

From Gene to Disease: Sickle Cell Anemia

Why Does a Deadly Disease Still Exist?

Purpose

In this lesson, students learn about the relationships among environment, genotype, and phenotype. Through a case study approach, students learn about sickle cell anemia, a deadly recessive disease that remains prevalent in the human population because being a carrier of the disease confers resistance against malaria. Students explore the evolutionary trade-offs involved in this classic example of heterozygote advantage.

Audience

This lesson was designed to be used in an introductory high school biology course.

Lesson Objectives

Upon completion of this lesson, students will be able to:

- describe how a mutation at one point in the DNA can change an organism's phenotype.
- draw and interpret pedigree and Punnett square models.
- analyze data tables and maps to make and support claims.
- explain the principle of an evolutionary trade-off, and how environmental conditions influence fitness.

Key Words

autosomal, carrier, epidemiology, genotype, hemoglobin, heterozygote advantage, heterozygous, homozygous, malaria, parasite, phenotype, recessive inheritance pattern, sickle cell anemia, sickle cell trait

Big Question

This lesson addresses the Big Question “*Where do we come from?*”

Standard Alignments

- **Science and Engineering Practices**
 - **SP2.** Developing and using models
 - **SP4.** Analyzing and interpreting data
 - **SP6.** Constructing explanations (for science) and designing solutions (for engineering)
 - **SP7.** Engaging in argument from evidence

◦◦ **MA Science and Technology/Engineering Standards (2016)**

- **HS-LS3-3.** Apply concepts of probability to represent possible genotype and phenotype combinations in offspring caused by different types of Mendelian inheritance patterns.
- **HS-LS3-4(MA).** Use scientific information to illustrate that many traits of individuals, and the presence of specific alleles in a population, are due to interactions of genetic factors and environmental factors.
- **HS-LS4-1.** Communicate scientific information that common ancestry and biological evolution are supported by multiple lines of empirical evidence, including molecular, anatomical, and developmental similarities inherited from a common ancestor (homologies), seen through fossils and laboratory and field observations.

◦◦ **NGSS Standards (2013)**

- **HS-LS3-1.** Ask questions to clarify relationships about the role of DNA and chromosomes in coding the instructions for characteristic traits passed from parents to offspring.
- **HS-LS4-2.** Construct an explanation based on evidence that the process of evolution primarily results from four factors: (1) the potential for a species to increase in number, (2) the heritable genetic variation of individuals in a species due to mutation and sexual reproduction, (3) competition for limited resources, and (4) the proliferation of those organisms that are better able to survive and reproduce in the environment.
- **HS-LS4-3.** Apply concepts of statistics and probability to support explanations that organisms with an advantageous heritable trait tend to increase in proportion to organisms lacking this trait.
- **HS-LS4-4.** Construct an explanation based on evidence for how natural selection leads to adaptation of populations.

◦◦ **Common Core Math/Language Arts Standards**

- **CCSS.ELA-LITERACY.RST.9-10.1.** Cite specific textual evidence to support analysis of science and technical texts, attending to the precise details of explanations or descriptions.
- **CCSS.ELA-LITERACY.RST.11-12.1.** Cite specific textual evidence to support analysis of science and technical texts, attending to important distinctions the author makes and to any gaps or inconsistencies in the account.
- **CCSS.ELA-LITERACY.RST.9-10.7.** Translate quantitative or technical information expressed in words in a text into visual form (e.g., a table or chart) and translate information expressed visually or mathematically (e.g., in an equation) into words.

Misconceptions Addressed

- This lesson addresses many common misconceptions about evolution and natural selection including:
 - Humans are not currently evolving. (Question 7)
 - Evolution guarantees perfect solutions to environmental challenges. (Question 8)
- Further information about student misconceptions on this topic can be found [here](#) as well as on the [Understanding Evolution website](#).

