How Genes Can Cause Disease – Introduction to Transcription and Translation¹

I. How can genes cause health problems?

Tony is upset that he has another nosebleed. He wonders why he gets so many nosebleeds and why they last so long. He asks his Uncle Carlos, who used to have the same problem when he was a boy.

Uncle Carlos says that he has hemophilia. He shows Tony a video, “What is hemophilia?” (https://www.youtube.com/watch?v=BoXBuJSURTJ). Watch the video.

Uncle Carlos explains that his body makes a defective version of the clotting protein, Factor VIII. He gets weekly injections of the normal version of Factor VIII, so he doesn’t get nosebleeds anymore.

1a. Why do people with hemophilia have more severe nosebleeds?

1b. Why don’t most of us need injections of Factor VIII to prevent nosebleeds?

Uncle Carlos explains that Tony has probably inherited a gene for hemophilia. Tony asks “What is a gene? How can a gene cause hemophilia?” To learn the answers, read the following.

A gene is a segment of DNA that gives the instructions for making a protein. Different versions of a gene can result in different versions of the protein. Different versions of the protein can result in different characteristics. This chart shows how different versions of the gene for the clotting protein, Factor VIII, can result in normal health or hemophilia.

<table>
<thead>
<tr>
<th>Gene in DNA</th>
<th>Protein</th>
<th>Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>One version of a gene gives instructions for making normal clotting protein.</td>
<td>When a blood vessel is injured, normal clotting proteins result in prompt blood clot formation.</td>
<td>After an injury, a blood clot stops the bleeding.</td>
</tr>
<tr>
<td>Another version of the gene gives instructions for making defective clotting protein.</td>
<td>Defective clotting protein results in very slow blood clot formation.</td>
<td>Excessive bleeding = hemophilia</td>
</tr>
</tbody>
</table>

2. Explain how different versions of a gene determine whether or not a person has hemophilia.

Other genes give the instructions for making other proteins which influence other characteristics. Next, you will learn more about how a gene gives the instructions for making a protein.

¹ By Drs. Ingrid Waldron and Jennifer Doherty, Department of Biology, University of Pennsylvania. ©, 2020. This Student Handout and Teacher Preparation Notes (with instructional suggestions and background biology) are available at http://serendipstudio.org/sci.edu/waldron/#trans.
II. How does a gene give the instructions for making a protein?

This figure shows that making a protein involves two major processes.

3a. First, the instructions in the gene in the DNA are copied to messenger RNA, which is usually abbreviated as mRN\(a\). This process is called ______________________. (transcription / translation) mRNA leaves the nucleus and enters the cytoplasm.

3b. Next, mRNA gives the instructions for making a protein. This process is called ______________________. (transcription / translation)

4a. The figure below gives some additional information about transcription and translation. Fill in the blanks to label two of the molecules in the figure.

4b. Both DNA and mRNA are polymers of nucleotides. 
   The four types of nucleotides in DNA are A, ___, ___, and ___.
   The four types of nucleotides in mRNA are ___, ___, ___, and ___.
   The only difference is that ___ is a nucleotide in DNA and ___ is a nucleotide in mRNA.

4c. During transcription, the sequence of nucleotides in a gene in the DNA determines the sequence of ________________ in mRNA.

Proteins are polymers of 20 different types of amino acids.

5. During translation, the sequence of nucleotides in mRNA determines the sequence of ________________ in the protein.

The sequence of amino acids in a protein determines the structure and function of the protein. For example, the sequence of amino acids determines whether a clotting protein is normal or defective.

Notice that:
- **Transcription** involves copying a message from a sequence of nucleotides in DNA to a matching sequence of nucleotides in mRNA.
- **Translation** involves translating from a sequence of nucleotides in mRNA to a sequence of amino acids in a protein.
6a. Complete this flowchart to describe an example of how different versions of a gene can result in different characteristics.

In the DNA, different versions of the gene for a clotting protein have a different sequence of __________________________

↓

different sequence of __________________________
in mRNA

↓

different sequence of __________________________
in the clotting protein

↓

different structure and function of the clotting protein

↓

different characteristics (e.g. normal clotting vs. hemophilia)

6b. Label the arrow that represents transcription.

6c. Label the arrow that represents translation.

7a. Which process takes place in the nucleus?  transcription ___  translation ___

7b. Explain why this process must occur in the nucleus.

