

## **Teacher Preparation Notes for “How Genes Can Cause Disease – Introduction to Transcription and Translation”<sup>1</sup>**

To begin this hands-on, minds-on activity, students learn that different versions of a gene give the instructions for making different versions of a clotting protein, which result in normal blood clotting or hemophilia. Then, students learn how genes provide the instructions for making a protein via the processes of transcription and translation. They develop an understanding of the roles of RNA polymerase, the base-pairing rules, mRNA, tRNA and ribosomes. Finally, students use their learning about transcription and translation to understand how a change in a single nucleotide in the hemoglobin gene can result in sickle cell anemia. Throughout, students use the information in brief explanations, figures and videos to answer analysis and discussion questions. In addition, students use simple paper models to simulate the processes of transcription and translation.

You can use this activity to introduce students to transcription and translation or to reinforce and enhance student understanding. If you plan to use this activity to introduce transcription and translation, the activity will probably require 4-5 50-minute periods. If your students already have a basic understanding of transcription and translation, you will probably be able to complete the activity in three 50-minute periods.

This activity is intended for students who have been introduced to:

- the structure and function of proteins and DNA (For this purpose we recommend "Introduction to the Functions of Proteins and DNA" (<https://serendipstudio.org/exchange/bioactivities/proteins>).
- DNA replication and the base-pairing rules (For this purpose we recommend the analysis and discussion activity, "DNA Structure, Function and Replication" (<https://serendipstudio.org/exchange/bioactivities/DNA>) or the hands-on activity, "DNA" ([https://serendipstudio.org/sci\\_edu/waldron/#dna](https://serendipstudio.org/sci_edu/waldron/#dna)).

If you prefer an analysis and discussion version of this activity which omits the paper models, see “How Genes Can Cause Disease – Understanding Transcription and Translation” (<https://serendipstudio.org/exchange/bioactivities/trans>).

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<sup>1</sup> By Drs. Ingrid Waldron and Jennifer Doherty, Department of Biology, University of Pennsylvania, 2023. These Teacher Preparation Notes and the related Student Handout are available at [https://serendipstudio.org/sci\\_edu/waldron/#trans](https://serendipstudio.org/sci_edu/waldron/#trans). We thank Amy Dewees, Erica Foley and Lori Spindler for helpful suggestions and NancyLee Bergey, Holly Graham and Mr. Ippolito for sharing helpful activities which provided us with many useful ideas.

- Sources for Figures in Student Handout and Related Learning Activities (pages 15-16)
- Templates for Making Needed Supplies for Hands-on Modeling (pages 16-22)

### Learning Goals

In accord with the Next Generation Science Standards:<sup>2</sup>

- Students will gain understanding of the following Disciplinary Core Ideas
  - LS1.A, Structure and Function, including "Genes are regions in the DNA that contain the instructions that code for the formation of proteins, which carry out most of the work of cells."
  - LS3.A, Inheritance of Traits, including "DNA carries instructions for forming species characteristics."
- Students will engage in Science Practices, including:
  - "Constructing Explanations... Apply scientific ideas, principles and/or evidence to provide an explanation of phenomena..."
  - "Developing and Using Models... use multiple types of models to provide mechanistic accounts and/or predict phenomena, and move flexibly between model types..."
- This activity provides the opportunity to discuss the Crosscutting Concepts:
  - Structure and function, including "Students model complex and microscopic structures and systems and visualize how their function depends on the shapes, composition, and relationships among its parts."
  - Cause and effect: Mechanism and explanation, including understanding "causal relationships by examining what is known about smaller scale mechanisms within the system."
- This activity helps to prepare students to meet Performance Expectations
  - 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."
  - 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."

### Additional Content Learning Goals

Genes influence our phenotype by the following sequence of steps:

nucleotide sequence in the DNA of a **gene**

→ nucleotide sequence in messenger RNA (mRNA)

*transcription*

→ amino acid sequence in a protein

*translation*

→ structure and function of the protein

(e.g. normal hemoglobin vs. sickle cell hemoglobin)

→ person's **characteristics** or **traits**

(e.g. normal health vs. sickle cell anemia)

Transcription is the process that copies the message in a gene into a messenger RNA (mRNA) molecule that will provide the instructions for making a protein. The sequence of nucleotides in a gene in the DNA determines the sequence of nucleotides in the mRNA molecule. Each DNA nucleotide is matched with a complementary mRNA nucleotide in accord with the base-pairing

<sup>2</sup> <http://www.nextgenscience.org/sites/default/files/HS%20LS%20topics%20combined%206.13.13.pdf>

rules: C pairs with G and A pairs with U (in RNA) or T (in DNA). To make the mRNA molecule, the enzyme RNA polymerase adds the complementary nucleotides one-at-a-time to the growing mRNA molecule.

A comparison between transcription and DNA replication shows:

Similarities	Differences
<ul style="list-style-type: none"> <li>- Both processes use a DNA strand and the base-pairing rules to determine which nucleotide is added next.</li> <li>- Both processes produce a polymer of nucleotides (a nucleic acid).</li> <li>- Both transcription and replication are carried out by a polymerase enzyme which adds nucleotides one-at-a-time.</li> <li>- Both DNA and RNA contain the nucleotides, C (cytosine), G (guanine) and A (adenine).</li> </ul>	<ul style="list-style-type: none"> <li>- A single gene is transcribed into an mRNA molecule, whereas the whole chromosome is replicated.</li> <li>- Transcription produces a single-stranded mRNA molecule, whereas replication produces a double-stranded DNA molecule.</li> <li>- The enzyme for transcription is RNA polymerase, whereas the enzyme for DNA replication is DNA polymerase.</li> <li>- T (thymine) in DNA is replaced by U (uracil) in RNA.</li> </ul>

Translation is the process that makes proteins. mRNA carries the genetic message from the nucleus to the ribosomes where proteins are synthesized. The sequence of nucleotides in an mRNA molecule specifies the sequence of amino acids in a protein. The sequence of amino acids determines the structure and function of the protein.

Each triplet codon in the mRNA codes for a specific amino acid in the protein. For each type of codon, there is a type of tRNA with a complementary triplet anticodon. For each type of tRNA, there is a specific enzyme that attaches the correct amino acid for the anticodon in that tRNA and the complementary codon in the mRNA. Inside the ribosome, each codon in the mRNA is matched with the complementary anticodon in a tRNA, and the ribosome forms covalent bonds between the amino acids as they are added one-at-a-time to the growing protein.

### Supplies

Use the templates shown at the end of these Teacher Preparation Notes to make the supplies for this activity. You can prepare the supplies yourself or have them professionally printed and cut. We recommend printing the boards and pieces on coated card stock or coated cover.<sup>3</sup> You may want to have all the RNA pieces printed one color, the amino acids printed a different color, etc.

