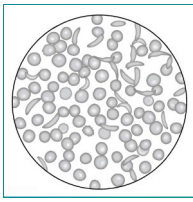


Why Do Some People with the Sickle Cell Genotype Not have Symptoms?

hhmi | BioInteractive

Activity
Educator Materials

OVERVIEW

In this inquiry-based activity, students engage in science practices to figure out why some people with a genetic condition that usually leads to sickle cell disease do not have disease symptoms. This activity is based on content covered in the Scientists at Work video *A Genetic Treatment for Sickle Cell Disease*. Instead of frontloading information from the film, the activity guides students through "figuring out" the key concepts first. As they investigate and make sense of the phenomenon, students engage in practices such as observing, questioning, and using and developing models.

This activity is meant to be given to students in separate parts, so that they can focus on figuring out one part before receiving the next and coherently build on their understanding. It is not recommended to provide all parts of the "Student Handout" as a packet together.

- In **Part 1**, students are introduced to the phenomenon through images and a video clip.
- In **Part 2**, they observe images of cells and hemoglobin (with and without the sickle cell mutation).
- In **Part 3**, they sort cards that show steps in the production of hemoglobin (with and without the sickle cell mutation).
- In **Part 4**, they identify the mutation that causes sickle cell disease by transcribing and translating gene segments.
- In **Part 5**, they construct models of the protein segments they translated in Part 4.
- In **Part 6**, they watch the entire video and explore potential treatments with genetic medicine.
- In the optional **extension**, they transfer what they've figured out to Huntington's disease.

Additional information related to pedagogy and implementation can be found on this resource's webpage, including suggested audience, estimated time, and curriculum connections. A **slide deck** is also available as a PowerPoint or Google Slides that you can use to implement this activity.

KEY CONCEPTS

- Mutations, even in a single nucleotide, can significantly change the structure and function of a protein. For example, a mutation that affects hemoglobin results in sickle-shaped red blood cells.
- Mutations that cause changes in protein structure and function can lead to genetic diseases, such as sickle cell disease.
- Not all mutations are harmful. For example, a mutation affecting fetal hemoglobin production can relieve the symptoms of sickle cell disease.

STUDENT LEARNING TARGETS

- Develop and use models to figure out how genes are transcribed and translated.
- Construct an evidence-based explanation of how genotype leads to phenotype.
- Analyze and interpret data to identify patterns that determine cause-and-effect relationships.

PRIOR KNOWLEDGE

It is helpful for students to have a basic understanding of:

- DNA, RNA, and amino acids
- transcription and translation

- protein structure and function
- mutations (in particular, substitutions)

MATERIALS

- copies of the "Student Handout"
- the "Gene Expression Cards" (two sets of eight cards each, labeled A–H)
- the "Genetic Code Chart"
- protein modeling materials (e.g., graph paper, slides, or a kit)
- access to the *A Genetic Treatment for Sickle Cell Disease* video and the *Central Dogma and Genetic Medicine* Click & Learn

TEACHING TIPS

- You can implement this activity using the slide deck provided on this resource's webpage, which is available as a PowerPoint or Google Slides.
  - The slides show the key videos, images, and tables from the student materials to facilitate class discussions.
  - Each part of the "Student Handout" (1–6) is explicitly listed in the slides. Accompanying information from this "Educator Materials" document is provided in the notes below each slide.
- Students should *not* watch *A Genetic Treatment for Sickle Cell Disease* before doing this activity. They will watch a short clip from the video in Part 1 to motivate discovery and provide an anchoring event for their learning experience. The full video is shown at the end of the activity, in Part 6.
- Distribute each part of the "Student Handout" separately. Students should receive the next part only after they have completed each previous part. It is *not* recommended to give students all parts of the handout at once.
- Allow students to engage in the activity without frontloading too much information. Scaffolding has more impact when done in the moment when students actually need it.
  - For example, don't discuss how to transcribe mRNA from DNA until students need to do this in Part 4.
- You can do the parts of this activity over multiple lessons. It is key that students build on each part in the sequence without adding extraneous information that could derail their understanding.
- Students can work individually or in teams to collaborate while problem solving.
- For Part 3, you will need to print or electronically share files for the "Gene Expression Cards" from this resource's webpage.
  - A PDF file is provided as a printable option. The first page is for the "typical" process, and the second page is for the "sickle cell" process. Print out each page separately, cut the cards out, and shuffle each set; you may wish to laminate them for repeated use. You can store the cards in labeled resealable bags or envelopes.
  - Individual card images (JPGs) are provided in the "Card Images" ZIP file. You can use a virtual whiteboarding or collaboration software (e.g., Google Jamboard, Miro) in which students can move and annotate card images.