Primary Sources

- **Bite** "[Malaria and Sickle Cell Anemia: Putting an Old Hypothesis to the Test](#)" based on:
 - Elguero, Eric, Délicat-Loembet M. Lucrèce, Virginie Rougeron, Céline Aranthay, Benjamin Roche, Pierre Becquart, Jean-Paul Gonzalez, Dieudonné Nkoghe, Lucas Sica, Eric M. Leroy, Patrick Durand, Francisco J. Ayala, Benjamin Ollomo, François Renaud, and Franck Prugnolle. 2015. "[Malaria continues to select for sickle cell trait in Central Africa.](#)" *Proceedings of the National Academies of Sciences of the United States of America* 112(22): 7051–7054. doi: 10.1073/pnas.1505665112
 - Piel, Frédéric B., Anand P. Patil, Rosalind E. Howes, Oscar A. Nyangiri, Peter W. Gething, Thomas N. Williams, David J. Weatherall, and Simon I. Hay. 2010. "[Global distribution of the sickle cell gene and geographical confirmation of the malaria hypothesis.](#)" *Nature Communications* 1:104. doi: 10.1038/ncomms1104.
- **Story about sickle cell's heterozygote advantage in *The New York Times***
 Jr., Donald G. McNeil. "[Biochemistry: Scientists Decode the Protective Element Sickle Cell Anemia Offers Against Malaria.](#)" November 14, 2011. Accessed June 16, 2018.
- **Story about sickle cell's heterozygote advantage in *Scientific American***
 Wadman, Meredith. "[Sickle-Cell Anemia Mystery Is Solved.](#)" November 10, 2011. Accessed June 16, 2018.
- **Misconceptions**
 Anderson, Diane I., Kathleen M. Fisher, and Gregory J. Norman. 2002. "[Development and Evaluation of the Conceptual Inventory of Natural Selection.](#)" *Journal of Research In Science and Teaching* 39(10): 952–978. doi: 10.1002/tea.10053

Materials

Copies of the Student Handout and Science Bite for each student

Time

This lesson should take approximately one or two 50-minute class periods.

Student Prior Knowledge

Students should have a basic understanding of how natural selection works. In addition, they should be familiar with interpreting pedigree and Punnett square models, and have had experience transcribing DNA to RNA and translating RNA to amino acids using a codon table.

Instructions and Teacher Tips

General Procedure

-  Have students read through the worksheet and answer the questions as they go, reading the Science Bite when instructed.
-  After students have completed the questions, consider bringing them together as a class or break into small groups to compare answers and to discuss any remaining questions. This lesson could be completed independently or in pairs.

Tips, Extensions, and Variations

-  If you have not yet covered transcription and translation, skip Question 2. If you have not yet covered Punnett Squares and Pedigrees, skip Questions 1 and 4.
-  Depending on the class, this lesson may take more than one day to complete. Consider assigning the Bite reading and final two questions for homework if you are pressed for time.
-  HHMI BioInteractive has a set of activities and resources on sickle cell anemia that could serve as extensions or remediation activities. Two of these resources are listed below.
 -  [This video](#) explores the work of Dr. Tony Allison, the first to figure out the connection between the prevalence of malaria and sickle cell anemia in Africa.
 -  [This](#) resource incorporates some clips from the video described below into its exploration of sickle cell anemia as an example of ongoing human evolution.

Big Question Discussion

This lesson should get students thinking about the big question “*Where do we come from?*” In particular, how do infectious diseases influence human evolution? If you choose to delve into the Big Question, consider following these suggested steps:

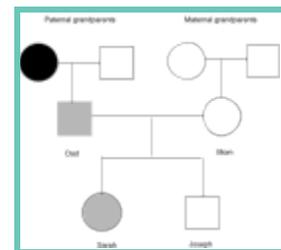
-  Warm-up with a few questions about inherited traits and familial characteristics: How did you become who you are? Who are you most like in your family? Why do we all have different phenotypes? How do phenotypes relate to genotypes?
-  Then, transition into the idea of infectious diseases vs. genetic diseases. What is the difference? Make sure they understand that infectious diseases can affect anyone (at least for the purposes of this lesson plan), as long as the correct infectious agent is in the environment; and that genetic diseases are a product of inheritance. If necessary, review dominant/recessive traits and the terms homozygous and heterozygous.

