A LESSON ON THE NATURE OF SCIENCE

OVERVIEW

Dr. Tony Allison's story is a compelling example of the nature of science. This worksheet complements the short film *The Making of the Fittest: Natural Selection in Humans* (http://www.hhmi.org/biointeractive/making-fittest-natural-selection-humans) by providing students with additional information about the decades of research done on sickle cell disease (also known as sickle cell anemia) before Dr. Allison's work. Students will appreciate how the work of others made Dr. Allison's discovery possible and how he made the link between sickle cell disease and malaria.

KEY CONCEPTS AND LEARNING OBJECTIVES

- Mutations that increase fitness of an organism increase in frequency in a population.
- Changes in the environment where a population lives can change which traits (and therefore genes) are favorable
- The frequency of an allele in a population can change depending on whether the allele is advantageous, deleterious, or neutral.
- In areas where the malaria parasite is present, individuals who are heterozygous for the sickle cell allele are at a selective advantage because they are protected against malaria but do not get sickle cell disease.
- A mutation that causes a genetic disease can also protect against an infectious disease.

Students will be able to

- read and interpret textual information; and
- make claims based on evidence.

CURRICULUM CONNECTIONS

Curriculum	Standards
NGSS (April 2013)	HS-LS3-1, HS-LS3-2, HS-LS4-2, HS-LS4-4 HS-LS1.A, HS-LS2.A, HS-LS3.B, HS-LS4.B, HS-LS4.C
Common Core (2010)	CCSS.ELA-Literacy.RH.9-10.3, CCSS.ELA-Literacy.RH.9-10.4, CCSS.ELA-Literacy.RH.9-10.3, CCSS.ELA-Literacy.W.9-10.2, CCSS.ELA-Literacy.RST.11-12.4, CCSS.ELA-Literacy.WHST.9-12.2
AP Biology (2012–13)	1.A.1, 1.A.2, 1.C.3, 3.A.3, 3.C.1, 4.C.1
IB Biology (2009)	4.1, 4.3, 5.4, D.2

KEY TERMS

allele, antimalarial, autosomal, carrier, character, dominant, evolution, genotype, HbA, HbS, hemoglobin, heterozygous, homozygous, hypothesis, in vitro, in vivo, malaria, mutation, natural selection, pedigree, phenotype, recessive, sickle cell anemia, sickle cell disease, sickling, trait

TIME REQUIREMENTS

This worksheet was designed to be completed within one 50-minute class period, or two if all discussion questions in "Teaching Tips" are addressed.

SUGGESTED AUDIENCE

This worksheet is appropriate for high school biology (all levels, including AP and IB) and introductory college biology.

PRIOR KNOWLEDGE

Students should know that traits are inherited and that some provide organisms with a greater chance to survive and reproduce. A basic understanding of genetics is helpful. Students may benefit from a short lesson on the genetics of sickle cell disease that highlights the inheritance patterns, genotypes, and phenotypes, as well as the terminology used to describe the phenotypes. Some understanding of the scientific process is helpful.