PROCEDURE AND ASSESSMENT GUIDANCE

This section outlines recommended procedures for each part of the activity in the "Student Handout." It also provides sample answers and other assessment guidance for the questions in the "Student Handout." Select the links below to go directly to each part of the activity:

PART 1: Making Observations and Asking Questions

Procedure

Students watch a clip from the video *A Genetic Treatment for Sickle Cell Disease*, which introduces two girls: Ceniya and Ingrid. It is important that students view only the clip provided. The goal is to activate student thinking about what is happening in the clip, *not* to explain the science that they will figure out later.

It is important for students to notice and wonder about the differences in Ceniya and Ingrid's symptoms, as well as the differences in their blood cells (Figure 1 in the "Student Handout"). Students should propose questions about these specific phenomena before moving to Part 2.

- Consider having students first think about their own responses individually, then discuss with a partner or in small groups. This allows students to become more confident when later sharing their ideas or asking questions in front of the whole class.
- This process helps students better engage in scientific communication with one another by giving them a context in which to analyze and interpret data.

Questions

1. What do you notice about the two blood smears in Figure 1?
   Students should mention the different shapes of cells. Some cells are round, and some are long and pointed. The smear from the individual like Ceniya has mostly round cells with only a few long ones. The smear from the individual like Ingrid has a higher proportion of long cells. (Students may also notice some "spiky" cells, but they are not required to know what these cells are for the purpose of this activity.)
2. What questions do you have after making your observations?
   Students may ask why the cells are different shapes and why the two individuals have different proportions of each shape.
3. What kind of information would you need to help answer your questions?
   Student answers will vary. Ideally, they will make some reference to genes here. You may want to guide them in this direction if not, since it will come up later in the activity.
4. Do you think all the cells in Figure 1 function the same way? Why or why not?
   Answers will vary. Students should comment that the differently shaped cells may function differently.

PART 2: Structure and Function of Hemoglobin in a Red Blood Cell

Procedure

Part 2 begins with two discussion questions that can be discussed in pairs, small groups, or as a whole class, at your discretion:

- *Based on what you observed in the video clip from Part 1, why do you think the shape of the typical red blood cell is so important to its function? (Consider how red blood cells travel throughout the body.)*

- *How does the shape of the sickled red blood cell interfere with its function?*

Students then observe images of typical and sickled red blood cells, as well as the hemoglobin molecules each cell contains (Figure 2 in the "Student Handout"). This motivates students to consider the gene(s) that can affect hemoglobin's structure and, ultimately, how red blood cells function. Students should be thinking about the concept of structure and function, which will also play a role in Part 3.

Consider allowing students to select from the Crosscutting Concepts cards from the "Using Three-Dimensional Learning Cards in the Science Classroom" activity to provide a lens (in particular, "Structure & Function") through which students view the information. Students can engage in sensemaking around this information to prepare for Part 3.

Questions

5. For the two types of red blood cells shown in Figure 2:
   a. What do the cells have in common?
      They both contain many hemoglobin molecules.
   b. How are the cells different?
      They have different shapes. The typical cell is round, and the sickled cell is thin and pointed like a crescent moon. Also, the hemoglobin molecules in the cells are organized differently. The typical cell has hemoglobin scattered throughout, and the sickled cell has hemoglobin arranged in long lines.
6. What does hemoglobin do for the body?
   Hemoglobin helps red blood cells carry oxygen to the cells of the body.
7. Based on Figure 2 and the video clip from Part 1:
   a. What happens to a red blood cell when hemoglobin is clumped?
      The shape of the cell changes from round to sickled.
   b. How would the change you just described affect the body?
      Sickled blood cells can get stuck in small blood vessels. If the blood cells cannot move easily through blood vessels, they cannot effectively carry oxygen to the cells of the body.
8. Hemoglobin is a type of protein.
   a. Where does the body store the original instructions for building proteins?
      Instructions to build proteins are stored in DNA (genes).
   b. What change in these instructions could cause the hemoglobin to clump?
      A change in the DNA (mutation) can change the protein's structure and behavior. In this case, a mutation could make hemoglobin more likely to clump.