If your students are reasonably careful and they or you will remove the tape from the nucleotides and amino acids after each class, you should only need one set of supplies for each student group in your largest class (plus some extras in case of loss or damage). Otherwise, you may need to have enough of the strips and pieces for each student group in all of your classes. Each group of 2-4 students will need:

- a page labeled Nucleus and a page labeled Ribosome (To encourage accurate modeling, we recommend that you cut out the 4 mm x 30 mm slots in the nucleus and ribosome pages and have your students insert the DNA and mRNA molecules through these slots so that initially only the beginning of the DNA or mRNA molecule can be seen.)
- Beginning of Hemoglobin Gene DNA strip (cut the page in strips)
- Second Part of mRNA strip (cut the page in strips)

<sup>3</sup> If you are able to have the pages and pieces laminated, they will be more durable for repeated use. The most economical alternative is to have both boards and all the pieces printed on white coated cardstock or coated cover.

- 9 RNA nucleotides (each student group will need 1A, 2 C, 3 G, and 3 U; cut the page in small squares, one letter per square)
- 6 tRNA molecules (cut each tRNA rectangle to include the words "Amino Acid" and the three nucleotides directly below Amino Acid)
- 6 amino acids (cut into rectangles, one amino acid per rectangle)
- transparent tape

Depending on your students, you may want to prepare a packet with all the supplies for each student group or you may want to dole out supplies as needed for each step in the simulation and have the 9 RNA nucleotides, the 6 tRNA molecules and the 6 amino acids for each student group in three separate small envelopes.

## **Recommendations for Implementation and Background Biology**

### General

To maximize student learning and participation, we recommend that you have your students work in pairs to answer each group of related questions. Student learning is increased when students discuss scientific concepts to develop answers to challenging questions. After your students have answered each group of related questions, we recommend that you have a class discussion to probe student thinking and help students develop a sound understanding of the concepts and information covered. You may want to offer students the opportunity to prepare revised versions of their answers to key questions in order to consolidate accurate understanding.

In the Student Handout, numbers in bold indicate questions for the students to answer, and capital letters in bold indicate steps in the modeling procedures.

The PDF of the Student Handout shows the correct format; please check this if you use the Word document to make revisions.

A key is available upon request to Ingrid Waldron ([iwaldron@upenn.edu](mailto:iwaldron@upenn.edu)). The following paragraphs provide additional instructional suggestions and background information – some for inclusion in your class discussions and some to provide you with relevant background that may be useful for your understanding and/or for responding to student questions.

### How can genes cause health problems?

The Student Handout includes multiple simplifications. For example, the Student Handout discusses two disorders that result from mutations of a single gene, but most human diseases and characteristics are influenced by multiple genetic and environmental factors. Also, a gene is defined as “a segment of DNA that gives the instructions for making a protein” (on page 1 of the Student Handout). A more sophisticated contemporary definition of a gene is “part of a DNA molecule that codes for an RNA molecule, which may be messenger RNA that codes for the sequence of amino acids in one or more proteins, ribosomal RNA, transfer RNA or regulatory RNA”. There is no single universally agreed-upon definition of a gene at this time. For additional information about the challenges and complexities of defining a gene, see <http://www.biologyreference.com/Fo-Gr/Gene.html>.

Hemophilia is a bleeding disorder due to defective blood clot formation. The video recommended on page 1 of the Student Handout provides a good two-minute introduction. A more comprehensive, highly readable and informative introduction is available at <https://learn.genetics.utah.edu/content/genetics/hemophilia/>.

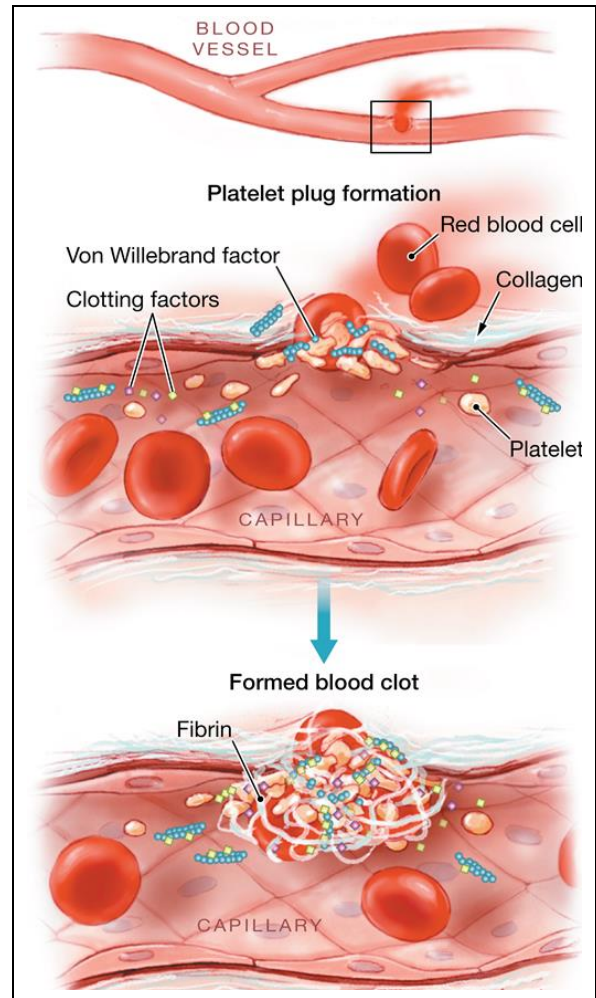
In most people, an injury to a blood vessel triggers the activation of a series of clotting proteins which results in the formation of a clot. Mutated versions of the gene for one of these clotting proteins can result in a protein that does not function properly. If the mutation results in an early stop codon in the gene, then no clotting protein may be produced. When one of the blood-clotting proteins is defective or absent, it takes an abnormally long time for a blood clot to form

(<https://courses.lumenlearning.com/ap2/chapter/hemostasis/>).

Different alleles of the gene for a clotting factor cause different degrees of loss of function for the clotting protein, and this results in different degrees of severity of hemophilia. In mild cases, a person may bleed longer than normal after serious injury or surgery. In severe cases, a person may experience spontaneous internal bleeding (e.g. in the joints), frequent large bruises, and nosebleeds that are hard to stop. Severe cases of hemophilia are treated with infusions of normal clotting factor, as often as two or three times per week.

Researchers are developing gene therapies which could provide more long-term relief of symptoms (<https://www.nature.com/articles/d41586-022-04327-7>;

<https://www.ema.europa.eu/en/news/first-gene-therapy-treat-severe-haemophilia>).



The most common causes of hemophilia are alleles of one of two clotting factor genes on the X chromosome. Since a male has only one X chromosome in each cell, if his X chromosome has an allele that codes for defective clotting protein, he will not be able to make blood clots properly and he will have hemophilia. In contrast, a female has two X chromosomes; since the alleles for defective clotting protein are recessive, a woman generally only has hemophilia if both of her X chromosomes have a recessive allele for defective clotting protein.<sup>4</sup> Thus, almost all people with hemophilia are male, and females may be heterozygous carriers. The chart on page 1 of the Student Handout does not include the fact that the alleles for hemophilia are sex-linked recessive. If your students are already familiar with the concepts of recessive alleles and homozygous vs. heterozygous individuals, you may want to include this information in your discussion. Otherwise, we recommend that you postpone discussion of these issues to our Genetics activity ([https://serendipstudio.org/sci\\_edu/waldron/#genetics](https://serendipstudio.org/sci_edu/waldron/#genetics)).