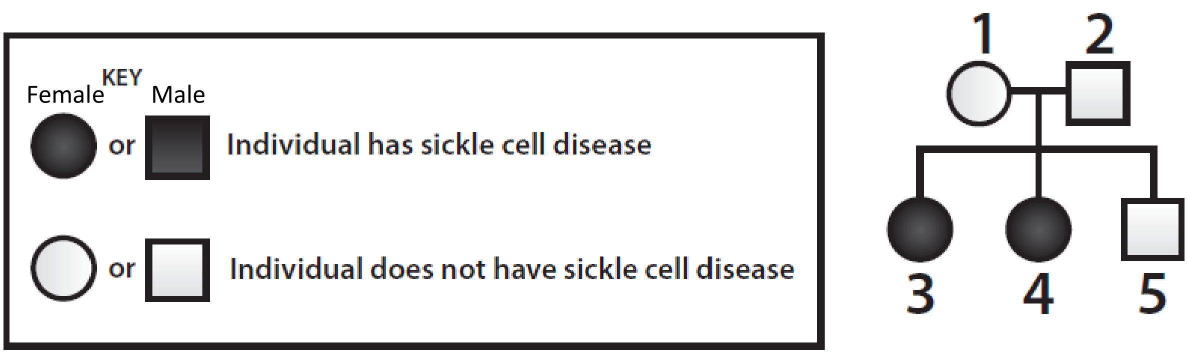
TEACHING TIPS

- Before watching the film, students should read the introduction and answer the questions in Part 1 about the early work on sickle cell disease and the process of science. Students then watch the film and hear the story from Dr. Allison himself. After the film, they answer additional questions.
- You may want to have your students read the background in the In Depth Film Guide for Teachers (http://www.hhmi.org/biointeractive/classroom-activities-natural-selection-humans) and watch the *Malaria: Human Host* (www.biointeractive.org/malaria-human-host) and *Malaria: Mosquito Host* (www.biointeractive.org/malaria-mosquito-host) animations for further information on the malaria life cycle.
- It may be helpful to discuss how the film uses term "character." "Sickle cell character" refers to the sickle cell allele. Individuals with the sickle cell character can be either heterozygous (*AS*) or homozygous (*SS*). In textbooks, "sickle cell trait" refers to the heterozygous state (*AS*). People with sickle cell trait are carriers.

SUGGESTED DISCUSSION QUESTIONS

You might discuss the following questions with your students *before* they watch the film.

1. Below is the pedigree chart of a family. Two of the children have sickle cell disease. The parents, individuals 1 and 2, were tested using the in vitro analysis developed by Dr. Victor Emmel (see the timeline in the handout). From the information provided, would the red blood cells of one or both of the parents exhibit sickling when tested? Support your answer.



The red blood cells of both parents (1 and 2) would exhibit sickling. They are both carriers. They have each contributed one sickle cell allele to children 3 and 4.

2. Would the red blood cells of child 5 exhibit sickling when tested? Explain.

There are not enough data to know whether the red blood cells of child 5 would exhibit sickling. The boy may have inherited the sickle cell allele from one of his parents but not both, because he does not have sickle cell disease. His genotype could be *AS* or *AA*. Because he does not have sickle cell disease, there is a 33.33% chance he has the *AA* genotype and will not exhibit sickling of red blood cells. There is a 66.67% chance he has inherited the *AS* genotype and will exhibit sickling of red blood cells.

You might discuss the following questions *after* your students have watched the film.

3. What might happen to sickle cell allele frequency if a cure for malaria were found and everyone were treated?

Students should understand that the malaria parasite acts as a selective pressure to maintain the high frequency of the sickle cell allele in a population. If the heterozygous (*AS*) condition no longer provides any selective advantage, the frequency of the sickle cell allele will gradually decrease. So, if a cure were found for malaria, the situation would be similar to living in a nonmalarial environment where the sickle cell allele is selected against.

4. Suppose scientists discovered an isolated island population where the mutation that causes sickle cell disease never arose. What might you see if this was also a malaria-endemic area?

Possible answers include the following:

- **We would likely see many individuals with severe cases of malaria.**
- **The mortality rate associated with malaria infections may be higher in the island population than in populations where the sickle cell allele is present.**
- **Scientists might discover the presence of a different mutation that provides some resistance to or protection against malaria.**

5. Discuss the various ways that scientists test their ideas. Experiments involve manipulating some factor in a system to see how the outcome is affected. Ideally, scientists try to control as many factors as possible. In some cases, manipulating factors or controlling all the variables is not possible. In those instances, scientists rely on other ways of collecting data, such as observational analysis. How did Dr. Allison test his ideas? What are some specific examples?

Dr. Allison could not do experiments on people, so he relied on observational analysis. He collected blood samples from thousands of children in many locations in East Africa. The analysis of these blood samples provided data that supported his hypothesis.

ANSWER KEY

PART 1

1. *Explain how analyzing the inheritance patterns of sickle cell disease through pedigrees allowed scientists to determine that the disease is autosomal recessive.*

An autosomal recessive disease is only apparent in homozygous individuals who inherit one recessive allele from each parent. Those who have sickle cell trait (heterozygous) carry one sickle cell allele but appear phenotypically normal. If heterozygous individuals mate, their offspring have a 25% chance of being homozygous for the sickle cell allele and having sickle cell disease. The inheritance pattern in an extended family pedigree indicates whether a disease is autosomal recessive. If the parents show no disease phenotype but are heterozygous and a child shows the disease, then it is indicative of an autosomal recessive disease. Generally, an autosomal recessive disease skips generations. An autosomal dominant disease exhibits a different inheritance pattern.

