A Single Letter: How DNA Mutations Can Lead to Disease

Overview
This lesson allows students to gain an understanding of the relationship between DNA and proteins, and how DNA mutations can lead to disease. Students will be introduced to the hemoglobin protein and its role in the body, then explore how a change in one DNA "letter" in the hemoglobin gene leads to the development of sickle cell disease.

Key Search Words
biology, biomedical science, genetics, gene, protein, protein synthesis, genetic mutation, genotype, phenotype, hemoglobin, sickle cell disease

Learning Objectives
After completing this lesson, students will be able to
- Summarize the process of protein synthesis
- Describe the relationship between genes and proteins
- Explain how a genetic mutation can lead to disease

Curriculum Alignment
NGSS
HS-LS1-1: Construct an explanation based on evidence for how the structure of DNA determines the structure of proteins, which carry out the essential functions of life through systems of specialized cells.

Classroom time required
50 minutes

Materials & Technology
- Hemoglobin block sets
    - children's interlocking building blocks or wooden blocks (at least 1") craft beads, small magnets, epoxy or super glue
- Containers or boxes
- Student handout
- Computers for student research
- Colored pencils

Safety
This activity uses common, everyday materials typically found in a classroom. Students should take all typical safety precautions, such as moving carefully around the room. They should also be careful when shaking the blocks, so as not to accidentally hit someone or something with a block.

Teacher Preparation for Activity

Background information: The point mutation that causes the change in the hemoglobin structure is a single base substitution. This base change (from a thymine to an adenine), leads to an amino acid substitution (from glutamine to valine). Glutamine is a hydrophilic amino acid, while valine is hydrophobic. On the hemoglobin blocks, the beads represent glutamine, while the magnets represent valine. Hydrophobic valines will be attracted to one another in an "attempt" to avoid water in the environment. This will cause the abnormal hemoglobin molecules to form long chains, altering the shape of the red blood cell and leading to the symptoms of sickle cell disease. Additional information can be found at this NIH site.

Lesson preparation: If they have not already been made, the hemoglobin blocks will need to be constructed. Construction directions can be found here and in the appendices. Each student or student group will need two storage containers - one labeled "Normal Red Blood Cell" and one labeled "Sickled Red Blood Cell." Large plastic food storage containers or shoe boxes work well. Each should also receive 5-10 of *each* type of block - normal hemoglobin molecules (blocks with beads) and sickle cell hemoglobin molecules (blocks with magnets). The blocks should NOT be in the containers when students receive them.

Note: This lesson may be sensitive for some students. The teacher may choose to change the background story on the student handout, particularly if they teach students that have sickle cell disease or have family or friends who have the disease.

Student Preparation for Activity

Students should have a solid understanding of the relationship between genotype and phenotype. They should be able to describe how a gene is used to create a protein, including the processes of transcription and translation. They should also understand the difference between a hydrophilic and hydrophobic molecule.

Procedure

Lesson Activities	Approximate Time Required
Activating Strategy The teacher will 1. Distribute the following to each student: a. Normal hemoglobin (blocks with beads) and sickle cell hemoglobin (blocks with magnets) block sets b. "Cell" containers (one labeled "Normal Red Blood Cell" and one labeled "Sickled Red Blood Cell") 2. Explain to students that the containers represent red blood cells in a healthy individual and an individual with sickle cell disease. 3. Instruct students to begin by placing the blocks randomly around the bottom of their associated container. *Note: The blocks should not be touching.* 4. Explain to students that in individuals with sickle cell disease, the sickle shape of the red blood cells forms when the cells are deoxygenated. a. The teacher will represent this condition; when the teacher does some motion (for example, turning off the lights in the room) to represent deoxygenation, the students should begin shaking their box. b. Instruct students to observe what happens to the hemoglobin molecules in each "cell." Students should stop when the teacher makes a motion to stop (such as turning the lights back on). 5. Ask students to brainstorm how they think this demonstration relates to DNA, mutations, or disease.	10 minutes
Lesson Activity The teacher will 1. Instruct students to work in teams to complete the student handout. 2. Review the handout as a whole group.	25 minutes
Conclusion The teacher will 1. Model the block activity again for the class, explaining what is happening and why. 2. Lead a discussion of what happened during the block activity and how this relates to sickle cell diseases. Possible discussion questions: ● What impact does the single-base substitution mutation have on the hemoglobin of individuals with sickle cell disease? ● Why do the sickle cell hemoglobin molecules stick together (polymerize)? How does this relate to the amino acid substitution? ● How do the chains of abnormal hemoglobin impact the shape of the cell? How does this lead to symptoms of sickle cell disease?	15 minutes

Differentiation

The teacher may choose to add labels to the bead and magnets on the hemoglobin blocks, indicating the name of the amino acid. A pre-activity reviewing the process of transcription and translation may be necessary. Instead of sketching how each type of hemoglobin behaves, some students may benefit from a paper version of the block activity that they can glue down and keep.