<sup>4</sup> In most heterozygous women, approximately half of her liver cells have the X chromosome with the normal allele active (due to random inactivation of one X chromosome in each cell), and these cells are able to make enough blood clotting protein to prevent hemophilia. However, in ~30% of heterozygous females, random inactivation of one X chromosome in each cell has resulted in less than half the cells in her liver having the X chromosome with the allele for the normal clotting protein active and these women may have mild hemophilia (e.g. with heavy prolonged menstrual bleeding and frequent nosebleeds).

### How does a gene give the instructions for making a protein?

This section introduces transcription and translation as the processes by which a gene gives the instructions for making for making a protein. This introductory section provides a helpful context for learning more about transcription and translation in subsequent sections. Students are reminded that DNA and RNA are polymers of nucleotides, whereas proteins are polymers of amino acids. To reinforce the analogies between transcription and copying a sentence and between biological translation and linguistic translation, you may want to include the following challenge question.

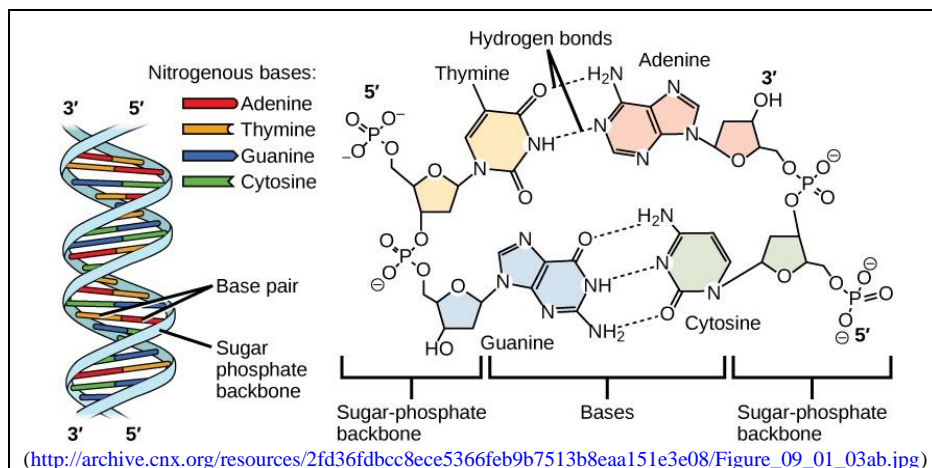
**5c.** Why is translation a good name for the process that makes a protein, but not a good name for the process that makes mRNA?

If your students are not familiar with the structure of mRNA, you may want to point out that mRNA is single-stranded, in contrast to the double-stranded DNA. The recommended 5-minute video, “What is DNA and how does it work?” (<http://statedclearly.com/videos/what-is-dna/>), will reinforce student understanding of the concepts in this section of the Student Handout.

### How does transcription make mRNA?

This section introduces the basic process of transcription. Many specific aspects of transcription are omitted to ensure that students develop a sound understanding of the basic process. This section provides an opportunity to discuss the Structure and Function Crosscutting Concept, including “Students model complex and microscopic structures and systems and visualize how their function depends on the shapes, composition, and relationships among its parts.” Suggestions for the implementation of the hands-on modeling procedures are presented in the next section of these Teacher Preparation Notes.

You can use this figure if your students need a refresher about DNA structure or why the rules that describe which nucleotides are complementary are called the base-pairing rules.<sup>5</sup>

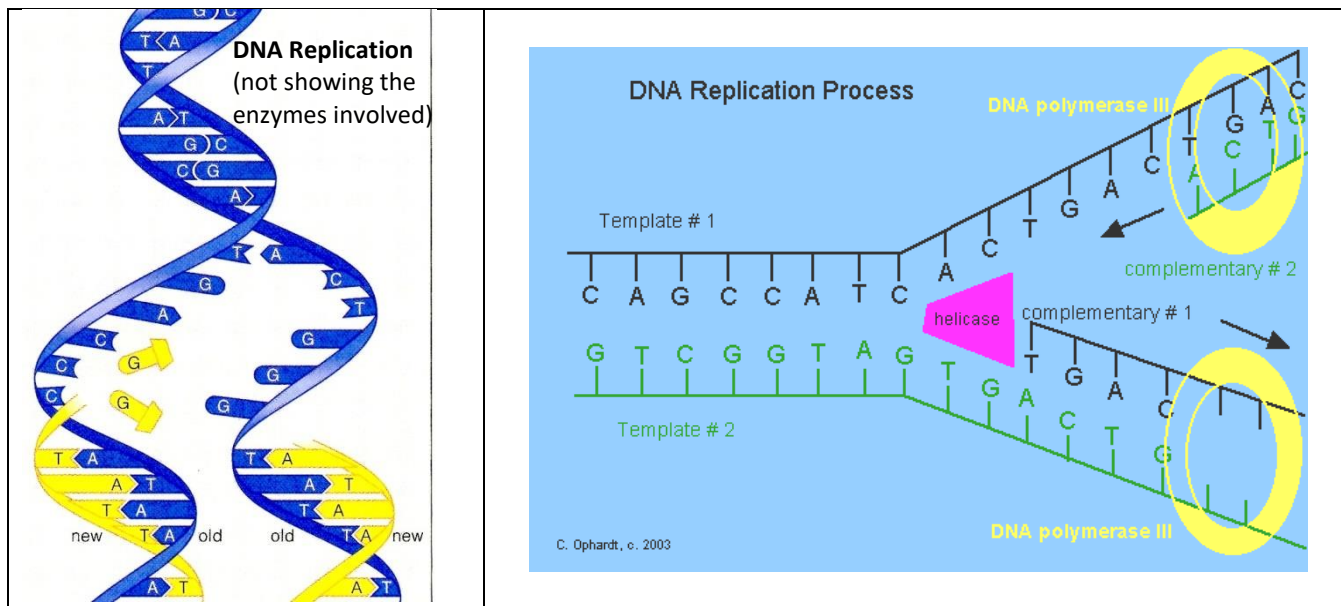


The top of page 6 of the Student Handout recommends a 2-minute animation that reviews the process of transcription (<https://www.biointeractive.org/classroom-resources/dna-transcription-basic-detail>). This animation shows the dynamic nature of transcription, which adds 50 nucleotides per second to a growing RNA molecule. Your students may ask about the transcription factors shown at the beginning of this animation. Because the Student Handout provides a basic introduction to transcription and translation, it does not mention transcription factors. Transcription factors initiate and regulate the transcription of a gene by regulating the

<sup>5</sup> To help students understand how the mRNA separates from the DNA during transcription, you may want to remind your students that the bonds within each DNA or RNA strand are covalent bonds, but base pairing involves weaker hydrogen bonds which are more readily broken. (There are many many hydrogen bonds connecting the two strands of a DNA molecule, which is why the bonds between the two DNA strands are quite stable.)

activity of RNA polymerase (which is shown in blue in the animation) (<https://www.khanacademy.org/science/biology/gene-regulation/gene-regulation-in-eukaryotes/a/eukaryotic-transcription-factors>).<sup>6</sup>

Suggestions concerning question 13 are provided on page 9 of these Teacher Preparation Notes. In questions 14-15, students compare transcription to DNA replication. You can use one of the figures below to remind your students about the process of DNA replication.



