

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

INTRODUCTION

In this activity, you will figure out why some people with a genetic condition that usually leads to sickle cell disease don't end up getting sick. As you investigate, you'll move through a series of tasks that involve observing, questioning, and using and developing models. These skills are essential in science and many other fields.

MATERIALS

- the "Gene Expression Cards"
- the "Genetic Code Chart"
- protein modeling materials (e.g., graph paper, slides, or a kit)
- a computer/device with online access

PART 1: Making Observations and Asking Questions

Watch this [video clip](#) to meet two girls, Ceniya and Ingrid, and learn about their cases.

The video mentions that Ceniya had a blood test right after she was born. Babies in the United States usually have blood tests and other exams to check for health issues. One type of blood test is a **blood smear**, which shows a person's blood cells.

Figure 1 shows blood smear results from individuals like Ceniya and Ingrid.

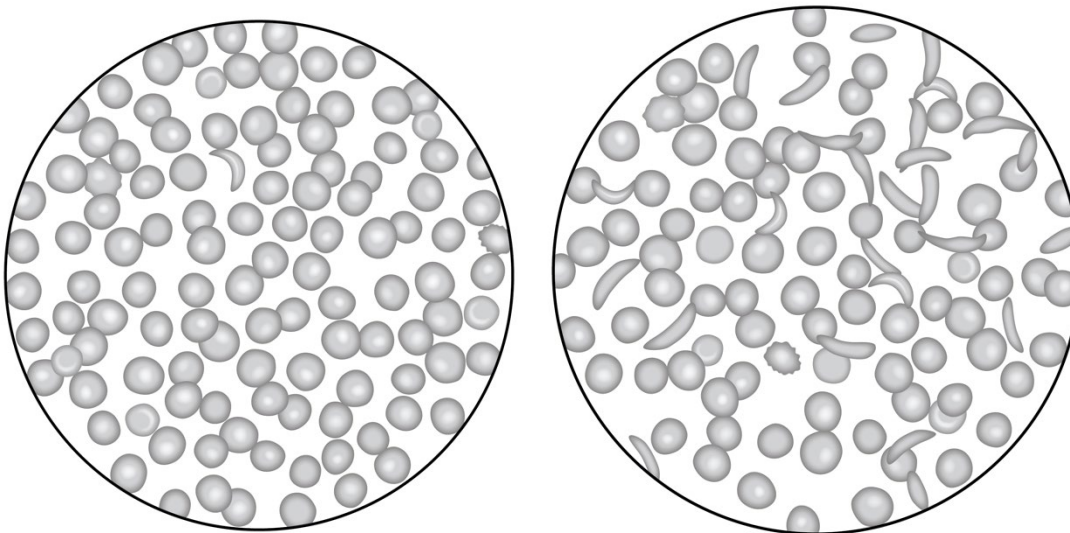


Figure 1. Illustrations of blood smears from individuals like (*left*) Ceniya and (*right*) Ingrid.

1. What do you notice about the two blood smears in Figure 1?

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

One type of blood cell, the **red blood cell**, contains a protein called **hemoglobin**, which it uses to carry oxygen to other cells. Red blood cells travel throughout the body via a large network of **blood vessels**: narrow tubes like veins, arteries, and capillaries that transport blood.

Consider the following questions. Be prepared to share your answers with others, or as directed by your instructor.

- *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?*

Figure 2 shows typical and sickled red blood cells, as well as the hemoglobin molecules found in each cell type.

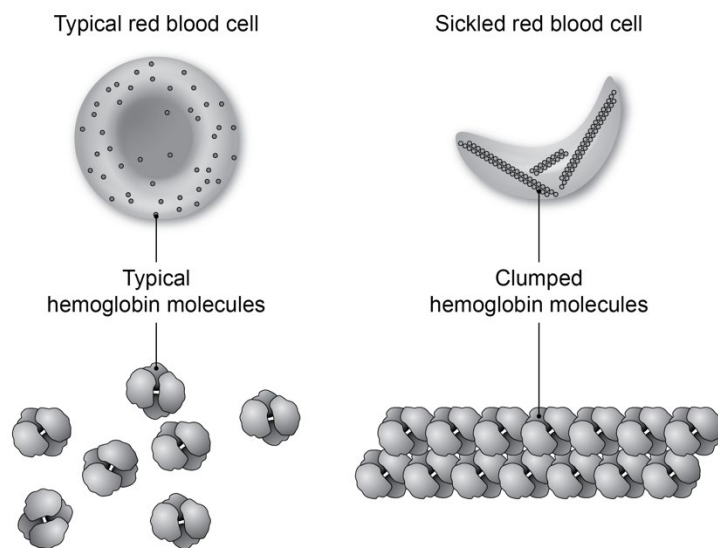


Figure 2. Typical and sickled red blood cells and their associated hemoglobin molecules.

