Sickle Cell Hemoglobin and Malaria:
An Adaptive Study of Natural Selection on an Infectious Disease

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Text, pages: 3-13
Bibliography, pages: 14-15
5 Figures
Outline: Sickle Cell Hemoglobin and Malaria: An Adaptive Study of Natural Selection on an Infectious Disease

I. Introduction
   A. Diseases caused by infectious agents have profoundly affected human culture, history and biology. This paper will examine the advantages and disadvantages of the evolution of the gene that produces sickle shaped hemoglobin.
   B. The purpose of this project is to research how natural selection of human genes can provide increased adaptive fitness when exposed to an infectious disease. The fitness consequences of genetic inheritance patterns will also be evaluated.

II. Literature Review
   A. Biology of the sickle cell hemoglobin
      1. Description and function of normal erythrocytes
      2. Genetics
      3. Consequences of sickle cell hemoglobin
   B. Sickle Cell Anemia
      1. Symptoms
      2. Treatments
      3. Possible Advantages
   C. Malaria
      1. Description of disease, symptoms
      2. Types of strains and life cycle of disease
      3. Sickle cell hemoglobin and malaria

III. Study Results/Discussion
   A. Specific data about the affect of sickle cell anemia and malaria statistics.
   B. Conclusion: Relationship between sickle cell hemoglobin and malaria
   C. Suggestions for future research

V. References
**Introduction**

Diseases caused by infectious agents have profoundly affected human culture, history and biology. In demographic terms, infectious diseases have devastated human populations from ancient to modern times. Infectious diseases along with unnamed viral and bacterial infections have likely claimed more lives than all wars, noninfectious diseases, and natural disasters have taken together. In response to the attack of microscopic invaders, human populations have been forced to adapt to infectious agents through genes and culture (Brown and Inhorn, 1990). This paper will examine the advantages and disadvantages of the evolution of the gene that produces sickle-shaped hemoglobin.

The purpose of this project is to research how natural selection of human genes can provide increased adaptive fitness when exposed to an infectious disease.

Information will be provided about the biology of the sickle cell hemoglobin, sickle cell anemia and malaria. Important correlations will be presented in order to examine the intricate relationship between an infectious disease and genes.

**Literature Review**

**Biology of Hemoglobin**

*Description of normal erythrocytes*

Vertebrate blood is classified as a type connective tissue consisting of several types of cells suspended in a liquid matrix called plasma. Blood plasma consists of two types of cells: red blood cells and white blood cells. *Figure 1* clearly shows the two types of cells found in plasma. Red blood cells function to transport oxygen and white blood cells function in defense with the immune system (Campbell et al., 1999). Red blood cells or erythrocytes are the most numerous blood cells. Each cubic millimeter of human
blood contains five to six million red blood cells and twenty-five trillion of these cells exist in the body (Campbell et al., 1999).

![Red and White Blood Cells in a blood vessel](image1)

*Figure 1, (Huskey, 1998)*

As seen in *Figure 1*, a human erythrocyte is a biconcave disk, thinner in the center than at its edges. The major function of erythrocytes is to carry oxygen. The erythrocyte possesses the ability to carry oxygen due to the presence of about 250 million molecules of hemoglobin (Campbell et al., 1999). Hemoglobin is an iron containing protein that reversibly binds oxygen. The iron found within hemoglobin is housed in four heme groups, as seen in *Figure 2*. By binding reversibly to oxygen gas through its iron atom, heme enables hemoglobin to pick up oxygen in the lungs and release it in the tissues (Alberts et al., 1998).

![Cartoon of Human Hemoglobin](image2)

*Figure 2, (Saladin, 1998)*
Along with four heme molecules, hemoglobin contains four polypeptides, as indicated in Figure 2, two alpha globins and two beta globins (Bindon, 2004). The beta globin gene is located on the short arm of chromosome 11 at p15.5. It is a member of the globin gene family, a group of genes involved in oxygen transport. The alpha globin gene, located on chromosome 16, is also a member of this gene family. Two beta globin protein chains combine with two alpha globin protein chains and a heme to form the predominant hemoglobin found in human adults, Hb A (Koch et al., 2000).

*Genetic Mutations of Hemoglobin*

In the human population over 475 beta globin gene variants or mutations exist and several of these mutations result in life threatening illnesses (Koch et al., 2000). This paper will focus only on the sickle cell hemoglobin, Hb S and its relation to sickle cell disease.

Under normal conditions, the alpha and beta genes in hemoglobin are transmitted separately because they are located on separate chromosomes. This form of transmission follows the genetic law of independent assortment which states that each pair of alleles segregates independently during gamete formation (Bindon, 2004). Therefore, individuals inherit an alpha gene and a beta gene from the mother and an alpha gene and a beta gene from the father. These genes then recombine to determine individual genotypes.