Possible extension activities:

- Task students with creating their own model of how some other point mutation causes disease (e.g. cystic fibrosis, Tay Sachs, beta-thalassemia).
- Task students with creating an infographic to educate the public about sickle cell disease, its genetic cause, how it affects patients, and how it might be cured with current and/or future treatments, including gene therapy.

Assessment/Check for Understanding

Task students with creating a role-play skit to demonstrate how a DNA mutation can lead to cellular changes and disease. Students may take on the role of different molecules, such as DNA or normal/abnormal hemoglobin. The teacher may choose to use sickle cell disease, or task students with finding a different example to act out.

Required resources

Hemoglobin block sets
- children's interlocking building blocks or wooden blocks (at least 1")
- craft beads
- small magnets
- epoxy or super glue

Containers or boxes
Student handout
Computers for student research
Colored pencils

Sources

National Institutes of Health. (2022, March 22). *Sickle Cell Disease: Causes and Risk Factors*. National Heart, Lung, and Blood Institute. https://www.nhlbi.nih.gov/health/sickle-cell-disease/causes.

Mouagip. (2009, February 18). *The standard RNA codon table organized in a wheel*. Wikipedia Commons. https://en.wikipedia.org/wiki/DNA_and_RNA_codon_tables#/media/File:Aminoacids_table.svg

Appendices

1. Student Handout
2. Student Handout Key
3. Block Construction Directions

Name: _____

A Single Letter: How DNA Mutations Can Lead to Disease

Background

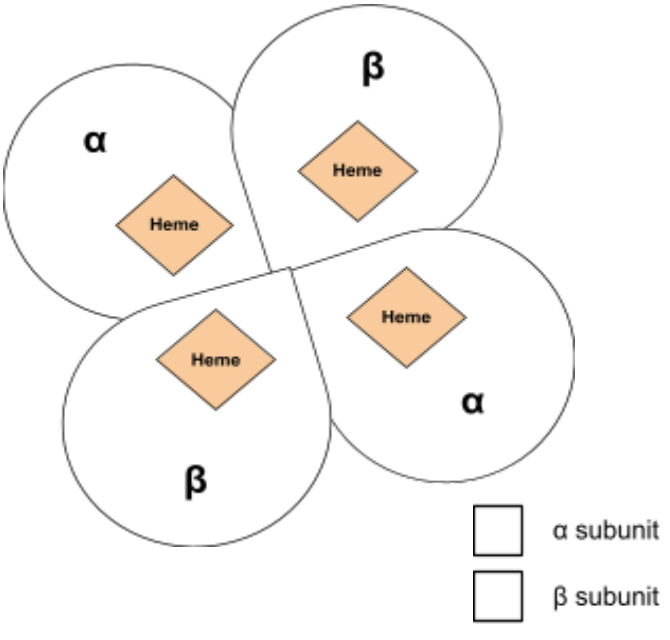
9-year old Jason Wright just woke up. His mother is sitting next to his hospital bed, talking to his doctor. Jason is in the hospital because he had a severe sickle cell disease **pain crisis.** During a pain crisis, irregularly shaped red blood cells get stuck in blood vessels, preventing oxygen from reaching body tissues. This can cause severe pain and swelling. Jason had severe pain in his legs and abdomen, so his mother brought him to the emergency department at the nearest hospital. Once Jason arrived at the emergency department, his care team began treatment by performing a **blood transfusion** and giving him medication to help reduce the pain. Jason was able to go home the next day, but his doctors warned him that it is likely this will happen again. How did this happen in the first place?

In this activity, you will explore the genetics of sickle cell disease, and see how a change in a single nucleotide led to the devastating disease that Jason is living with.

Part 1: Normal Hemoglobin

Sickle cell disease is caused by an abnormal version of a protein called **hemoglobin**. This protein's job is to carry oxygen to your body cells and to remove carbon dioxide waste. How is hemoglobin made in the body?