5. For the two types of red blood cells in Figure 2:
 - a. What do the cells have in common?
 - b. How are the cells different?
6. What does hemoglobin do for 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?
 - b. How would the change you just described affect the body?

8. Hemoglobin is a type of protein.
 - a. Where does the body store the original instructions for building proteins?

 - b. What change in these instructions could cause the hemoglobin to clump?

PART 3: Gene Expression Cards

As you work through this part of the activity, keep this driving question in mind:

Where is the origin of the change that results in clumped hemoglobin molecules and sickled red blood cells?

To help make sense of the processes that produce hemoglobin, follow these steps:

- Get the “Gene Expression Cards” from your instructor. These are two sets of cards 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).
 - 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).
 - Sort the “typical” set of cards into the order in which you think the stages take place. Do your best to think through the different stages presented on the cards, discussing and arguing from evidence as needed. You will have a chance to revise your order later.
 - Next to each sorted card from the first set, place the card with the matching letter from the “sickle cell” set.
 - Once you’ve finalized your card order, answer the questions below.
9. Record the letters of the cards, in order, in the far-left column of Table 1. What is your reasoning for putting the cards in this order?
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.

Table 1. Order and explanations of the stages on the cards.

Card Letter	What is shown on the “typical” card?	What changes on the “sickle cell” card?

Now open the [Central Dogma and Genetic Medicine](#) Click & Learn. Select the “Central Dogma” section at the top, then work through each tab under that section. They will present a model of the same processes illustrated on the cards. You can then revise your own model (the order of your cards) based on this new information.

11. Did you change your card order after working through the Click & Learn? If so, what changed and why?

12. Based on your cards:

- a. A change in which molecule(s) leads to changes in the resulting hemoglobin?

- b. Which processes carry the effect of this change through to the resulting hemoglobin?

PART 4: Transcribing and Translating

Below are parts of the DNA sequence for the *HBB* gene. There are two tables: one for the typical gene and one for the gene with the mutation that can lead to sickle cell disease. The sequences are broken into groups of three nucleotides each, called **codons**.

For each table, you will transcribe the DNA into RNA. Then, you will translate the RNA into amino acids using the “**Genetic Code Chart**,” which will be provided by your instructor.

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							
Amino acid							

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							
Amino acid							

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.

- b. Is the mutation that occurred an addition, deletion, substitution, or inversion?

- c. How did the mutation impact the resulting amino acid sequence?

PART 5: Modeling Proteins

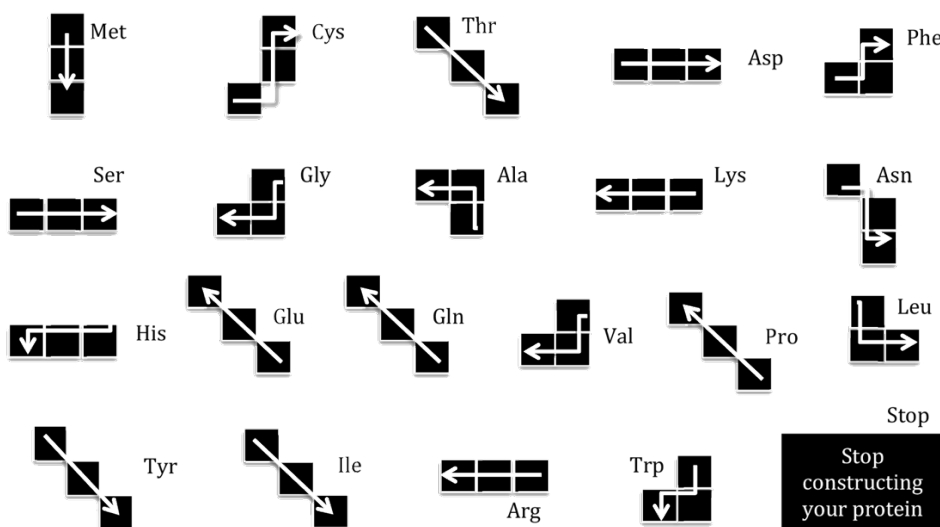
As you work through this part of the activity, keep this driving question in mind:

How would the changes in protein structure alter the function of the hemoglobin molecules?

After translating the amino acid sequences for the genes in Part 4, you will now construct models that represent the resulting protein segments. These models can help us better understand how a mutation can change the structure of a protein and thus the protein’s function. Follow the instructions below to construct your models.

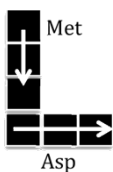
Step 1

Examine the amino acid key below, which you will use for your model. As shown, each amino acid has a specific shape represented by three boxes.

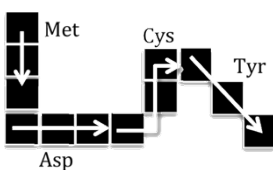


The first amino acid in a sequence can be drawn anywhere you like. Each new amino acid should be drawn with its *first* box (start of the arrow) connected to the *last* box (end of the arrow) of the previous amino acid, in the direction of the previous amino acid’s arrow.