### Modeling Procedures for the Transcription and Translation Sections

We recommend that you have your students work in pairs or in groups of four to model transcription and translation. Each student should have a specific role in the modeling procedures. For example, in a group of four students modeling transcription (page 5 in the Student Handout), one should read the instructions for the RNA polymerase, one should act as the RNA polymerase, one should read the instructions for the cytoplasm, and one should act as the cytoplasm.

We find that you have to be very explicit in your instructions for the modeling procedure in order to prevent students from racing ahead in ways that undermine the learning goals. You will probably want to demonstrate the steps in the modeling procedure. Also, you may want to show your students an animation which summarizes the modeling procedure (available at <https://serendipstudio.org/exchange/waldron/gene>; prepared by Erik Johnson, River Valley High School).

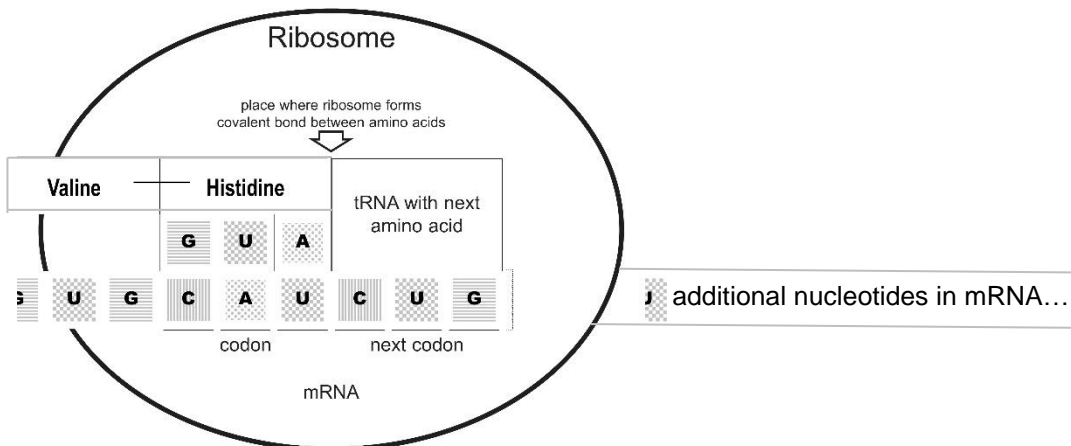
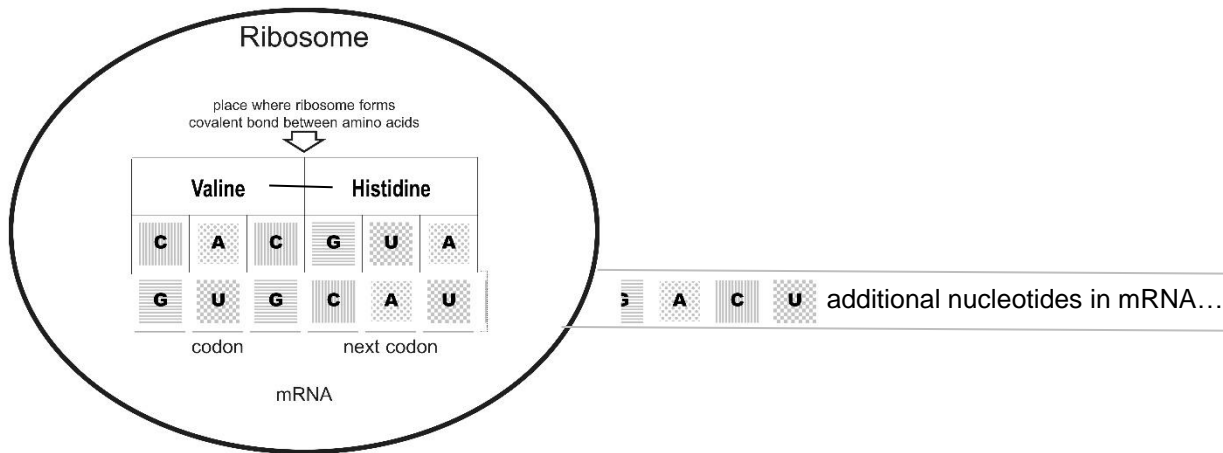
To use this modeling activity to facilitate student understanding of how transcription takes place, students should add each nucleotide one at a time, mimicking the actual activity of RNA polymerase. Some students will want to lay out all the mRNA nucleotides and tape them together all at once; this is more efficient in getting the task done, but less effective in modeling and understanding the real biological process. Similarly, during translation, students should mimic the actual function of the ribosome by bringing in each tRNA with its amino acid one at a time. To encourage students to do the modeling correctly, we recommend that you require your

<sup>6</sup> For an introduction to the interactions between transcription factors and regions of the DNA, see <https://www.biointeractive.org/classroom-resources/regulation-eukaryotic-dna-transcription>.

students to check off each box before proceeding to the next step, and make sure they use the slots in the nucleus and ribosome pages.

To help your students understand why RNA polymerase adds nucleotides one at a time, you may want to point out that a typical protein has hundreds of amino acids so a typical mRNA has hundreds or thousands of nucleotides. Have your students think about the problems that would arise if natural selection or a molecular biologist tried to design an enzyme that could simultaneously arrange and join together the whole sequence of hundreds or thousands of nucleotides in an mRNA molecule. Similarly, to help your students understand why ribosomes add amino acids one at a time, you may want to have your students think about the problems of trying to design a ribosome that could simultaneously arrange and bond together the whole sequence of amino acids in a protein, especially considering that there are many thousands of different types of proteins in a cell.

In the Procedure for Modeling Translation, one of the students in each student group is designated as “cytoplasm”. We have chosen to use this more familiar term instead of cytosol, which would be more accurate since the ribosome is part of the cytoplasm. Page 9 of the Student Handout has a diagram which shows the students how their model ribosome should look after the first few steps in modeling translation. The following diagrams show how the model ribosome should look during the next few steps. The line between the amino acids represents the tape which represents the covalent peptide bond.