Remember that **genes** carry the instructions for making **proteins.** The hemoglobin protein is actually made of four subunit protein chains: two alpha (**α**) subunits and two beta (**β**) subunits. Figure 1 to the right shows a simplified hemoglobin molecule. Note that each subunit also has a **heme** group attached. This is where oxygen and carbon dioxide are carried. *On the diagram, color the α and β subunits different colors.*

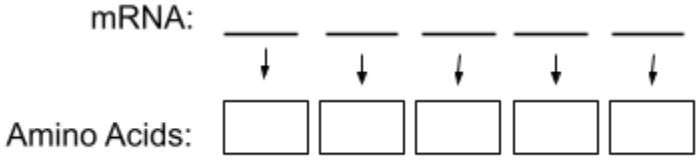


HBB Gene: GAC TGA GGA CTC CTC

mRNA: ____ ____ ____ ____ ____

The **α** and **β** subunits are coded for by the *HBA* and *HBB* genes, respectively. Remember that in order to make a protein from these genes, the DNA instructions must first be converted into an RNA "message" to be carried to a ribosome.
*In the space to the left, transcribe a small part of the HBB gene by using the DNA template sequence to create messenger RNA (**mRNA**). Don't forget, DNA uses thymine, but RNA uses uracil!*

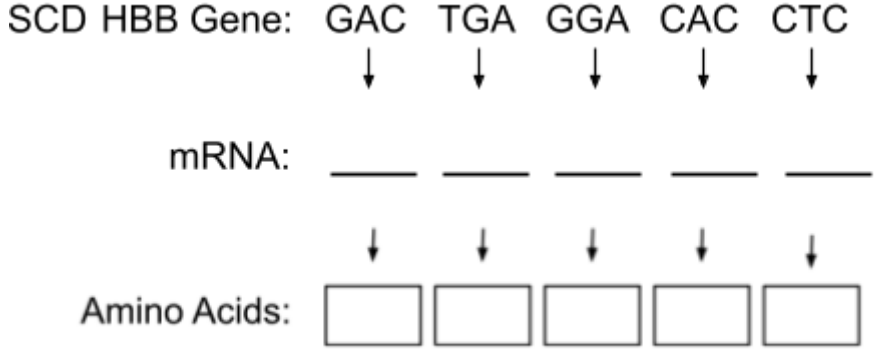
Now that you have transcribed part of the gene, it's time to create the hemoglobin β subunit protein. Remember that in order to create a protein, a ribosome must "read" the instructions contained in the mRNA. Ribosomes read mRNA in three-base segments known as **codons**. Each codon codes for a specific **amino acid**. Copy the mRNA strand you created on the front of this sheet in the space below. Then, use the attached codon chart to "translate" the mRNA into a hemoglobin β subunit protein.



Reflection Question 1: Note that amino acids are often coded for by more than one codon, with the third base in the sequence typically being the most diverse. What do you think the significance of this redundancy is?

Part 2: Sickle Cell Disease

Sickle cell disease is a recessive genetic disorder. The worst cases of sickle cell disease result when a person inherits a mutated *HBB* gene from both parents. Below is the same segment of the *HBB* gene that you transcribed and translated in Part 1. Begin by transcribing and translating the DNA sequence. Then, highlight any differences you see from the normal *HBB* gene in Part 1.



Reflection Question 2: In the case of sickle cell disease, a single-nucleotide substitution causes a different amino acid to be added to the hemoglobin β subunit protein chain. What if the affected nucleotide was completely removed instead of replaced? How would this impact the resulting protein chain?

Now that you've seen how the sickle cell disease mutation impacts the amino acid sequence of the hemoglobin β subunit, let's examine how this impacts red blood cells. Glutamic acid is a **hydrophilic** amino acid, whereas valine is a **hydrophobic** amino acid. In your own words, define these terms in the space below:

Hydrophilic:

Hydrophobic:

Return to the hemoglobin blocks from the start of this lesson. The black beads on the normal hemoglobin blocks represent glutamic acid. The magnets on the sickle cell hemoglobin represent valine. *Note that this is a simplified model; the actual locations of these amino acids within the hemoglobin molecule may be different.* Using what you know about hydrophobicity, **sketch** and **explain** how the block model represents what happens to normal *and* sickle cell hemoglobin. During periods of low oxygen, how do the different types of hemoglobin molecules behave differently? Why?

Research sickle cell disease. In the space below, **sketch** and **describe** how each type of hemoglobin protein affects the red blood cells that contain them. How does the altered hemoglobin structure lead to changes in the entire red blood cell structure?

Reflection Question 3: Research the symptoms of sickle cell disease. How does the altered red blood cell shape lead to the symptoms of sickle cell disease that Jason is experiencing? Why was Jason given a blood transfusion? **Explain** in the space below. Include **sketches** where appropriate.