PART 3: Gene Expression Cards

Procedure

Students are asked to keep this driving question in mind as they work through this part of the activity:
Where is the origin of the change that results in clumped hemoglobin molecules and sickled red blood cells?

At this point, give students the **"Gene Expression Cards,"** which can be downloaded from the "Materials" box on this resource's webpage. There are two sets of eight cards each, labeled A–H.

- The "**typical"** set shows the stages of the process that results in nonclumping hemoglobin and round red blood cells (left side of Figure 2 in the "Student Handout").

- The **"sickle cell"** set shows the stages of the process with sickle cell disease, which results in clumped hemoglobin and sickled red blood cells (right side of Figure 2).

Shuffle each set into a random order before giving them to students. Students will sort the cards to begin sensemaking the various stages in the production of hemoglobin.

As described in the "Student Handout," students should sort the "typical" card set first, then place the matching cards from the "sickle cell" set. At this point, it is *not* critical for students to get the order of the cards correct. As new information is provided, they can revise their model (the order of their cards) and build on their conceptual understanding of these processes.

Questions

9. Record the letters of the cards, in their final order, in the far-left column of Table 1. What is your reasoning for putting the cards in this order?
   The scientifically accepted order is shown in the table below. Students' orders and reasoning will vary, but they should cite evidence from the cards.

10. Complete the rest of Table 1. In the middle column, briefly summarize the stages shown on the "typical" cards. In the far-right column, explain how what is shown on the "sickle cell" cards differs.
    Sample responses are shown in the table below.

Card Letter	What is shown on the "typical" card?	What changes on the "sickle cell" card?
D	***This is DNA that contains the* HBB *gene.***	***A nucleotide changed in the* HBB *gene, resulting in slightly different DNA.***
A	***The DNA with the* HBB *gene is transcribed to RNA through the process of transcription.***	***The RNA is transcribed from the DNA with the nucleotide change. So, the RNA also has a nucleotide change.***
C	***This is the mRNA produced through transcription of the* HBB *gene.***	***The mRNA has a nucleotide change.***
E	***The mRNA is translated to amino acids through the process of translation, which builds a polypeptide.***	***The polypeptide is built from the mRNA with the nucleotide change. So, the polypeptide has an amino acid change.***
B	***This is the HBB polypeptide produced through translation of the mRNA.***	***The HBB polypeptide has an amino acid change.***
G	***This is the hemoglobin molecule, which contains the HBB polypeptide.***	***The hemoglobin contains the HBB polypeptide with the amino acid change.***
H	***These are multiple hemoglobin molecules, which are separate from each other.***	***The hemoglobin molecules with the amino acid change stick together and form a larger molecule.***
F	***This is a red blood cell, which contains hemoglobin molecules.***	***The hemoglobin molecules stick together inside the red blood cell. The cell's structure becomes sickle shaped.***

11. Did you change your card order after working through the Click & Learn? If so, what changed and why?
Student answers will vary, but they should cite evidence from the cards.

12. Based on your cards:
    a. A change in which molecule(s) leads to changes in the resulting hemoglobin?
    Students should mention DNA. They may include additional molecules like mRNA.
    b. Which processes carry the effect of this change through to the resulting hemoglobin?
    Transcription and translation

PART 4: Transcribing and Translating

Procedure

Students transcribe and translate a short segment of the *HBB* gene for both the "typical" (wild-type) and "sickle cell" (mutant) genotypes. Make sure to **provide them with copies of the "Genetic Code Chart"** at this point, as they will need it to translate mRNA codons into amino acids.