New forms of genes or alleles, such as sickle cell hemoglobin Hb S, originate only by mutation or a change in the nucleotide sequence of the DNA (Campbell et al., 1999). Sickle cell hemoglobin is a single point mutation occurring when there is a
substitution of valine for glutamic acid at the sixth amino acid position in the beta globin gene (Koch et al., 2000). Hb S mutations occur in cell lines that produce gametes, therefore, the mutation is passed along to offspring (Campbell et al., 1999). By following the Mendelian pattern for co-dominant autosomal alleles, the Hb S mutation can form three different genotypes (Bindon, 2004). When the A hemoglobin gene and the S hemoglobin gene (replacing the normal hemoglobin gene) combine they can form: AA homozygous dominant (normal genotype and phenotype), AS heterozygote (sickle cell genotype but not phenotype: carrier) and the SS homozygous recessive (abnormal genotype and phenotype: leads to sickle cell anemia) (Bindon, 2004). Sickle cell traits are inherited from parents in the same way as blood type or hair color.

Consequences of sickle cell hemoglobin

After the mutation is inherited and erythrocytes produce abnormal hemoglobin many problems develop. These problems become apparent during deoxygenation of hemoglobin. When abnormal S-hemoglobin gives up the oxygen it is carrying, the erythrocytes form dense aggregates of cells. The aggregate of cells transform into long rod-like structures, creating a complex helical molecule in the erythrocyte that causes stiffness and the sickle shape (Bindon, 2004). A comparison of sickle cells to normal erythrocytes can be seen in Figure 3. Unlike normal red cells, which are usually smooth and flexible, sickled erythrocytes cannot squeeze through small blood vessels. Instead, they stack up and cause blockages that deprive organs and tissues of oxygen-carrying blood. This process produces periodic episodes of pain and eventually can damage tissues and vital organs (Campbell et al., 1999). Normal erythrocytes live about 120 days in the bloodstream, but sickled red cells die after about 10 to 20 days. Because they
cannot be replaced fast enough, the blood is chronically short of red blood cells, a condition called anemia (Campbell et al., 1999).

Image of normal and sickle cell erythrocytes

*Figure 3, (Machalek, 2000)*

**Sickle Cell Anemia**

Symptoms

Sickle cell anemia is a disease caused by an autosomal recessive genetic mutation in the formation of hemoglobin. Individuals who are affected with sickle cell anemia have two copies of the mutation Hb SS and the primary hemoglobin present in their erythrocytes is sickle hemoglobin (Koch et al., 2000). The symptoms of sickle cell anemia do not follow a general pattern and can vary in each individual. All the different conditions and symptoms documented stem from the central fact that the sickle-shaped erythrocytes tend to get stuck in narrow blood vessels, blocking the flow of blood (Bownas, 2002).

Symptoms of sickle cell anemia are wide-ranging, affecting many different organs of the body. One of the first diagnoses of the disease among small children is swelling of the hands or feet. This common symptom occurs when blood vessels in hands or feet are
blocked; pain and swelling can result, along with fever (Bownas, 2000). The shortage of erythrocytes can cause: unpredictable pain in any joint or body organ, fatigue, paleness, shortness of breath, yellowing of the skin and eyes, which are signs of jaundice, and delayed growth and puberty in children (Bindon, 2004; Bownas, 2000).

Along with symptoms, individuals diagnosed with sickle cell anemia experience many complications. In general, both children and adults with sickle cell anemia are more vulnerable to infections. This vulnerability is the result of spleen, the organ that filters blood, damage from sickled erythrocytes. Spleen damage prevents the organ from destroying bacteria in the blood. All individuals with the disease, especially young children, are susceptible to bacterial infections such as sepsis, pneumonia and meningitis (Bindon, 2004). Pneumococcal infections was the principal cause of death in children with sickle cell anemia until physicians began routinely giving penicillin on a preventive basis to those who are diagnosed at birth or in early infancy (Bownas, 2000). Damaged walls in erythrocytes due to sickling can cause them to stick to blood vessel walls, resulting in narrowed or blocked small blood vessels in the brain which can lead to serious, life-threatening strokes (Bindon, 2004; Bownas, 2000). This disease also causes a predisposition for acute chest syndrome caused by infection or trapped sickled cells in the lungs (Bownas, 2000).

_Treatment of sickle cell anemia_

Despite decades of research and millions of dollars, scientists have not discovered a cure for sickle cell anemia. While many researchers are still searching for clues to a cure, individuals can only alleviate the symptoms and prevent complications. Some
common ways that sickle cell anemia can be treated are: blood transfusions, painkilling
drugs, intravenous fluids, oral antibiotics such as penicillin and by using the anticancer
drug hydroxyurea (Bownas, 2000). An alternative form of treatment that has been
employed in some institutions is genetic counseling. Genetic counseling among carriers
and diagnosed individuals is considered by many to have great potential in the fight
against sickle cell anemia (Meredith, 1977).

Possible advantages of the disease

On rare occasions a mutant allele, such as the sickle cell hemoglobin, may actually fit its
bearer to the environment better and enhance the reproductive success of the individual.
This is not likely in a stable environment, but becomes more probable when the
environment is changing and mutations that were once selected against are now favorable
under the new conditions (Campbell et al., 1999). In areas of the world where malaria is
a major health concern, Hb S carriers have been naturally selected, because the trait
grants some resistance to malaria.