Codon Chart

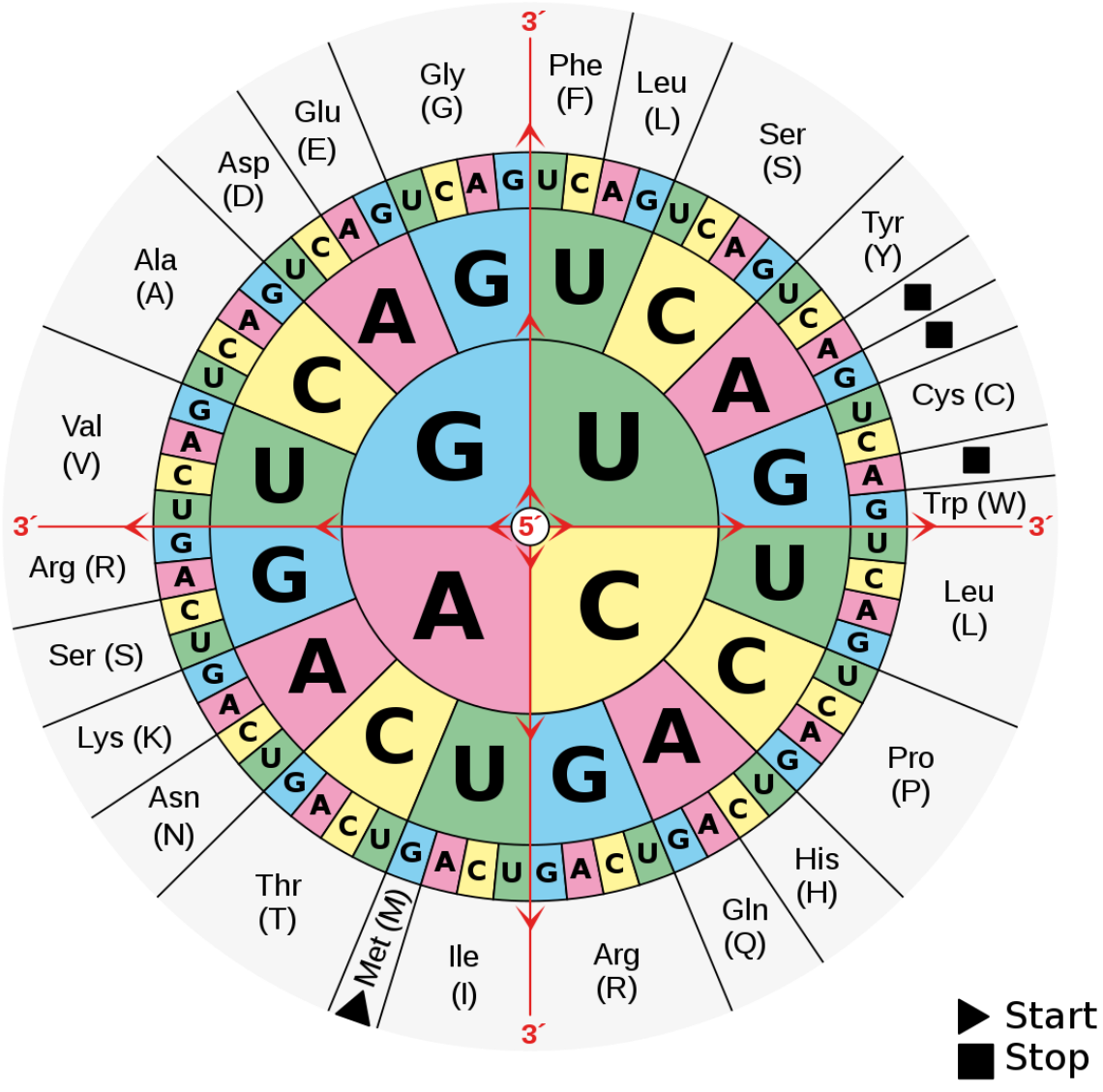


Image Source: Wikipedia Commons

Name: _____KEY_____

A Single Letter: How DNA Mutations Can Lead to Disease

Background

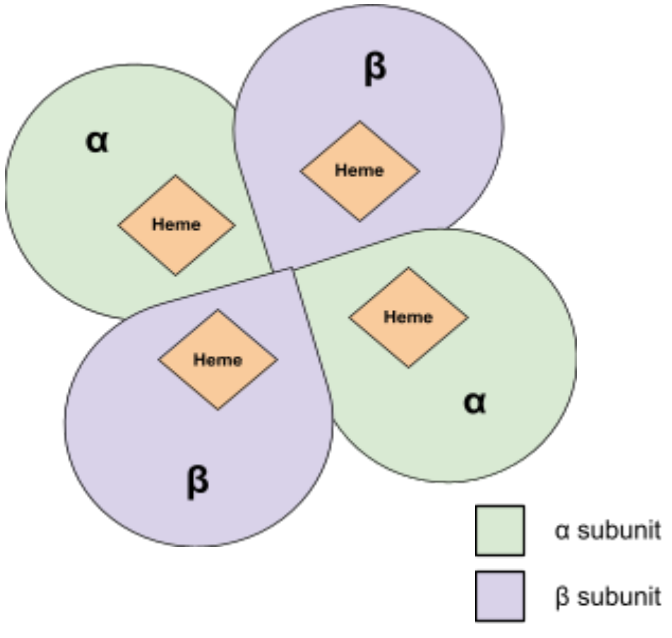
9-year old Jason Wright just woke up. His mother is sitting next to his hospital bed, talking to his doctor. Jason is in the hospital because he had a severe sickle cell disease **pain crisis.** During a pain crisis, irregularly shaped red blood cells get stuck in blood vessels, preventing oxygen from reaching body tissues. This can cause severe pain and swelling. Jason had severe pain in his legs and abdomen, so his mother brought him to the emergency department at the nearest hospital. Once Jason arrived at the emergency department, his care team began treatment by performing a **blood transfusion** and giving him medication to help reduce the pain. Jason was able to go home the next day, but his doctors warned him that it is likely this will happen again. How did this happen in the first place?

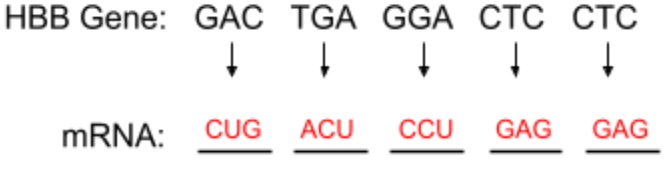
In this activity, you will explore the genetics of sickle cell disease, and see how a change in a single nucleotide led to the devastating disease that Jason is living with.

Part 1: Normal Hemoglobin

Sickle cell disease is caused by an abnormal version of a protein called **hemoglobin**. This protein's job is to carry oxygen to your body cells and to remove carbon dioxide waste. How is hemoglobin made in the body?

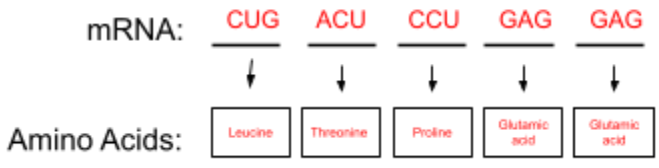