- After students have read the Bite and completed the analysis questions, include these questions in the wrap-up discussion: What did you inherit from past generations? What do you pass on to future generations? How do your environment and your genotype interact?

Background Information and Research Details

- [Malaria](#) is a serious disease caused by a parasite called *Plasmodium falciparum* (or *vivax* or *malariae*) that commonly infects a certain type of mosquito in the genus *Anopheles*, which feeds on humans. The parasite hides in the mosquito's saliva and is thus transferred from infected person to infected person. Because mosquitoes are required to transmit the parasite, they are called *vectors* of the disease.
 - In humans, the parasites grow in the liver and then mature in red blood cells. Once mature, the parasites burst out of the red blood cells, destroying them, and infect more red blood cells, continuing the cycle. Importantly, the parasites are *dependent* on red blood cells to maintain infection and cause illness.
 - People who get malaria are typically very sick and have high fevers, shaking chills, and a flu-like illness. It is often difficult to avoid getting malaria in countries where it is endemic (native) due to the prevalence of the mosquito vector and inadequate access to treatment, but travelers can take preventative medications, carry insect repellent, and sleep under mosquito-proof bedding to avoid contracting the illness. Malaria drugs do exist, but incur very serious side effects. Additionally, many species of *Plasmodium* that cause malaria have become resistant to these drugs. Ongoing research is searching for a widespread vaccine.
 - About 1,700 cases of malaria are diagnosed in the United States each year. The vast majority of cases in the United States are in travelers and immigrants returning from countries where malaria transmission occurs, many from sub-Saharan Africa and South Asia.
- [Sickle cell anemia](#) is a genetic disease caused by a single point mutation in a gene that is responsible for beta-globin, a component of hemoglobin in red blood cells. This single mutation alters a single amino acid in the protein, changing a hydrophilic amino acid to a hydrophobic amino acid and changing the structure of the protein. This structural change causes aggregation, and red blood cells become hard, sticky, and C-shaped, aggregating in blood vessels and decreasing red blood cells' capacity to carry oxygen to the body. This results in pain, weakness, and often death in children before the age of 5, particularly in countries with poor health infrastructure.
 - Sickle cell anemia is a recessive genetic disorder. One must inherit one mutant copy of the gene (*HbS*) from each parent to have sickle cell anemia. If one normal copy (*HbA*) is inherited, the individual exhibits sickle cell trait; these individuals are typically healthy and live normal lives, but can pass the gene onto their children. On rare occasions, individuals with sickle cell trait can have "pain crises" if they are at particularly high altitudes, are deprived of oxygen, experience high-pressure conditions (such as scuba diving), and other extreme environments.

