What Is It And Where Did It Come From

SICKLE CELL DISEASE
What is Sickle Cell Disease?

- Sickle cell disease is a disease of the blood
  - It is due to an abnormal hemoglobin (the red pigment of blood)
- It is inherited (it comes from the parents and is passed to children)
- It causes many problems, including:
  - Pain
  - Disability
  - Loss of organs (strokes, kidney failure, bone damage, etc.)
  - Premature death
What is Hemoglobin?

- Hemoglobin is the red pigment of blood.
- It carries oxygen from the lungs to every part of the body.
- It consists of 4 units called chains.
- Each chain has about 145 building blocks (amino acids).
- These chains are wound around in a very complicated way.
How Is the Hemoglobin of Sickle Cell Disease Different?

- Two of the building blocks (amino acids) in sickle cell hemoglobin are different from normal
How Is the Hemoglobin of Sickle Cell Disease Different?

- Two of the building blocks (amino acids) in sickle cell hemoglobin are different from normal.
- This is due to a change in the gene for hemoglobin.
  - One piece out of about 2,000 is changed.
Fundamental Defect in Sickle Cell Disease

Hb A

-PRO-GLU-GLU-

Hb S

-PRO-VAL-GLU-

GENE

-GGA-C\textbf{T}C-CTC-\textbf{T}C-CTC-

-GGA-C\textbf{A}C-CTC-\textbf{A}C-CTC-

Hemoglobin Chain
How Is the Hemoglobin of Sickle Cell Disease Different?

- Sickle cell hemoglobin can be detected by examining the blood in the laboratory
  - An individual may have: normal hemoglobin,
  - Both normal and sickle hemoglobin (sickle cell trait), or
  - Only sickle hemoglobin (sickle cell disease)
Identification of Hb S Status by Electrophoresis

**β GLOBIN GENES**

- **Normal (Hb AA)**
  - +

- **Sickle Cell Trait (Hb AS)**
  - +

- **Sickle Cell Disease (HbSS)**
  - +

**HEMOGLOBIN ELECTROPHORESIS**

- A
- S
How is Sickle Cell Disease Inherited (Passed in the Family)

- Most inherited characteristics are determined by two genes
  - One gene comes from the father
  - One gene comes from the mother
- When one parent has the trait, half of the children are likely to have the trait
Genetics of Sickle Cell Disease

Diagram showing the inheritance of normal and sickle cell trait.
How is Sickle Cell Disease Inherited (Passed in the Family)

- When one parent has the trait, half of the children are likely to have the trait.
- When both parents have the trait:
  - One fourth of the children will likely be normal.
  - One half will likely have the trait.
  - One quarter will likely have the disease.
Genetics of Sickle Cell Disease
Why Does the Hemoglobin of Sickle Cell Disease Cause Problems?

- Two of the building blocks in the hemoglobin are different from normal.
- This difference allows the molecules of hemoglobin to stick together in a particular pattern.
Formation of "Crystals" of Sickle Hemoglobin

Unpolymerized → Nucleation → Random Rods → Parallel Rods
THE SHAPE CHANGE OF SICKLING

NORMAL

SICKLED
SICKLING IN THE PERIPHERAL CIRCULATION

O₂
Sickling in a Small Vessel
Sickling in a Small Vessel
Sickling in a Small Vessel

Area of Low Oxygen
A Tale of Five Individuals

HOW DID SICKLE CELL DISEASE ARISE?
How Did Sickle Cell Arise?

- The change in the sickle hemoglobin molecule (Hb S) is caused by a mistake in the gene responsible for that chain of hemoglobin.
Where Did This Happen?

- In India in one individual, ~3,500 years ago
  - It spread to Eastern Arabia
  - Sickle cell persists in the “Hill Tribes” of India
    - Sickle cell disease is more plentiful in one state of India than in the entire United States
The Harappa-Dilmun Axis

Akkad
Elam
Dilmun

Indus Valley Civilization
Where Did This Happen?

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- In Africa in four individuals
  - Near the Congo, ~2,000 years ago
  - Near Nigeria, just a little later
  - In West Africa, sometime later
  - In Cameroons, fairly recently
Where Did It Spread?

- Locally at each site of origin
  - The area covered indicates how long the gene has been there
  - By trade routes
- Wherever people from the area migrated or were taken – especially by the African slave trade
  - To Sicily, Greece, and Turkey by the Arab trade in African slaves
  - To the New World by the transatlantic slave trade
Why Did The Abnormal Gene Become So Common?

- By Darwinian (natural) selection
Population Before Disease Strikes
Disease Strikes
Population After Disease Strikes
Some People (in Green) Are Resistant to the Disease
Some People (in Green) Are Resistant to the Disease When It Hits
The Percentage of Resistant People Is Increased
What Is Malaria?

- Human malaria started many, many years ago, probably from birds
- Organism develops within red blood cells
- Transmitted by tropical mosquitoes
Malaria

- Became a public health problem after settled life began in tropics
  - People lived close enough together that the mosquitoes could spread the organism
- Malaria occurs throughout the tropics
  - 1-2 million people affected each year
  - 216 million cases in 2101
  - >300,000 deaths in 2010
Sickle Cell Disease and Malaria

- Sickle cell trait protects against malaria
  - The reason is not known
  - Based on population studies
- Malaria is fatal in sickle cell disease
- This is called “trait advantage”
  - One dose of the gene is helpful
  - Two doses of the gene are harmful
- Why everybody in Africa does not have sickle cell trait:
  - If everybody had the trait, too many people would have the disease
Other Changes In Red Cells That Confer Protection Against Malaria

- Hemoglobin C
  - Started in one person in Burkina Faso about 1000 years ago
- Hemoglobin E
  - Started in people in Southeast Asia
- Thalassemia
  - Many kinds, mostly with “trait advantage”
  - One kind (α thalassemia) has so little downside in people with two doses of the gene as to become universal in the population
- G6PD deficiency
Other Changes In Red Cells That Confer Protection Against Malaria

- Absence of Duffy blood group
  - Almost all Africans lack this factor; all other people have it
  - One person started the gene many, many years ago
- Two doses of the gene have no downside
- The absence of the factor means that one type of malaria (called “vivax malaria”) cannot invade the red cell
  - Vivax malaria does not now exist in Africa
What Has Been The Effect of These Protections or Their Lack on History

- People lacking them could not live in tropical, malarious Africa
- Natives of the tropical parts of the New World were decimated when malaria was introduced
  - Descendants of African slaves, who were resistant, replaced them
- Local patterns of living in the southern States were altered
  - “Upcountry” homes in South Carolina
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<th>Age</th>
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Cf. doc. Église de l’Immaculée-Conception 8 Décembre 1989 "28 P."
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Summary

- Sickle cell arose as a protection against malaria
- It started from no more than 5 individuals
- It increased in the population by natural selection of individuals with the trait
- Thus, it is one of several “improvements” that allowed people to live where malaria is common