Remember that **genes** carry the instructions for making **proteins.** The hemoglobin protein is actually made of four subunit protein chains: two alpha (**α**) subunits and two beta (**β**) subunits. Figure 1 to the right shows a simplified hemoglobin molecule. Note that each subunit also has a **heme** group attached. This is where oxygen and carbon dioxide are carried. *On the diagram, color the α and β subunits different colors.*





The **α** and **β** subunits are coded for by the *HBA* and *HBB* genes, respectively. Remember that in order to make a protein from these genes, the DNA instructions must first be converted into an RNA "message" to be carried to a ribosome.
*In the space to the left, transcribe a small part of the HBB gene by using the DNA template sequence to create messenger RNA (**mRNA**). Don't forget, DNA uses thymine, but RNA uses uracil!*

Now that you have transcribed part of the gene, it's time to create the hemoglobin β subunit protein. Remember that in order to create a protein, a ribosome must "read" the instructions contained in the mRNA. Ribosomes read mRNA in three-base segments known as **codons**. Each codon codes for a specific **amino acid**. Copy the mRNA strand you created on the front of this sheet in the space below. Then, use the attached codon chart to "translate" the mRNA into a hemoglobin β subunit protein.

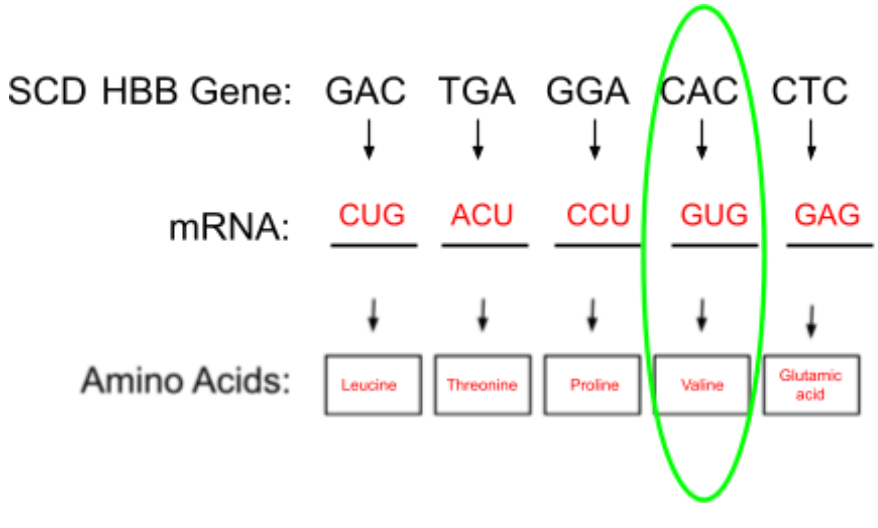


Reflection Question 1: Note that amino acids are often coded for by more than one codon, with the third base in the sequence typically being the most diverse. What do you think the significance of this redundancy is?