If students have limited experience with base pairing rules and translating codons, guide them through an example first. If students require additional support, you may want to show them how to translate and transcribe the typical gene segment as a class, then allow them to do the sickle cell segment on their own.

Questions

13. Below the DNA sequence in Table 2, record the appropriate mRNA and amino acid sequences.

Table 2. Part of the typical *HBB* gene sequence.

Codon Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**
DNA	CAC	GTG	GAC	TGA	GGA	CTT	CTC
mRNA	***GUG***	***CAC***	***CUG***	***ACU***	***CCU***	***GAA***	***GAG***
Amino acid	***Val***	***His***	***Leu***	***Thr***	***Pro***	***Glu***	***Glu***

14. Below the DNA fragment in Table 3, record the appropriate mRNA and amino acid sequences.

Table 3. Part of the *HBB* gene sequence with the mutation that can lead to sickle cell disease.

Codon Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**
DNA	CAC	GTG	GAC	TGA	GGA	CAT	CTC
mRNA	***GUG***	***CAC***	***CUG***	***ACU***	***CCU***	***GUA***	***GAG***
Amino acid	***Val***	***His***	***Leu***	***Thr***	***Pro***	***Val***	***Glu***

15. Based on your results above:
    a. Describe any differences between the "typical" and "sickle cell" *HBB* gene sequences. Include the numbers of any affected codons.
    In codon 6, the "sickle cell" sequence has an A where the "typical" sequence had a T.
    b. Is the mutation that occurred an addition, deletion, substitution, or inversion?
    Substitution
    c. How did the mutation impact the resulting amino acid sequence?
    It changed one amino acid from Glu to Val.

PART 5: Modeling Proteins

Procedure

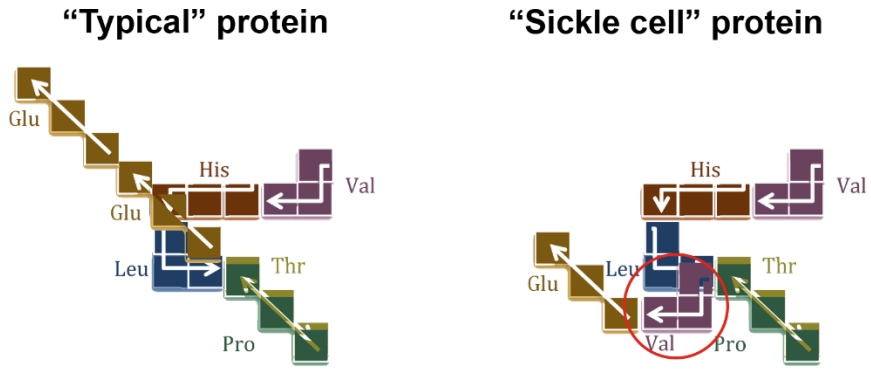
Students are asked to keep this driving question in mind as they work through this part of the activity:
How would the changes in protein structure alter the function of the hemoglobin molecules?

Students now construct models of the amino acid sequences that they translated in Part 4. The main takeaway is that a change in a DNA sequence may ultimately lead to a change in the amino acid sequence and, as a result, the protein structure.

The models can be built in a variety of ways, such as the following:

- Some students can build models for the "typical" sequence, while others build models for the "sickle cell" sequence. They can then compare their models. Or, if time allows, each student may build both models.
- The "Student Handout" provides instructions for drawing the models on **graph paper**. If you prefer, you can have students build their models using protein modeling kits or other hands-on materials (pipe cleaners, beads, etc.).
- If you are teaching online, students can build their models by rearranging images of the amino acid blocks. The "Protein Modeling" slides, provided on this resource's webpage as a PowerPoint or Google Slides, contain images and instructions that students can use.

Students should submit their completed models to you. Example models, based on the "Protein Modeling" slide images, are provided below. The red circle indicates the amino acid (Val) at which the shape of the "sickle cell" protein first changes from the "typical" one.



PART 6: Possible Treatments

Procedure

Though many things could be discussed here, it is important to maintain the focus of students on the processes illustrated in the previous parts of this activity.

