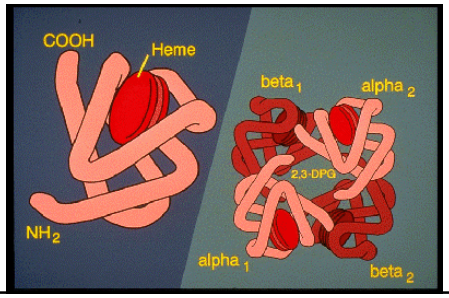
- Hemoglobin is the primary protein constituent of red blood cells
  - Transports oxygen by binding with it tightly as the red blood cells pass through the capillaries of the lungs
  - As oxygenated red blood cells circulate through the heart and to the other body tissues, hemoglobin loosens its hold on the oxygen so that it can pass readily out of the red cells and be made available to peripheral cells for respiration

Function of Hemoglobin 2

- Deoxygenated hemoglobin molecules in peripheral capillaries bind loosely with carbon dioxide and help remove this waste product of cellular respiration to the lungs for expiration
- The binding capacity of hemoglobin molecules is a function of the oxygen pressure
  - high in the lungs, bind tightly
  - low in peripheral capillaries, bind loosely

Structure of Hemoglobin

- 4 polypeptides (globins) and 4 iron-based oxygen-binding heme molecules



Hb^A

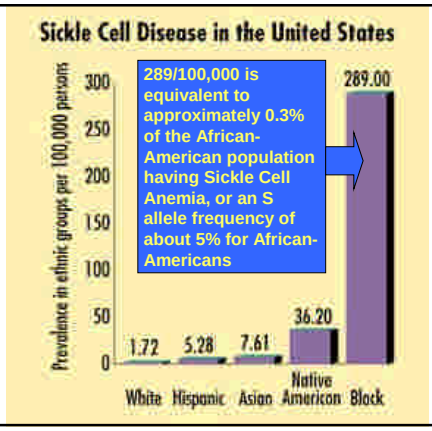
- "Wild"or most common form, found in all human populations

Beta Hemoglobin	6th	26th
DNA sequence	C-T-C	C-T-C
Amino Acids	Glutamic Acid	Glutamic Acid

Hb^S

- Sub-Saharan Africa, Mediterranean, Middle East, India, Southeast Asia

Beta Hemoglobin	6th	26th
DNA sequence	C-A-C	C-T-C
Amino Acids	Valine	Glutamic Acid



Hb^C

- Predominantly West African populations

Beta Hemoglobin	6th	26th
DNA sequence	T-T-C	C-T-C
Amino Acids	Lysine	Glutamic Acid

Hb^E

- Southeast Asia

Beta Hemoglobin	6th	26th
DNA sequence	C-T-C	T-T-C
Amino Acids	Glutamic Acid	Lysine

Genetics of Sickle Cell

- The alpha and beta globin genes are transmitted separately, as parts of the 16th and 11th chromosome pair, respectively
  - Transmission follows Mendel's Law of Independent Assortment for genes located on different homologous chromosome pairs
  - Each individual has two alpha globin genes and two beta globin genes inheriting one gene of each pair from the mother and one from father

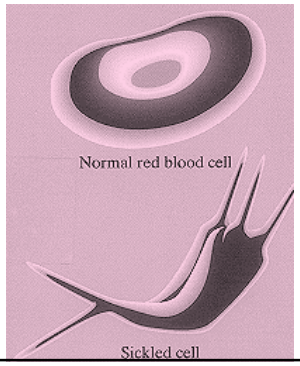
Genetics of Sickle Cell

- Three genotypes can form from combinations of the A and S alleles
  - AA Homozygous Normal; "Normal"
  - AS Heterozygote; "Sickle Cell Trait"
  - SS Homozygous sickler; "Sickle Cell Anemia"
- Inheritance follows a Mendelian pattern for a co-dominant autosomal allele
  - When two heterozygotes mate, ¼ of their offspring are predicted to be SS, ¼ would be normal, and ½ would carry the allele

Sickling

- Red blood cells begin to sickle when hemoglobin molecules have given up their oxygen in the capillaries
- The S-hemoglobin molecules bind together into long fibers, forming a complex helical molecule within the red blood cell

Sickled vs. Normal RBC



Sickling 2

- The formation of these fibers is dependent on the presence of valine at the β-6 position to bind one beta chain with the beta chain of another hemoglobin molecule
- For sickling of the red blood cell to occur it takes from 0.1 to 1 second of extreme deoxygenation of the hemoglobin molecules

Sickling 3

- The deoxygenation necessary for sickling occurs in the capillaries after oxygen has been given off to the muscle cells and before the RBCs can return to the lungs
- Cells with higher concentrations of hemoglobin S form fibers more rapidly and are therefore more likely to sickle