Although the modeling procedure mimics important aspects of transcription and translation, some aspects of the modeling procedures are unrealistic. Some examples are noted on pages 5



and 8 of the Student Handout. For example, the relative dimensions of molecules and organelles are distorted. As the students create their mRNA, both the DNA and the mRNA will extend beyond the nucleus, whereas in real eukaryotic cells transcription takes place entirely within the nucleus. The DNA molecule is about 250,000 times longer than the cell's diameter, but the flexible DNA is coiled and folded within the nucleus (as shown in the video "What is DNA and how does it work?"; see bottom of page 3 of the Student Handout). Also, during transcription in a cell, multiple RNA nucleotides are constantly entering and leaving the RNA polymerase. For each DNA nucleotide, only the complementary RNA nucleotide that has the right shape and charges to form hydrogen bonds with that specific DNA nucleotide will remain in place and be covalently bonded to the preceding RNA nucleotide. Similarly, for translation, tRNA molecules enter the ribosome at random; non-matching tRNA will enter and then leave the ribosome; when a tRNA with an anti-codon that is complementary to the mRNA codon enters the ribosome, the amino acid carried by that tRNA will be covalently bonded to the growing polypeptide.

### Synthesis Questions and General Comments on Transcription and Translation Sections

To encourage students to actively synthesize their own basic understanding of transcription and translation, we strongly recommend having your students complete questions 13 and 24 (on pages 6 and 9 of the Student Handout), perhaps as a homework assignment if you do not have enough class time. If you feel that these questions will be very challenging for your students, we have several suggestions to help your students succeed.

- If your students have trouble learning vocabulary, you may want to precede questions 13 and 24 with questions that ask for definitions of the terms listed (or perhaps a matching question in which you provide your preferred definitions for these terms).
- You may want to suggest that students review page 4 of the Student Handout as they plan their answers for question 13. Similarly, you may want to suggest that students review page 7 of the Student Handout as they plan their answers for question 24.
- As an introduction to these questions, you may want to provide a concept map or graphic organizer for your students to review or complete (e.g. [http://lsaportfolio.weebly.com/uploads/5/8/7/4/58741929/8859660\\_orig.png](http://lsaportfolio.weebly.com/uploads/5/8/7/4/58741929/8859660_orig.png) or [https://o.quizlet.com/atJ6mLwUywPTs2a-U8.vwg\\_b.png](https://o.quizlet.com/atJ6mLwUywPTs2a-U8.vwg_b.png)).
- You could provide the beginning of a first sentence to help your students get started.
- We recommend that students work in pairs to develop an answer.

After class discussions of question 13 and 24, we recommend that you have each student revise his/her answers to the question so he/she can consolidate an accurate understanding of transcription and translation.

This activity includes several different types of models of transcription and translation. A model is a simplified representation of a real-world phenomenon. Like all models, the models in this activity involve simplifications which help to clarify important points, but also limit the accuracy of the models as representations of the actual complex biological processes. Different types of models serve different purposes for learning about and understanding the processes of transcription and translation. The figures on page 2 of the Student Handout provide a basic framework that provides a context for understanding the complexities that follow. The figures on pages 4 and 7 show more specifics of how transcription and translation are accomplished in the cell. The recommended videos illustrate the dynamic nature of these processes. Finally, the hands-on modeling procedures help to engage students in actively mimicking and understanding these processes.

To ensure that students develop a good understanding of the basic processes of transcription and translation, this activity omits many complexities. For example, the Student Handout does *not* mention:

- the initiation and termination phases of transcription and translation (some information on the initiation phase of transcription is given on the previous page)
- introns, exons and splicing  
([https://bio.libretexts.org/Bookshelves/Biochemistry/Book%3A\\_Biochemistry\\_Free\\_and\\_Easy\\_\(Ahern\\_and\\_Rajagopal\)/05%3A\\_Flow\\_of\\_Genetic\\_Information/5.05%3A\\_RNA\\_Processing](https://bio.libretexts.org/Bookshelves/Biochemistry/Book%3A_Biochemistry_Free_and_Easy_(Ahern_and_Rajagopal)/05%3A_Flow_of_Genetic_Information/5.05%3A_RNA_Processing))
- how polypeptides fold and may combine with other polypeptides to form proteins  
([https://chem.libretexts.org/Bookshelves/Biological\\_Chemistry/Supplemental\\_Modules\\_\(Biological\\_Chemistry\)/Proteins/Protein\\_Structure/Protein\\_Folding](https://chem.libretexts.org/Bookshelves/Biological_Chemistry/Supplemental_Modules_(Biological_Chemistry)/Proteins/Protein_Structure/Protein_Folding))
- transcription produces multiple copies of mRNA from a gene; multiple ribosomes move along an mRNA molecule, producing multiple copies of the polypeptide
- differences in which genes are transcribed in different types of cells, which correspond to the differences in the types of proteins in different types of cells (e.g., hemoglobin abundant in red blood cells vs. contractile proteins abundant in muscle cells)  
(<https://www.khanacademy.org/science/biology/gene-regulation/gene-regulation-in-eukaryotes/a/overview-of-eukaryotic-gene-regulation>)
- a standard genetic code chart or codon wheel. (Our preference is to use the abbreviated codon chart on page 11 of the Student Handout, so students can concentrate on understanding the basic process of translation, and then, if desired, practice using the codon wheel in a separate activity. For example, in the analysis and discussion activity, "Mutations and Muscular Dystrophy"  
(<https://serendipstudio.org/exchange/bioactivities/mutation>), students review transcription and translation, use a codon wheel to analyze different types of mutations, and evaluate which types of mutation result in the more severe Duchenne muscular dystrophy vs. the milder Becker muscular dystrophy.)

If your students already have a good grasp of the basics of transcription and translation, you may want to include some of these additional complexities.

#### Translation – How does mRNA give the instructions for making a protein?

We suggest that you introduce this section by asking your students which would be more challenging – copying a sentence or translating it and writing down the translated sentence? Just as translating a sentence is more complex than copying it, molecular translation is more complex than transcription. In transcription, the shape and chemical structure of each mRNA nucleotide matches the shape and chemical structure of the complementary DNA nucleotide. In contrast, in translation, the shape and chemical structure of each amino acid does *not* match the shape and chemical structure of the corresponding mRNA codon. In this section, students will learn how translation is accomplished inside a cell.