2. *Discuss how the timeline demonstrates that science is a social process done by people working together and sharing information with the scientific community and the public.*

The timeline lists the work of many scientists. Each one made an important contribution to the analysis and understanding of sickle cell disease, and each one built on the research of others. Students may provide examples such as the following: Dr. James Herrick, Dr. Victor Emmel, Dr. E. Vernon Hahn, and Dr. Elizabeth Gillespie established that sickle cell disease was a disease of the blood. Dr. Linus Pauling used his knowledge of blood and sickle cell disease to pinpoint the disease to a specific protein. And Dr. William Taliaferro, Dr. John Huck, and Dr. James Neel established the genetic basis of the disease. All these scientists' contributions helped form Dr. Allison's background knowledge, which allowed him to develop his hypotheses about malaria and sickle cell disease.

PART 2

1. *Provide two examples of how Dr. Allison used the work and observations of other scientists to complete his own research.*

Any combination of scientists listed in the timeline is fine. Possible answers include, but are not limited to, the following:

- **Dr. Allison used the chemical test developed by Dr. Geneva Daland and Dr. William Castle when he collected and analyzed blood samples from children in Africa.**

- **His knowledge of the inheritance pattern of sickle cell disease was informed by the work of Dr. Neel, who mathematically established that sickle cell disease is autosomal recessive.**
- **The knowledge of sickle cell disease began with Dr. Herrick's diagnosis.**

2. *List at least two pieces of data supporting the hypothesis that there is a link between the sickle cell allele and malaria.*

The parasite load was lower in the red blood cells of children with the sickle cell allele than in the red blood cells of those without it.

There were many more children with the sickle cell allele in regions of East Africa where malaria was endemic than in regions where it wasn't endemic.

The frequency of children with the sickle cell allele was much lower in the arid and highland areas of East Africa than in the coastal and wetland regions.

Other areas of the world where malaria is endemic also show an elevated frequency of the sickle cell allele.

3. Both environmental factors and genetics can account for an individual's susceptibility to infectious disease. For the sickle cell–malaria example, explain how genetics accounts for an individual's susceptibility to infectious disease.

Individuals with the *AA* genotype (homozygous for normal hemoglobin) are susceptible to malaria infection. Individuals with the *AS* genotype (heterozygous) are more resistant to malaria in part because of the inability of the malaria parasite to reproduce successfully in these individuals. *SS* individuals are resistant to malaria, but they suffer from health problems associated with having sickle cell disease. Therefore, in a malarial environment, *AS* individuals experience greater fitness than either *AA* or *SS* individuals do.

4. *Describe how the relationship between sickle cell disease and malaria is an example of natural selection in humans.*

Natural selection is a process by which organisms most suited to their environment survive and reproduce at higher rates. In a malarial environment, heterozygous individuals (*AS*) are more likely to survive and reproduce because they are more resistant to malaria. Individuals with the *AS* genotype are selected for, while individuals with the *AA* genotype are selected against. As a result, the frequency of the sickle cell allele is much higher in areas where malaria is common. Although the sickle cell allele is harmful in the homozygous state (*SS*), it is not removed from the population. It remains present in the heterozygous genotype from generation to generation. In the absence of malaria, the sickle cell allele has no selective advantage.

5. *In science, discoveries often lead to new questions for future investigation. With the knowledge that you have gained about malaria and sickle cell disease through this worksheet, propose two questions that scientists could ask about either of these diseases or the link between them.*

Give students credit for any scientifically valid questions they propose. Some suggestions include the following:

- **How does a fetus with sickle cell disease survive? Is there enough oxygen crossing the placenta to prevent sickling?**
- **Are any animal models being used in sickle cell research?**
- **How does the sickle cell allele protect against malaria infection?**
- **Do other animals that are susceptible to malaria have sickle cell disease or something like it?**
- **Is there a chance that gene therapy could be used to correct the sickle cell mutation?**
- **Are there other genetic changes that protect against malaria, either on the hemoglobin gene or on other genes?**

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