Met, Asp would look like this (first box for Asp is connected *below* Met because Met’s arrow points *down*):



Met, Asp, Cys, Tyr would look like this:



Step 2

Fold a sheet of graph paper in half widthwise. You can start your model for the “typical” amino acid sequence (Table 2) in the center of the top half. You can add your model for the “sickle cell” amino acid sequence (Table 3) in the center of the bottom half.

Step 3

Using the key above, start drawing your models on the graph paper. For each amino acid, shade in the boxes on your graph paper and add a label for the amino acid three-letter abbreviation (Met, Asp, etc.).

You may want to use a different color or shading pattern for each amino acid. Note that some amino acids may overlap, because this model represents a three-dimensional molecule.

Step 4

Once both models are done, you can use them to determine where the shape of the protein segment has changed. **Circle, or otherwise indicate, the point at which the shape of the “sickle cell” protein first changes from the “typical” one.**

Step 5

Submit your models to your instructor.

PART 6: Possible Treatments

Individuals with only one copy of the *HBB* mutation do not have symptoms of sickle cell disease. Individuals with two copies of the *HBB* mutation, which is called the **sickle cell genotype**, typically *do* have symptoms.

Ceniya has the sickle cell genotype. So why doesn't she have symptoms? Let's find out.

Watch the [entire video](#) about Ceniya and Ingrid. Then read [this article](#) about fetal hemoglobin. Use what you've learned to answer the questions below.

16. How is fetal hemoglobin different from adult hemoglobin?

17. Why is this difference biologically important?

18. What typically happens to the production of fetal hemoglobin after birth?

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?

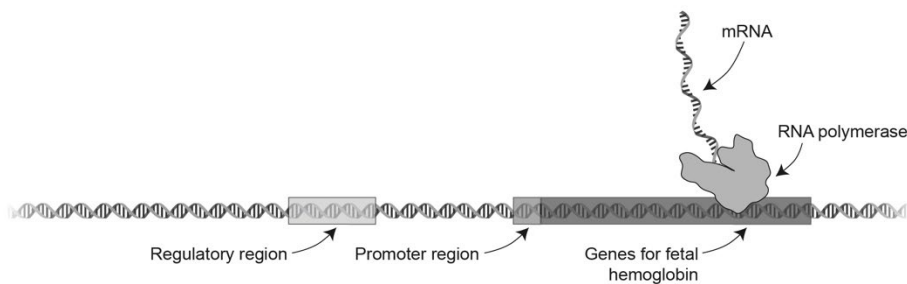


Figure 3. A model that illustrates the relative locations of the genes for fetal hemoglobin and their regulatory region.

Your instructor will assign you a potential method for treating genetic diseases. Open the [Central Dogma & Genetic Medicine](#) Click & Learn you visited in Part 3, then select the "**Genetic Medicine**" tab at the top right. Work through the section on your assigned method, discussing in small groups or as directed by your instructor.

20. Briefly describe your treatment method.

21. Suggest how your method could be used to help treat sickle cell disease.

22. You will now report out on your answers to the class, or as directed by your instructor. You can record the other methods that your class discussed in the table below.

Method	How it could be used to treat sickle cell disease

23. 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.

EXTENSION: Transfer Task with Huntington’s Disease

Huntington’s disease is a rare inherited disease that causes nerve cells in the brain to break down over time. This can lead to problems with movement, loss of thinking and memory skills, and eventually death. For those with the mutation that causes Huntington’s disease, symptoms usually appear from ages 30 to 40.

Since symptoms typically don’t appear until adulthood, scientists have developed other ways to test for Huntington’s disease. One scientist who contributed to this work is Nancy Wexler (Figure 4), who lost her mother to Huntington’s disease and has since been diagnosed with Huntington’s herself.



Figure 4. Nancy Wexler, a scientist who has spent many years studying Huntington’s disease. Her research has helped develop a genetic test for Huntington’s.

To test for Huntington’s disease, we need to know about the associated mutation. Below are DNA sequences from a gene related to Huntington’s disease. The sequences are from three individuals who may develop the disease but have not yet shown symptoms. Compare these sequences and think about what patterns emerge, then answer the questions that follow.

Individual #1:

GGAGCCCAGCA
GCAGCAGCAGAGC

Individual #2:

GGAGCCCAGCA
GCAGCAGCAGCAGCAGCAGAGC

Individual #3:

GGAGCCCAGCA
GCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGAGC

1. How are the sequences similar to one another?

2. How are the sequences different from one another?

Scientists have discovered that the short sequence CAG repeats continuously within this gene. Most people have fewer than 36 repeats and do not develop Huntington's disease. However, people with more than 36 repeats are more likely to have the disease.

3. How could these repeats affect the mRNA that is transcribed from these sequences?

4. How could these repeats affect the resulting protein? Explain using evidence from the previous parts of this activity.

5. How could these changes affect the protein's ability to function?