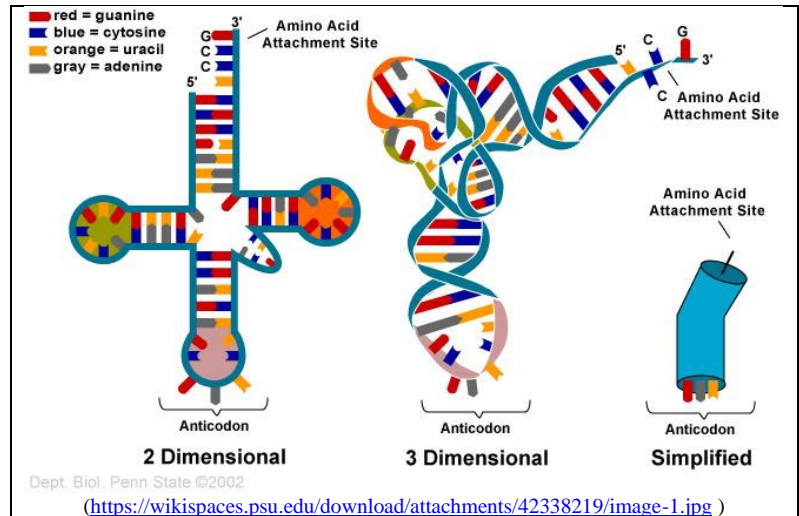
As you discuss codons, it may be helpful to make an analogy between using different combinations of the 4 nucleotides to code for each of the 20 different types of amino acids and using different combinations of 26 letters to make thousands of different words. One big difference is that each codon is exactly 3 nucleotides long, whereas the number of letters in a word is variable. There are  $4 \times 4 \times 4 = 64$  codons, compared to only 20 amino acids.<sup>7</sup> As would

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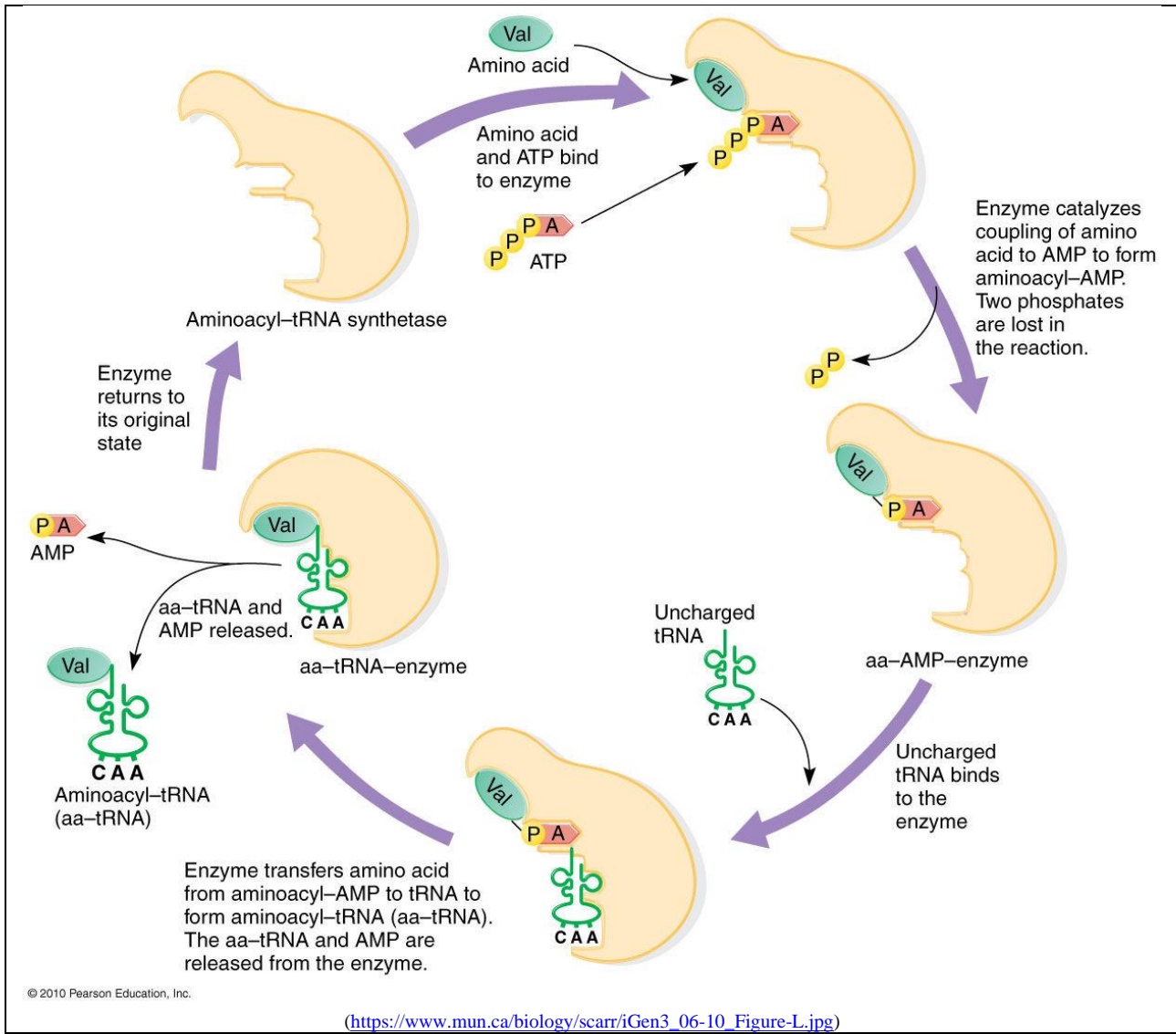
<sup>7</sup> In some organisms (including humans) there is a twenty-first amino acid which is incorporated in some proteins (<https://en.wikipedia.org/wiki/Selenocysteine>).

be expected, there can be multiple codons for a single amino acid. (There is a start codon, and there are also three stop codons.)

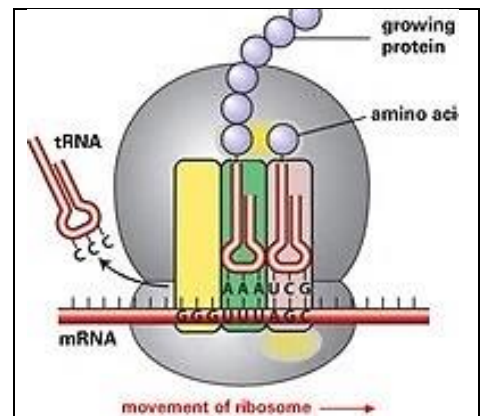
In humans, there are 48 different types of tRNA, compared to 61 different codons for amino acids in mRNA. Some types of tRNA have anticodons that are able to match with two different codons that have the same first two nucleotides but differ in the third nucleotide (both are codons for the same amino acid). This figure shows how a tRNA molecule folds into an upside-down L shape.



As discussed on pages 7-8 of the Student Handout, the tRNA molecules play a central role in translating from the nucleotide sequence in mRNA to the amino acid sequence in proteins. For accurate translation, it is crucial that each tRNA be attached to the correct amino acid for its anticodon. This is accomplished by enzymes that attach the correct amino acid for the anticodon in each type of tRNA. The figure below illustrates the action of one of these enzymes.