The diversity of the third base in many codons allows for "silent mutations," or mutations that don't impact the resulting amino acid sequence of the protein. If a mutation occurs in this third position, it will often lead to the same amino acid being coded, preventing any structural or functional changes to the resulting protein.

Part 2: Sickle Cell Disease

Sickle cell disease is a recessive genetic disorder. The worst cases of sickle cell disease result when a person inherits a mutated *HBB* gene from both parents. Below is the same segment of the *HBB* gene that you transcribed and translated in Part 1. Begin by transcribing and translating the DNA sequence. Then, highlight any differences you see from the normal *HBB* gene in Part 1.



Reflection Question 2: In the case of sickle cell disease, a single-nucleotide substitution causes a different amino acid to be added to the hemoglobin β subunit protein chain. What if the affected nucleotide was deleted instead of replaced? How would this impact the resulting protein chain?

If the nucleotide was deleted instead of replaced, it would cause a "frameshift mutation," moving the reading frame. This would impact every codon that came after that point, and likely most amino acids, as well. In the case of hemoglobin, this would lead to a non-functional hemoglobin molecule.

Now that you've seen how the sickle cell disease mutation impacts the amino acid sequence of the hemoglobin β subunit, let's examine how this impacts red blood cells. Glutamic acid is a **hydrophilic** amino acid, whereas valine is a **hydrophobic** amino acid. In your own words, define these terms in the space below:

Hydrophilic:

"Water-loving," is attracted to water

Hydrophobic:

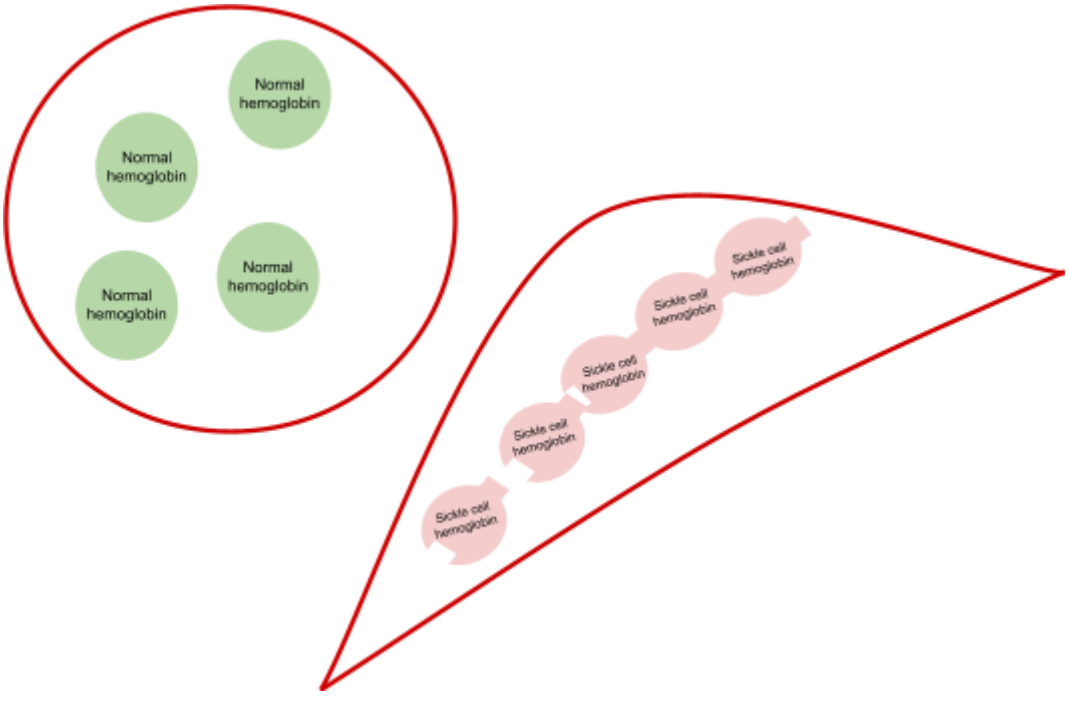
"Water-hating," is repelled by water

Return to the hemoglobin blocks from the start of this lesson. The black beads on the normal hemoglobin blocks represent glutamic acid. The magnets on the sickle cell hemoglobin represent valine. *Note that this is a simplified model; the actual locations of these amino acids within the hemoglobin molecule may be different.* Using what you know about hydrophobicity, **sketch** and **explain** how the block model represents what happens to normal *and* sickle cell hemoglobin. During periods of low oxygen, how do the different types of hemoglobin molecules behave differently? Why?