- There is no standard cure for sickle cell anemia, but the disease can be managed. A bone marrow transplant can technically “cure” sickle cell anemia in very young children, but this is rarely used due to potential side effects, including infertility and death, that increase in risk with age. Bone marrow transplants often come from healthy relatives. Because red blood cells originate from bone marrow, this allows the recipient to be populated with healthy, normal red blood cells.
- It is not entirely understood why sickle cell trait is protective against malaria, but some evidence has been provided. For instance, it appears that when red blood cells are infected with parasites, red blood cells rupture more easily when they contain defective hemoglobin; this prevents parasite reproduction in the red blood cells. Additionally, the parasites consume hemoglobin as a part of their life cycle, but sickling hemoglobin is more difficult to digest.
- Most people with sickle cell trait have no symptoms and live entirely normal, healthy lives. However, some environmental conditions, such as high altitudes, dehydration, or overexertion, can cause some symptoms to arise. In rare cases, sickle cell trait can cause death. You can read the [CDC's fact sheet on sickle cell trait](#) for more information.
- Your students may wonder why the researchers had to break open red blood cells to analyze hemoglobin instead of just doing what sounds like the simplest thing—looking at cells under a microscope and seeing if any sickle. It turns out the answer is a little bit complicated, but very interesting! Even people with full-blown sickle cell anemia don't always have sickled blood cells floating in their vessels; the disease is kind of fickle that way. Also, when you take blood cells out of the human body, you're totally changing their surrounding environment! So who knows how they'll look under the microscope. Red blood cells are also so fragile that even healthy ones may not necessarily hold their shape. So the researchers narrow their analysis to only the relevant protein: hemoglobin, which is encoded by the mutant gene. What they actually do is test how soluble the hemoglobin is. Sickle cell hemoglobin is significantly less soluble due to a single base pair change in the gene that ends up substituting a hydrophobic amino acid for what is normally a hydrophilic amino acid. This compromises protein structure and makes the outside of the protein more “sticky,” leading to clumping and lower solubility.



Answers

1. Using the key provided, draw a pedigree model of sickle cell in Sarah's family. Include three generations: Sarah and Joseph, their parents, and both sets of grandparents.

A very small portion of the DNA sequences of Sarah and Joseph's hemoglobin alleles are shown below. The sequences have been broken into codons for you.

2. Circle the difference(s) you notice between the two sequences.

Sarah	TAC	CAC	GTG	GAC	TGA	GGA	CTC	CTC
Joseph	TAC	CAC	GTG	GAC	TGA	GGA	CAC	CTC

3. Use your knowledge of transcription and translation to answer the following questions.
- a. Complete **Table 2**. A codon table has been provided.

	Sarah								Joseph							
DNA	TAC	CAC	GTG	GAC	TGA	GGA	CTC	CTC	TAC	CAC	GTG	GAC	TGA	GGA	CAC	CTC
RNA	AUG	GUG	CAC	CUG	ACU	CCU	GAG	GAG	AUG	GUG	CAC	CUG	ACU	CCU	GUG	GAG
Amino acids	Met	Val	His	Leu	Thr	Pro	Glu	Glu	Met	Val	His	Leu	Thr	Pro	Val	Glu
Hemoglobin phenotype	Abnormally folded								Normally folded							

- b. Based on your completed table, explain why Joseph and Sarah have different hemoglobin phenotypes.

A single mutation in the DNA (from CAC to CTC) causes a different amino acid (glutamine instead of valine) to be added to the growing amino acid chain. This in turn causes the protein to fold incorrectly and causes the sickle cell hemoglobin phenotype.

- c. Why do you think abnormally folded hemoglobin would make it harder for the protein to carry oxygen?

Sample answer: The abnormal shape would make it harder to carry oxygen because the oxygen binding sites are not accessible.

The maps below show the prevalence of sickle cell anemia and malaria in Africa. Different shades of gray and black indicate the percent of people native to that area that have either malaria (left) or sickle cell anemia (right).

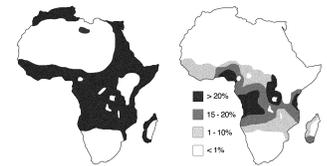


Figure 2. Geography of Malaria and Sickle Cell Anemia. Maps show malaria prevalence (left) and sickle cell anemia prevalence (right) in Africa. Source: [Wikimedia Commons](#).

4. What do you notice about the maps in **Figure 2**? How are they similar? How are they different?

Sample answer: There is greater prevalence of sickle cell anemia through central Africa where there also tends to be high incidence of malaria. However, there are areas in northern Africa with a lot of malaria, but fewer than 1% of the population has sickle cell anemia.

5. If Sarah has a child with a man who also has sickle cell trait, what are the chances that the child will have sickle cell anemia? Sickle cell trait? Draw a Punnett square to support your answer. Use the allele symbols given in **Table 1**.