Inside the ribosome there is a ribozyme (RNA enzyme) that transfers the amino acid from the tRNA to the growing polypeptide chain. This ribozyme breaks the covalent bond between the tRNA and its amino acid and simultaneously forms a new covalent peptide bond between this amino acid and the next amino acid to be added to the growing polypeptide chain.<sup>8</sup>



When students watch the recommended 2-minute video, “Translation” (<https://www.biointeractive.org/classroom-resources/translation-basic-detail>), you may want to pause the video at 1 minute and 40 seconds and have them analyze how this animation

<sup>8</sup> This figure is from [https://sophialearning.s3.amazonaws.com/packet\\_logos/110859/large/protein-synthesis-ribosome.jpg?1370878929](https://sophialearning.s3.amazonaws.com/packet_logos/110859/large/protein-synthesis-ribosome.jpg?1370878929).

corresponds to the figure on the bottom of page 7 of the Student Handout. A ribosome adds about 2-20 amino acids per second in eukaryotes and bacteria, respectively.

### How a Version of the Hemoglobin Gene Can Cause Sickle Cell Anemia

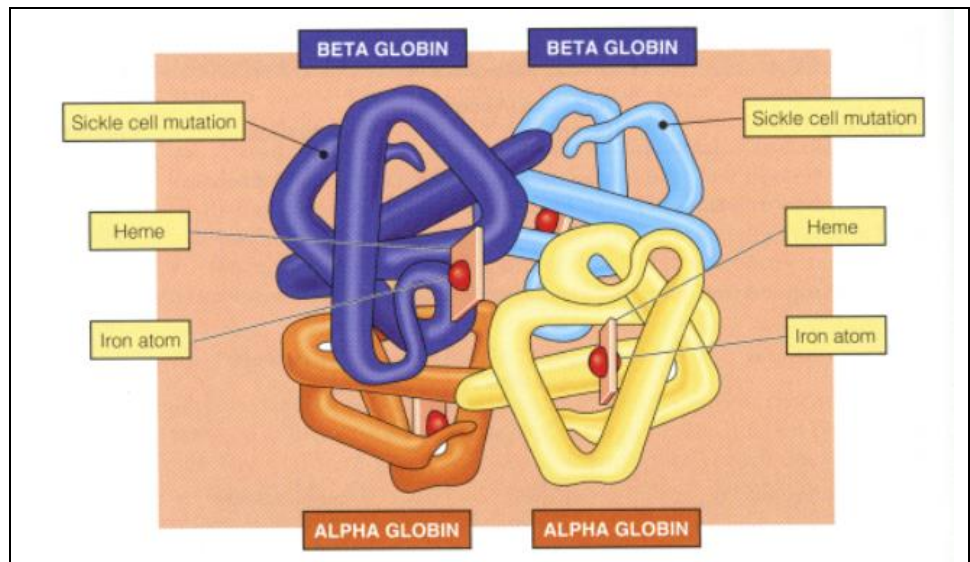
This section begins with a 4.5-minute recommended video, which provides an overview of sickle cell disease (“How This Disease Changes the Shape of Your Cells” at <https://www.youtube.com/watch?v=hRnrIpUMyZQ>).

Page 10 of the Student Handout summarizes the effects of homozygous sickle cell alleles, which result in sickle cell anemia. As discussed, sickled red blood cells can clog the small blood vessels. This clog should be distinguished from the clot that forms when a blood vessel has been injured (see page 5 of these Teacher Preparation Notes). The following paragraphs provide additional information.

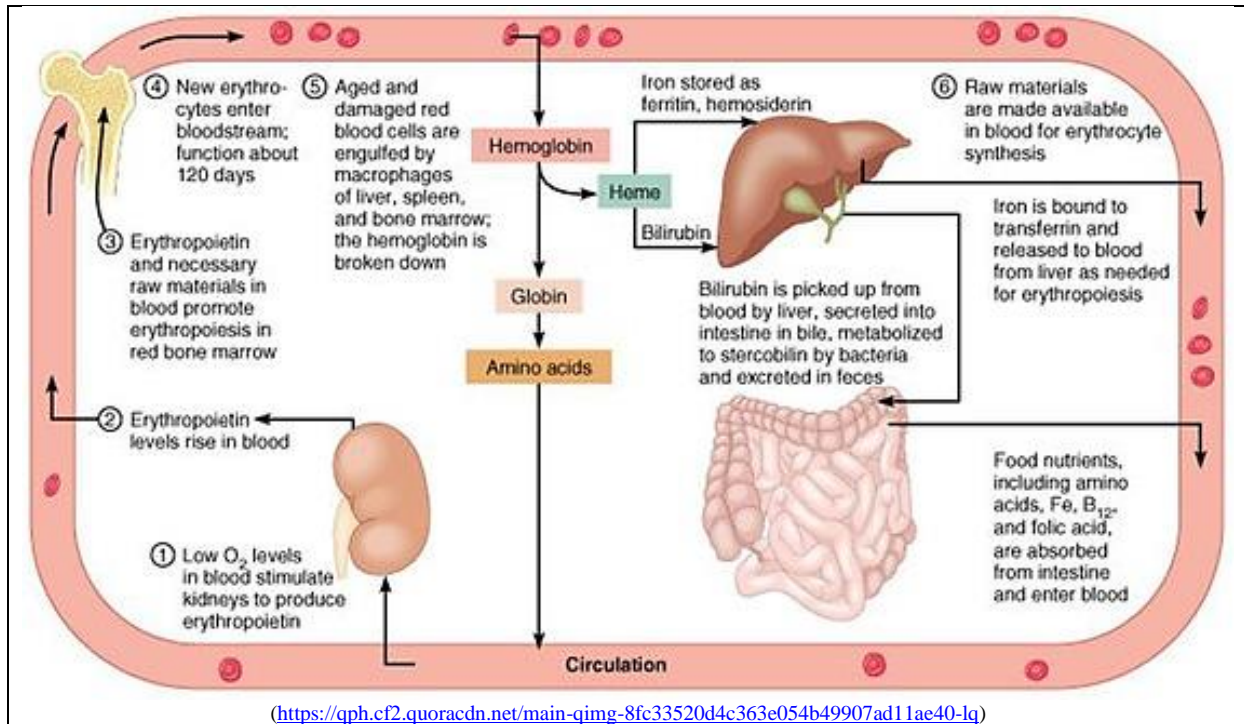
The figure at right shows one type of sickle, a tool which is probably unfamiliar to many students.



Hemoglobin is made up of four polypeptides, two beta globin and two alpha globin. In this activity, students model transcription and translation of the beta globin gene. We ignore the gene for the alpha globin polypeptides, since that gene is the same in normal and sickle cell hemoglobin.



To help your students understand how anemia results from the shorter lifespan of red blood cells with sickle-cell hemoglobin, you may want to explain that the rate of producing new red blood cells can't keep up with the increased rate of dying of the red blood cells with sickle-cell hemoglobin. (The figure below shows the lifecycle of red blood cells.) Anemia can result in fatigue and shortness of breath.