8. Why does a cell need to carry out transcription before translation?

Watch the video “What is DNA and how does it work?” at http://statedclearly.com/videos/what-is-dna/. This video will review what you have learned and introduce some new information, which includes a description of the function of ribosomes.

9. In question 6a, write ribosome next to the process that occurs in ribosomes.
III. How does a gene in the DNA give the instructions to make an mRNA molecule?

This figure summarizes how transcription of a gene copies the sequence of nucleotides in the DNA into a corresponding sequence of nucleotides in an mRNA molecule.

In the region of the gene, the two DNA strands are temporarily separated.

Each DNA nucleotide in the gene is matched with a **complementary RNA nucleotide** which has a matching shape and charge distribution.

Each RNA nucleotide is joined to the previous RNA nucleotide to make the growing mRNA molecule.

10. Fill in each blank in this figure with DNA or mRNA.

The **base-pairing rules** summarize which pairs of nucleotides are complementary. The base-pairing rules for transcription are similar to the base-pairing rules in the DNA double helix.

11. Use the information in the above figure to complete this table.

<table>
<thead>
<tr>
<th>Base-Pairing Rules for Complementary Nucleotides:</th>
<th>between the two strands of a DNA double helix</th>
<th>between DNA and mRNA (during transcription)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G pairs with C.</td>
<td>G pairs with ____</td>
<td></td>
</tr>
<tr>
<td>T pairs with A.</td>
<td>T in DNA pairs with ____ in mRNA.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A in DNA pairs with ____ in mRNA.</td>
<td></td>
</tr>
</tbody>
</table>

Transcription is carried out by the enzyme **RNA polymerase** which:

- separates the two strands of a DNA double helix
- matches each DNA nucleotide with a complementary RNA nucleotide
- joins each RNA nucleotide to the previous nucleotide in the growing mRNA molecule.

12. Why is RNA polymerase a good name for this enzyme? Explain each part of the name: RNA, polymer and ase.
Procedure for Modeling Transcription

In this modeling activity, your goal is to mimic how mRNA is made inside a cell. During transcription RNA polymerase adds one nucleotide at a time to the growing mRNA molecule.

To model transcription accurately, complete each step in the procedure and check the box before you begin the next step.

A. Your group should get:
   - a page showing an RNA polymerase molecule inside a nucleus
   - a paper strip showing a single strand of DNA labeled "Beginning of Hemoglobin Gene"
   - RNA nucleotides
   - tape.

One of you will be the RNA polymerase. Another group member will be the cytoplasm which surrounds the nucleus and supplies the nucleotides which are used to make the mRNA molecule.

B. RNA polymerase: Insert the "Beginning of Hemoglobin Gene" DNA molecule through the slot in the RNA polymerase diagram so the first two nucleotides of the gene are on the dashes labeled DNA.

Your RNA polymerase should look like this figure. (Note: A real RNA polymerase molecule and RNA nucleotides are much smaller than the nucleus. Real DNA molecules are much longer than the diameter of the nucleus, but they are very thin, flexible, and folded inside the nucleus.)

C. Cytoplasm: Use the base-pairing rules to choose an RNA nucleotide that is complementary to the first DNA nucleotide. Give this nucleotide to the RNA polymerase person.

D. RNA polymerase: Put this RNA nucleotide in the box labeled RNA nucleotide.

E. Cytoplasm: Give the next RNA nucleotide (complementary to the next DNA nucleotide) to the RNA polymerase person.

F. RNA polymerase: Put this nucleotide in the box labeled "next RNA nucleotide". Join the two RNA nucleotides together with transparent tape; the tape represents the covalent bond between these two nucleotides in the growing mRNA molecule. Then, move the DNA molecule and the mRNA molecule one space to the left.

G. Repeat steps E and F as often as needed to complete transcription of the beginning of the hemoglobin gene by adding one nucleotide at a time to the mRNA molecule.
To see the process of transcription in action, view the animation “DNA Transcription” at https://www.biointeractive.org/classroom-resources/dna-transcription-basic-detail.

13. Summarize how transcription makes mRNA. A complete answer will include:
gene, mRNA, sequence, nucleotides, complementary, RNA polymerase, base-pairing rules.

The next two questions compare transcription with DNA replication.