Students begin by watching the video *A Genetic Treatment for Sickle Cell Disease* in its entirety, which will reinforce some of what they discovered during this activity and also allude to potential treatments for sickle cell disease. Students then read this article about fetal hemoglobin, which discusses possible treatments using methods like CRISPR-Cas9.

Next, students revisit the *Central Dogma & Genetic Medicine* Click & Learn to learn about the following treatment methods in genetic medicine:

- CRISPR-Cas9

- Gene therapy
- Gene switches (This section uses sickle cell disease as a case study, so it may be the easiest for students to complete.)
- Exon skipping
- RNA interference
- Small molecule drug

Assign each method in the Click & Learn to a student or group of students. Students should learn about the method from the Click & Learn, consider how it could be used to treat sickle cell disease, then share with the class. Students can record what others share in the table provided in the "Student Handout."

Ultimately, students should come away with the idea that not all mutations are harmful. Though the mutation that leads to sickle cell disease can be harmful, the mutation that allows cells to keep producing fetal hemoglobin is beneficial for individuals like Ceniya.

Questions

16. How is fetal hemoglobin different from adult hemoglobin?
    Fetal hemoglobin is more effective at transporting oxygen.
17. Why is this difference biologically important?
    It allows a fetus to get oxygen from their parent's blood.
18. What typically happens to the production of fetal hemoglobin after birth?
    Fetal hemoglobin is typically switched off by about six months of age.
19. Remember that a specific mutation in the *HBB* gene can lead to sickle cell disease. How is this similar to what has occurred in Ceniya's genetic "switch" (regulatory region in Figure 3) for fetal hemoglobin?
    Both have a mutation that can affect proteins.
20. Briefly describe your treatment method.
    Answers will vary.
21. Suggest how your method could be used to help treat sickle cell disease.
    Answers will vary. Students could consider how the methods may be able to edit sequences to repair or insert bases.
22. Are all mutations harmful? Explain, using evidence from the previous parts of this activity, how one mutation may lead to negative consequences, but another may be beneficial.
    No, not all mutations are harmful. The mutation in the* HBB *gene can be harmful because it may lead to sickle cell disease. However, the mutation that allows continued production of fetal hemoglobin is beneficial for individuals like Ceniya, since it keeps them from having the symptoms of sickle cell disease.

EXTENSION: Transfer Task with Huntington's Disease

Procedure

During this extension, which can be used as a formative assessment, students transfer their understanding of gene expression to a new context: Huntington's disease. Students read some background information, then observe patterns in gene sequences to make sense of the cause-and-effect relationships inherent in this disease.

Questions

1. How are the sequences similar to one another?
   All the sequences contain many repeats of CAG.
2. How are the sequences different from one another?
   Some sequences are longer than others because they have more CAG repeats.
3. How could these repeats affect the mRNA that is transcribed from these sequences?
   They would make the mRNA sequence longer.
4. How could these repeats affect the resulting protein? Explain using evidence from the previous parts of this activity.
   If the mRNA is longer, more amino acids will be added when it is translated. These extra amino acids may change the size and shape of the protein.
5. How could these changes affect the protein's ability to function?
   Changes in the protein's structure can change the protein's function. It may behave differently and/or lose its typical function.

OPTIONAL EXTENSIONS

You could follow this activity with other BioInteractive resources, including:

- *Trinucleotide Repeat:* This short animation may be used after students have completed the "Transfer Task." It shows how a trinucleotide repeat, like the one in Huntington's disease, is replicated and integrated into the genome.
- *Genetic Mutations and Disease:* Students may move on to this Click & Learn to dive deeper into different types of mutations and how they can lead to different diseases.
- *Central Dogma and Genetic Medicine:* Though students already examined parts of this Click & Learn during the activity, they may want to explore other parts to better understand the central dogma and how this understanding impacts potential treatments for genetic diseases.

CREDITS

Written by Jason Crean, HHMI; Kristin Rademaker
Edited by Esther Shyu, HHMI
Reviewed by Tatiana Tatum, Saint Xavier University, IL; Erica Flounders, Lyons Township High School, IL
Illustrations by Heather McDonald