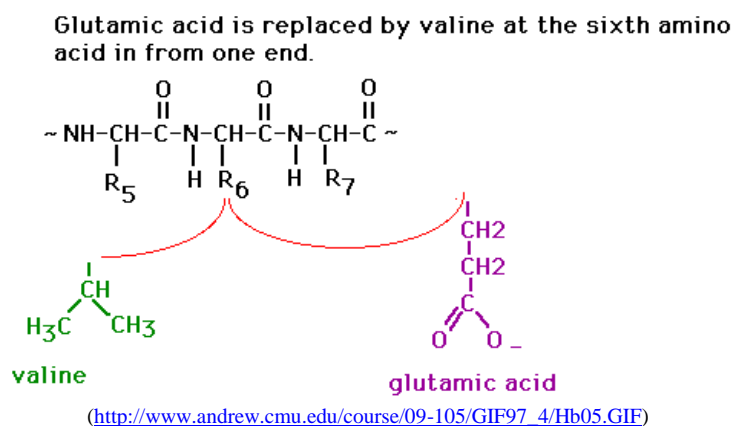


The severity of sickle cell anemia in different individuals varies from relatively mild sickle cell anemia with few sickling crises and nearly normal health and survival to severe sickle cell anemia with frequent sickling crises, significant organ damage and early death. The majority of people with sickle cell anemia have an intermediate severity. One factor that contributes to variation in the frequency of sickling crises is that some people with sickle cell anemia spontaneously produce relatively high levels of fetal hemoglobin (which contains gamma globin instead of beta globin polypeptides), and fetal hemoglobin inhibits clumping of sickle cell hemoglobin into rods. Hydroxyurea, which increases the production of fetal hemoglobin, is one treatment for sickle cell anemia. A good summary of the medical aspects of sickle cell anemia, including symptoms, diagnosis and treatment is available at <https://www.mayoclinic.org/diseases-conditions/sickle-cell-anemia/symptoms-causes/syc-20355876>. Recent progress in gene therapy for sickle cell anemia is analyzed in “Gene Editing with CRISPR-Cas – A Cure for Sickle Cell Anemia?” (<https://serendipstudio.org/exchange/bioactivities/GeneEdit>).

Even in a person who has severe sickle cell anemia, most red blood cells are not sickled most of the time. The degree of clumping of sickle cell hemoglobin into rods varies, depending on factors such as differences in dehydration, oxygen levels in the blood, and multiple genetic factors. For example, dehydration increases the concentration of hemoglobin in red blood cells which increases the tendency of sickle cell hemoglobin to clump into rods. The resulting sickled red blood cells can block some of the small blood vessels, which can cause pain and organ damage (called a sickling crisis). An infection that induces vomiting and diarrhea can result in dehydration which can cause a sickling crisis. However, the causes of most sickling crises are unknown.

The top half of page 11 of the Student Handout guides students in analyzing the specific molecular biology of the normal vs. sickle-cell alleles of the hemoglobin gene and the resulting

normal vs. sickle-cell hemoglobin proteins.<sup>9</sup> As discussed in the Student Handout, the lower solubility of nonpolar valine in the watery cytosol of the red blood cell (compared to the high solubility of ionic glutamic acid) contributes to the tendency of sickle-cell hemoglobin to clump together in long rods inside the red blood cells. This difference in the solubility of amino acid 6 is crucial because amino acid 6 is in a key location on the outside of the hemoglobin molecule (labeled sickle cell mutation in the figure on the previous page). This provides a good example of how the specific sequence of amino acids plays a crucial role in determining the form and function of a protein.



This section provides a good opportunity to discuss the Crosscutting Concept, Cause and effect: Mechanism and explanation, including that scientists often understand “causal relationships by examining what is known about smaller scale mechanisms within the system.”

The top of page 12 of the Student Handout, including question 28, introduces students to the biology of a person who is heterozygous for the sickle-cell hemoglobin allele. This condition is called sickle cell trait. A person with sickle cell trait rarely has symptoms of sickle cell anemia, because each red blood cell contains both normal and sickle cell hemoglobin and the normal hemoglobin generally prevents clumping of the sickle cell hemoglobin. Athletic associations recommend testing for sickle cell trait and, for athletes who have sickle cell trait, taking appropriate precautions to prevent extreme exertion and dehydration in order to further reduce the small risk of exercise-related sudden death. Harmful health effects of sickle cell trait are rare, and life expectancy is not detectably reduced. Sickle cell trait has beneficial health effects in areas where malaria is prevalent; individuals with sickle cell trait have less serious malaria infections because the malaria parasite doesn't grow as well in their red blood cells.

In discussing question 29, you may want to point out that our bodies are made up of roughly 100,000 different types of proteins and each protein is made up of hundreds or thousands of amino acids. Thus, there are many many opportunities for variation in proteins and phenotypic characteristics.

### Sources for Student Handout Figures

- Figure of boy with bloody nose on page 1 from <https://www.nhsdirect.wales.nhs.uk/assets/images/encyclopaedia/Nosebleed.jpg>
- Upper figure on page 2, upper figure on page 4, bottom figure on page 7, and figure on page 9 modified from Krogh, Biology – A Guide to the Natural World

<sup>9</sup> As discussed on the previous page, students analyze transcription and translation of the beginning of the gene for the beta globin polypeptides in the hemoglobin tetramer protein.

- Bottom figure on page 2 and top figure on page 7 modified from <https://owlcation.com/stem/protein-production-a-step-by-step-illustrated-guide>
- RNA polymerase on the bottom of page 4 modified from <http://www.zo.utexas.edu/faculty/sjasper/images/17.6b.gif>
- tRNA on page 7 modified from <https://image1.slideserve.com/1916888/structure-of-trna-n.jpg>
- Sickle cell anemia figure on the top of page 10 from <http://bioinformatics.org/jmol-tutorials/jtat/hemoglobin/images4all/sickle4.png>

Other Student Handout figures were made by the authors.

### **Related Learning Activities**

“The Genetics of Sickle Cell Anemia and Sickle Cell Trait – How One Gene Affects Multiple Characteristics” (<https://serendipstudio.org/exchange/bioactivities/geneticsSCA>) is an analysis and discussion activity. In this activity, students analyze information about the molecular and cellular basis for sickle cell anemia and sickle cell trait. This provides the basis for understanding how a single gene can affect multiple phenotypic characteristics. Students also create a Punnett square, analyze a pedigree, and evaluate the relative advantages of Punnett squares and pedigrees as models of inheritance. The Teacher Notes include several optional questions which apply student understanding of the biology of sickle cell trait to practical and policy issues.

"Molecular Biology: Major Concepts and Learning Activities"

(<https://serendipstudio.org/exchange/bioactivities/MolBio>) is an overview that reviews key concepts and learning activities. Topics covered include basic understanding of the important roles of proteins and DNA, DNA structure and replication, and the molecular biology of how genes influence traits, including transcription, translation, and the molecular biology of mutations. To help students understand the relevance of these molecular processes, the suggested learning activities link alleles of specific genes to human characteristics such as albinism, sickle cell anemia and muscular dystrophy. Several possible follow-up activities are suggested, including "Mutations and Muscular Dystrophy" (available at <https://serendipstudio.org/exchange/bioactivities/mutation>).