Sickling 4

- Hemoglobin S concentration is a function of cell age, with the concentration increasing as the red blood cell ages
- Hence, the older the red blood cells, the more likely they are to sickle
- The result is a downward spiral of continuous depletion of red blood cells, resulting in anemia

Symptoms of Sickle Cell Anemia

- As a result of sickling and the premature aging of red blood cells from sickling, there are fewer than normal red blood cells, the general condition referred to as anemia
- There is an increased risk of severe infections, especially bacterial infections--such as sepsis (a blood stream infection), meningitis, and pneumonia, especially in early childhood
  - The risk of infection is increased because the spleen does not function normally

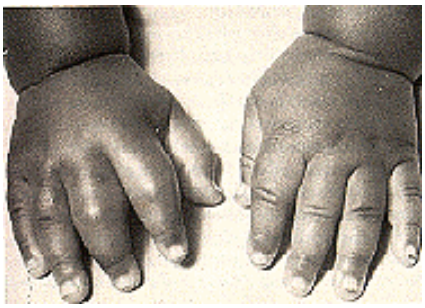
Symptoms of Sickle Cell Anemia

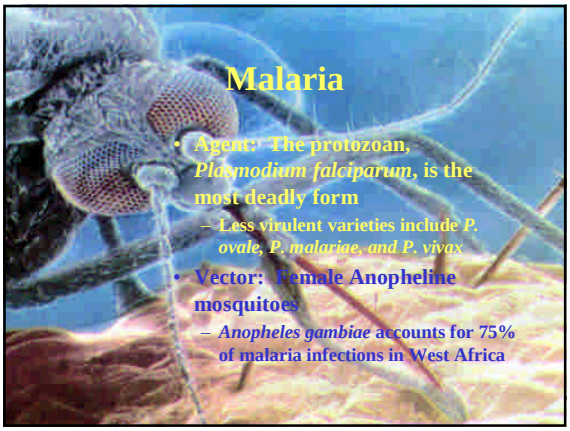
- Splenic sequestration crisis:
  - The spleen is the organ that filters blood
  - In children with sickle cell disease, the spleen can enlarge rapidly from trapped red blood cells creating a situation that can be life-threatening.
- Stroke:
  - This happens when blood vessels in the brain are blocked by sickled red blood cells
  - Signs include seizure, weakness of the arms and legs, speech problems, and loss of consciousness.

Symptoms of Sickle Cell Anemia

- Children with sickle cell anemia experience slowed growth and delayed maturation, including puberty as a result of the anemia and infections
- There are repeated, painful episodes, called vaso-occlusive crises, associated with blockages of the circulatory system
  - Frequently seen as swelling of extremities
- There is a progressive degeneration of organs from impaired circulation

Swollen Hands from Sickling

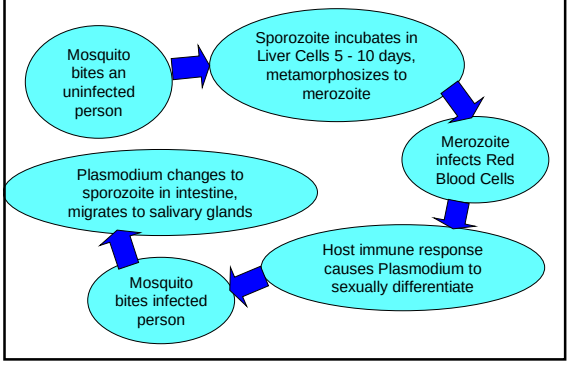




Malaria

- Host: Man, although higher primates can also may harbor *P. malariae*
  - Monkeys harbor other plasmodium species which can infect man
- Symptoms: Cyclic (sometimes) high fever, chills and sweating, headache, coagulation defects, shock, anemia (inducing jaundice), kidney failure, acute encephalitis, coma

The Malaria Cycle of Infection

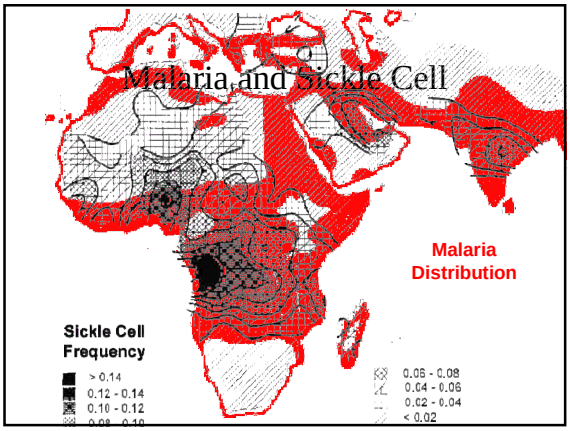


Sickle Cell and Malaria

- There are three lines of evidence suggesting an association between the sickle cell allele and Malaria:
  - Geographic correlations
  - Epidemiological associations
  - Biochemical studies