14. The first column of this table describes DNA replication. Fill in the blanks in the second column to summarize the differences between DNA replication and transcription.

<table>
<thead>
<tr>
<th>DNA replication</th>
<th>Transcription</th>
</tr>
</thead>
<tbody>
<tr>
<td>The whole chromosome is replicated.</td>
<td>________________ is transcribed.</td>
</tr>
<tr>
<td>DNA is made. DNA is double-stranded.</td>
<td>mRNA is made. mRNA is ________________-stranded.</td>
</tr>
<tr>
<td>DNA polymerase is the enzyme which carries out DNA replication.</td>
<td>_____ polymerase is the enzyme which carries out transcription.</td>
</tr>
<tr>
<td>T is used in DNA; A pairs with T in DNA.</td>
<td>In RNA, T is replaced by ____; A in DNA pairs with ___ in mRNA.</td>
</tr>
</tbody>
</table>

15. Fill in the blanks in the paragraph below to describe the similarities between transcription and DNA replication.

Both transcription and DNA replication produce nucleic acids which are polymers of ________________ (C, G, A, and T or U). Both processes depend on a ________________ enzyme which adds one ________________ at a time. To determine which nucleotide is added next, both transcription and DNA replication use the nucleotide sequence in a ______ strand and the ___________________________ rules.
IV. How does an mRNA molecule give the instructions to make a protein?

There are only 4 types of nucleotides in mRNA and 20 types of amino acids in proteins. This figure shows how 4 types of nucleotides can provide a unique code for each of the 20 types of amino acids.

16a. The mRNA code for each type of amino acid is a sequence of _______ nucleotides, called a **codon**.

16b. In the figure, circle the mRNA codon that codes for the amino acid Phe.

During protein synthesis, **transfer RNA** (tRNA) molecules bring the right amino acids for each mRNA codon.

This figure shows one type of tRNA with the amino acid Phe attached. Notice that the three nucleotides in the anti-codon of this tRNA molecule are complementary to the three nucleotides in the mRNA codon for Phe.

17a. Each type of tRNA carries a specific amino acid and has an **anticodon** with three nucleotides that are complementary to the three ____________ in the mRNA codon for that amino acid.

17b. What is the anticodon in the tRNA that carries the amino acid Gly?

18. For each type of tRNA, there is a specific enzyme that attaches the correct amino acid for the anticodon in that tRNA. These enzymes are needed for step ______ in the figure below.

Inside a ribosome, a codon in an mRNA molecule is matched by the base-pairing rules with an anticodon in a tRNA (step 3). This tRNA brings the next amino acid to be added to the growing protein molecule.

19. In the ribosome, circle a codon in the mRNA and the complementary anticodon in a tRNA molecule.

Each amino acid is joined to the previous amino acid in the growing protein molecule (step 4). Then, the ribosome moves along the mRNA to the next codon (step 5).
20. What part of translation depends on the base-pairing rules?

21. tRNA stands for transfer RNA, since a tRNA molecule transfers an amino acid to the growing protein molecule. You could also think of tRNA as translation RNA. Explain how tRNA molecules help the ribosome to translate the sequence of nucleotides in mRNA to a sequence of amino acids in a protein.

Procedure for Modeling Translation
To model the steps in translation, one of you will be the ribosome, and another will be the cytoplasm. Complete each step in the procedure and check it off, before beginning the next step.

Preparation
A. Your group should get:
   - the mRNA you made when you modeled transcription
   - a strip labeled "Second Part of mRNA"
   - a page showing a ribosome
   - 6 tRNA molecules and 6 amino acids.

22. For tRNA to do its job, each tRNA molecule must be attached to the correct amino acid that corresponds to the anticodon in that type of tRNA. To know which amino acid should be attached to each tRNA molecule, use the base-pairing rules to complete this table.

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>Thr (Threonine)</th>
<th>His (Histidine)</th>
<th>Pro (Proline)</th>
<th>Leu (Leucine)</th>
<th>Glu (Glutamic acid)</th>
<th>Val (Valine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticodon in tRNA molecule that carries this amino acid</td>
<td>UGA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRNA codon</td>
<td>ACU</td>
<td>CAU</td>
<td>CCU</td>
<td>CUG</td>
<td>GAG</td>
<td>GUG</td>
</tr>
</tbody>
</table>

23. Your partner wants to save time by skipping question 22 and the tRNA molecules. He wants to use the mRNA strip and the table above to arrange the amino acids in the correct sequence and tape them all together. Explain why this would not be a good simulation of the actual sequence of steps needed to carry out translation.