Malaria

Description of Disease

Malaria is a life-threatening parasitic disease transmitted by the bite of the female
Anopheles mosquito (Campbell et al., 1999). This disease is transferred through the
female mosquito because blood is required to nurture her eggs. Once the malaria parasite
is inside the human host, it undergoes a series of changes as part of its life cycle. The
various stages inside the body allow the Plasmodium to evade the immune system, infect
the red blood cells and liver, and finally develop into a form that is able to infect a
mosquito when it bites an infected person. Back inside the mosquito, the parasite changes until it reaches the stage where it can infect a human host (http://www.rbm.who.int, 2000). The intricate life cycle of Plasmodium can be seen in Figure 4.

Life History of *Plasmodium*, the parasite that causes malaria

![Life Cycle of *Plasmodium*](image)

*Figure 4, (Campbell et al., 1999)*

Four types of human malaria exist: *Plasmodium vivax*, *Plasmodium malariae*, *Plasmodium ovale* and *Plasmodium falciparum*. *P. vivax* and *P. falciparum* are the most common and falciparum the most deadly. *Plasmodium falciparum* malaria is most
common in Africa, south of the Sahara, causing an extremely high mortality rate in this region (http://www.rbm.who.int, 2000).

Malaria symptoms appear on average about 9 to 14 days after the bite of the infectious mosquito. This disease produces fever, shock, kidney failure, coma, headache, vomiting and flu-like symptoms. If drugs are not available for treatment or the parasites are resistant to the, the infection can progress rapidly to becoming life threatening. Malaria can kill by infecting and destroying red blood cells and by clogging the capillaries that carry the blood to the brain or other vital organs (http://www.rbm.who.int, 2000).

**Study Results/Discussion**

Statistics

Sickle cell anemia affects millions throughout the world, therefore in this paper all world populations are considered. This disease is particularly common among people whose ancestors come from sub-Saharan Africa; Spanish-speaking regions (South America, Cuba, Central America); Saudi Arabia; India; and Mediterranean countries such as Turkey, Greece, and Italy. In the United States, it affects around 72,000 people, most of whose ancestors come from Africa (Bownas, 2002). Between 1989 and 1993, there was an average of 75,000 hospitalizations per year in the United States among individuals with sickle cell disease. These hospitalizations cost $475 million annually (Davis et al., 1997). Sickle cell anemia occurs in about 1 in every 500 African-American births and 1 in every 1000 to 1400 Hispanic-American births. About 2 million Americans, or 1 in 12 African Americans, carry the sickle cell trait (Bownas, 2002).

Approximately 40% of the world’s population, estimated at about 2 billion people, is at risk of being infected with malaria (http://www.rbm.who.int, 2000). Regions
of the world where malaria is currently present is indicated by the colored portions of the map in Figure 5. Malaria is found throughout the tropical and sub-tropical regions of the world and causes more than 300 million acute illnesses and at least 1 million deaths annually. Ninety percent of deaths due to malaria occur in Africa, south of the Sahara, predominately among young children (http://www.rbm.who.int, 2000).

Worldwide malaria distribution in 2002 shown by the colored portions of the map

Figure 5, (World Health Organization, 2002)

Conclusion: Relationship between sickle cell hemoglobin and malaria

As agents of natural selection, infectious diseases have played a major role in the evolution of the human species (Brown and Inhorn, 1990). The genetics of the sickle cell trait have created fitness advantages and disadvantages. An advantage of inheriting this gene, if heterozygous, is increased immunity to malaria. Disadvantages include inheriting the homozygous recessive alleles and developing sickle cell anemia and its painful symptoms. Malaria provides molecular evidence of a long-running encounter
between a resourceful parasite and an array of host defense mechanisms (Hill et al., 1997). Analysis of this has provided insights into the relationship between sickle cell hemoglobin and malaria.

Many important correlations are present that indicate that sickle cell hemoglobin and malaria are undoubtedly linked. First, the distribution of the sickle cell trait in tropical Africa parallels with that of malaria, so it is reasonable to say that malaria is a selective agent producing high frequencies of the sickle cell trait (Bindon, 2004; Wiesenfeld, 1967). Second, erythrocytes of the individuals carrying the sickle cell trait tend to sickle when infected by the malaria parasite. Those infected cells flow through the spleen, which flushes them out because of their sickle shape and the parasite is eliminated along with them (Ebert and Sterns, 2001). Third, because sickle cell hemoglobin does not provide an adequate host for *Plasmodium*, due to decreased potassium levels, this cell disrupts the life cycle of the parasite (Bindon, 2004). Malaria has produced an environment selective for the mutation of sickle cell hemoglobin, creating inheritance patterns that allow it to be passed through generations.

*Suggestions for further research*

To increase the scope of this paper further research into the relationship between malaria and sickle cell anemia can be performed. It would be helpful to analyze more factors such as cultural and agricultural effects. The current research for the treatment and cure of sickle cell anemia and malaria were not included in this paper. However, by analyzing these new ideas and techniques one could obtain a greater understanding of both diseases. Also, it would be interesting to compare and contrast the sickle cell trait with other human defense mechanisms against malaria such as G6PD deficiency.
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