Geographic Correlations

- Clinal studies show a substantial overlap between the distribution of malaria in the and the frequency of the sickle cell allele
  - The Malaria belt extends across the Southern Mediterranean, sub-Saharan Africa, the Middle East, India, Southeast and Island Southeast Asia, and Northern Australia, the S allele exceeds a frequency of 10% only in Africa
  - In the Mediterranean β thallasemia and G-6-PD are elevated, while in India and Southeast Asia, Hemoglobin E and α thallasemia predominate



Epidemiological Correlations

- A comparison of *Plasmodium falciparum* parasites in blood samples from children of SS and AS genotypes in Nigeria to that of children with AA genotypes showed:
  - SS and AS children had lower frequencies and lower densities of parasites than AA children (lower levels of malaria infection)
  - Fertility did not differ between AA and AS, but 29% more AS individuals survived to adulthood (selection based on survival of malaria, not increased fertility of heterozygotes)

Biochemical studies

- The interaction of the *Plasmodium* parasite and sickle cell hemoglobin takes place in the red blood cell
- *Plasmodium* metabolism causes sickle cell hemoglobin to form the fibers that results in sickling
  - The acidification of the cytoplasm from the parasite's metabolism causes the hemoglobin to release its oxygen, making it prone to fiber formation

Biochemical studies

- The development of *Plasmodium* is disrupted by sickling of the red blood cells
  - Sickled cells may be prematurely removed by the spleen, or
  - The sickling may deplete cell reserves of potassium which is required for the parasite to grow

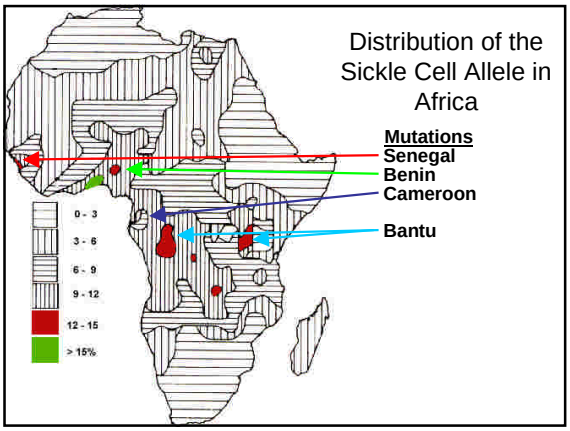
Biochemical studies

- Individuals who are homozygous for the sickling allele (SS) would experience accelerated sickling in parasitized red blood cells
  - Hence they have a high degree of resistance to the most severe complications of malaria
- *Plasmodium* also induces sickling in most red blood cells for heterozygous individuals (AS), resulting in lower than normal rates of mortality and severe symptoms

Why does sickle cell reach such high frequencies in West Africa?

Geographic Distribution in Africa

- There are several major centers of high frequency of the S allele in Central Africa and West Africa
- These different centers apparently arrose from separate mutations
  - Indicated by different nucleotide sequences in the non-coding section of the beta globin gene on the 11th chromosome



Cultural Factors

- Spread of swidden agriculture into previous Tropical Rainforest regions 2-3,000 years ago
- Slash-and-burn or swidden agriculture clears large areas of tropical rainforest
- Clearing of the forest and high levels of rainfall erodes the soils which are lateritic and relatively impermeable, making for formation of pools

Cultural Factors

- During the rainy season pools of fresh water, exposed to sunlight because of the forest clearing, form, which along with high humidity creates an ideal breeding habitat for *Anopheles gambiae*
- Agricultural expansion supports more people, living in sedentary villages

Diet and Sickle Cell

- Today the consumption of cassava (*Manihot esculenta*) may confer an adaptation to both malaria and sickling
- Cyanate metabolites, such as thiocyanate, inhibit the growth cycle of *Plasmodium* in the RBC
- These metabolites also reduce the likelihood of sickling

Diet and Sickle Cell

- Cassava cannot have played a role in the evolution of sickle cell frequencies since it has been introduced only in the past hundred or so years
- Historically there have been three horticultural complexes in the West Africa, each one dating back between 2-3,000 years

Diet and Sickle Cell

- Three West African crop complexes:
  - Yam
  - Rice
  - Sorghum and Millet
- Yam is the only crop with cyanates which could prevent sickling
- Yam growing populations should (and do) show the highest Sickle cell frequencies

The Sickle Cell Model