25% chance of sickle cell anemia (*HbSS*), 50% chance of sickle cell trait (*HbAS*)

<i>Hb</i>	<i>A</i>	<i>S</i>
<i>A</i>	<i>HbAA</i>	<i>HbAS</i>
<i>S</i>	<i>HbAS</i>	<i>HbSS</i>

The table below compares the malaria infection rate in two African countries by genotype. Both countries have a relatively high incidence of malaria.

	% of individuals infected with malaria	
	<i>Genotype 1</i>	<i>Genotype 2</i>
Kenya	31.6	19.3
Tanzania	2.96	0.64

Table 3. Genotype vs. Malaria Infection Rate. Comparison of malaria infection rates in two countries by genotype. Sources: [Kenya] [Williams et. al. 2005](#); [Tanzania] [Makani et. al. 2010](#).

6. Make a claim about which Genotype (1 or 2) is *HbAA* and which Genotype (1 or 2) is *HbAS*. Support your claim with data from **Table 3**.

Genotype 1 is *HbAA* and Genotype 2 is *HbAS*. According to Table 3, individuals with genotype 2 (*HbAS*) are infected less often than individuals with genotype 1 (*HbAA*), which suggests that having genotype 1 (*HbAS*) is an advantage in an area with high malaria incidence.

7. Based on the data in **Figure 2**, your Punnett square, and **Table 3**, construct an argument, based on evolution, explaining why there is a high rate of sickle cell anemia among people of central African descent. In your answer, be sure to mention both positive and negative selection pressures associated with the genotypes *HbAS* and *HbSS*.

In areas with high incidence of malaria, such as central Africa (Figure 2), there is an advantage (a positive selection factor) to having one copy of the sickle cell allele (*HbAS*) because it helps to reduce the chances of contracting malaria (Table 3). This advantage keeps the allele circulating in the population, but leads to a high incidence of sickle cell anemia, because when two carriers of the allele have children, there is a 25% chance (Punnett square) the child will have sickle cell anemia (*HbSS*). Although having sickle cell anemia will prevent malaria, it is an overall disadvantage in any environment because it reduces a person's chance to have children. People of central African descent living elsewhere in the world, like Sarah and Joe, have inherited alleles from their ancestors. So even though they do not live in an area with a lot of malaria, they still have a high frequency of the sickle cell allele.

8. **Connect to the Big Question** Evolution is defined as a change in allele frequencies in a

population over time. Explain how the research into malaria and sickle cell anemia is evidence that human populations have evolved in response to environmental factors such as infectious disease. Cite specific evidence from the lesson in your answer.

Sample answer: The research described in the Bite provides evidence that malaria, an infectious disease, has influenced human evolution. **Table 3** shows that when malaria is not common, the sickle cell allele, *HbS*, is not very common. However, in areas with a high incidence of malaria, such as in Gabon, it is. Thus, you can conclude that when malaria moves into a population, the *HbS* allele frequency increases. Changing allele frequency in a population is the definition of evolution.

9. Use what you have learned about malaria and sickle cell anemia to explain which of the following claims about evolution is more accurate:

Claim 1: Evolution ensures that individuals in a population obtain perfect solutions to environmental challenges.

Claim 2: Evolution results in existing variations that provide advantages to environmental challenges becoming more common in a population.

Sample answer: Claim 2 is more accurate. The sickle cell allele is common in areas with high incidence of malaria. This is because having sickle cell trait increases an individual's fitness in that environment and natural selection results in traits with positive fitness becoming more common in a population. However, sickle cell trait is not a perfect solution. Having sickle cell trait does not guarantee you don't get malaria, as shown in Table 3. It also has a serious disadvantage—namely, it means a 25% chance of passing a deadly disease onto a biological child if the other parent also has sickle cell trait. Evolution can only act on existing variations, so although it isn't a perfect solution to counteracting malaria, the sickle cell allele has spread in high malaria environments because it is better than nothing, and to our knowledge, there isn't another variation in the population that is better.