In normal hemoglobin molecules, the hydrophilic glutamic acid side chains are attracted to water. Since most of the intracellular environment is water, this means that the hemoglobin molecules can move around freely within the red blood cell. In sickle cell hemoglobin molecules, the valine side chains (represented by the magnets) are repelled by the cellular water and will self-assemble into long polymer chains as the valine side chains clump together.

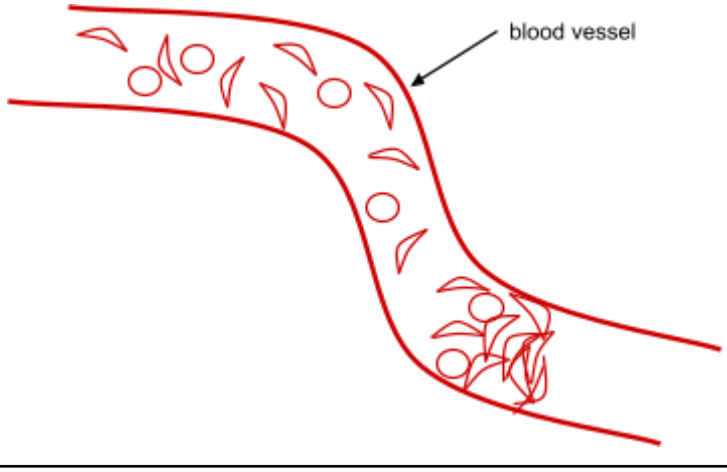
Research sickle cell disease. In the space below, **sketch** and **describe** how each type of hemoglobin protein affects the red blood cells that contain them. How does the altered hemoglobin structure lead to changes in the entire red blood cell structure?

In someone with sickle cell disease, the long chains of abnormal hemoglobin molecules that form push on and stretch out the red blood cell from within, leading to the sickled shape that is characteristic of the disease.



Reflection Question 3: Research the symptoms of sickle cell disease. How does the altered red blood cell shape lead to the symptoms of sickle cell disease that Jason is experiencing? Why was Jason given a blood transfusion? **Explain** in the space below. Include **sketches** where appropriate.

These sickle-shaped red blood cells become stuck in blood vessels, forming a blockage that prevents oxygen from reaching body tissues. The location(s) of the blockages will determine the location and severity of the pain, so Jason likely had blockages in vessels in his abdomen and legs. If a blockage occurs in the brain, it can even lead to a stroke. A blood transfusion temporarily provided Jason with healthy donor red blood cells, but those will eventually die.



Codon Chart

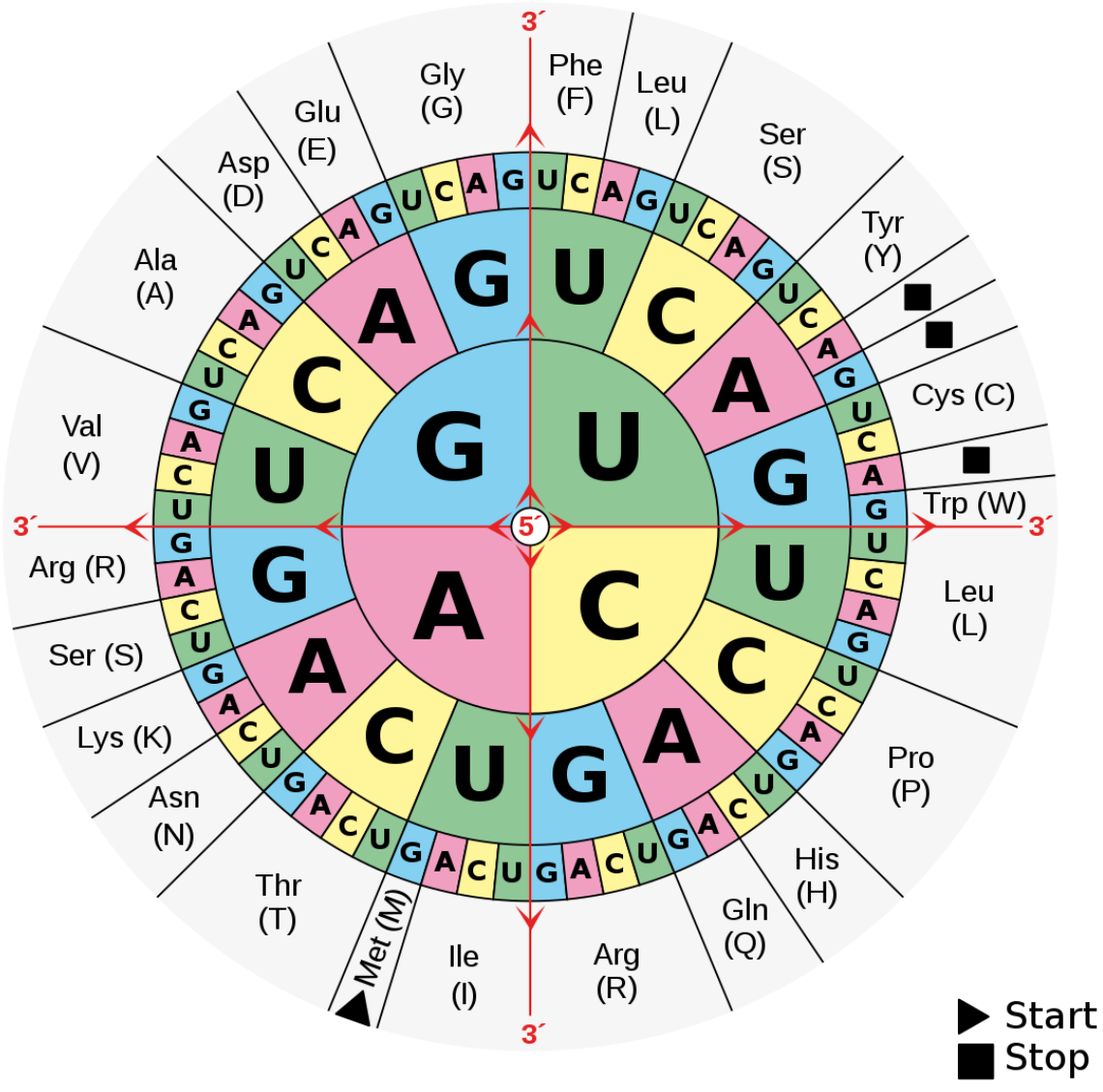


Image Source: Wikipedia Commons

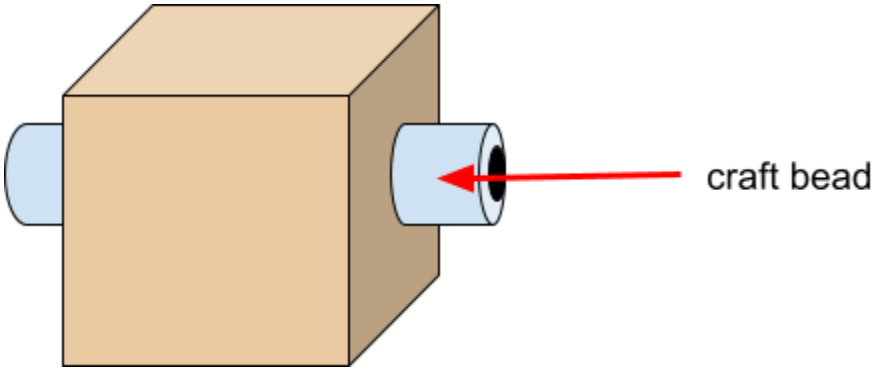
Block Construction Directions

Required Materials:

- children's interlocking building blocks or wooden blocks (at least 1")
- craft beads
- small magnets
- epoxy or super glue

Normal Hemoglobin Blocks

Glue two small craft beads on opposite sides of each of the normal hemoglobin blocks. These beads represent the amino acid glutamic acid. When the students add these to their box that represents a red blood cell and shake it, the blocks will not attach to each other. Use the same color for all blocks so that students understand that each bead represents the same type of amino acid. Alternatively, the teacher may choose to simply draw a circle or dot in place of the beads. *Each student or student group will need **5-10 normal hemoglobin blocks.***



Sickle Cell Hemoglobin Blocks

Glue two small magnets on opposite sides of each of the sickle cell hemoglobin blocks. These beads represent the amino acid valine. When the students add these to their box that represents a red blood cell and shake it, the magnets will attach, creating a chain of hemoglobin molecules. This represents the polymerization that occurs due to the hydrophobic nature of the valine amino acids. *Each student or student group will need **5-10 sickle cell hemoglobin blocks.***