B. Cytoplasm: Use the above table to match each tRNA molecule with the correct amino acid for that type of tRNA. Tape the amino acid to the tRNA very lightly, because they will only be joined temporarily and will soon separate.

C. Cytoplasm: Tape the CUG end of the mRNA you made to the ACU end of the Second Part of mRNA strip.

Note: A real mRNA molecule has many more nucleotides than your strip has. Also, a real tRNA molecule has many more nucleotides than the three nucleotides of the anticodon.
Modeling the Steps in Translation

D. **Ribosome**: Insert the **mRNA** through the slot in the model ribosome, with the first three nucleotides of the mRNA in the "codon" position.

E. **Cytoplasm**: Use the base-pairing rules to supply the **tRNA** that has the correct **anticodon** to match the first codon in the mRNA.

F. **Ribosome**: Place this **tRNA** with its amino acid in position.

24. Your model ribosome should look like this figure. Circle the anticodon of the tRNA.

G. **Cytoplasm**: Supply the **tRNA** that has the correct **anticodon** to match the codon in the "next codon" position.

H. **Ribosome**: Place the tRNA in position. Detach the left amino acid from its tRNA and tape it to the amino acid on the right.

I. **Ribosome**: Move the mRNA and matching tRNAs with amino acids one codon to the left. Release the tRNA on the left to the cytoplasm.

J. **Repeat steps G-I** as often as needed to attach all six amino acids in the correct sequence to form the beginning of the hemoglobin protein.

To see the process of translation in action, watch “Translation” at [https://www.biointeractive.org/classroom-resources/translation-basic-detail](https://www.biointeractive.org/classroom-resources/translation-basic-detail).

25a. Fill in the blanks to label each type of molecule in this figure.

25b. Explain each step in the process shown in the figure. A complete answer will include each of the molecules shown and these words: codon, anticodon, base-pairing rules, nucleotides, sequence, enzyme, ribosome.
V. How one Version of the Hemoglobin Gene Causes Sickle Cell Anemia

The protein hemoglobin in our red blood cells carries oxygen. One version of the gene for hemoglobin gives the instructions to make normal hemoglobin, which dissolves in the cytosol of red blood cells. These normal, disk-shaped red blood cells can squeeze through even the smallest blood vessels.

In contrast, another version of the hemoglobin gene gives the instructions to make sickle cell hemoglobin. Sickle-cell hemoglobin can clump in long rods inside the red blood cells. These rods make the red blood cells longer and sickle-shaped.

These sickle-shaped red blood cells can block small blood vessels. This cuts off the oxygen supply, causing intense pain and damage to body organs. Also, sickled red blood cells don’t last as long as normal red blood cells; this results in low levels of red blood cells (anemia).

To understand more about how sickle cell hemoglobin can cause sickle cell anemia, watch the first 2 ½ minutes of the video, “How This Disease Changes the Shape of Your Cells” at https://www.youtube.com/watch?v=hRnr1pUMyZQ. This video refers to a genetic mutation, which is a change in a gene. A mutation results in a different version of the gene. Different versions of the same gene are called alleles.

26a. Fill in the blanks in this chart to describe how the normal hemoglobin allele results in normal health and the sickle cell hemoglobin allele results in sickle cell anemia.

<table>
<thead>
<tr>
<th>Gene in DNA</th>
<th>Protein</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 copies of the allele that codes for normal hemoglobin</td>
<td>Normal hemoglobin dissolves in the cytosol of red blood cells.</td>
<td>Disk-shaped can squeeze through the small blood vessels → normal health</td>
</tr>
<tr>
<td>2 copies of the allele that codes for sickle cell hemoglobin</td>
<td>Sickle cell can clump in long rods inside red blood cells.</td>
<td>When sickle cell hemoglobin clumps in long rods, → sickle-shaped red blood cells → block small blood vessels → not enough → pain, damage to body organs. Also, these red blood cells die faster than they can be replaced → (low red blood cells). Person has sickle cell anemia.</td>
</tr>
</tbody>
</table>

26b. Name the process or processes represented by the first arrow in the chart.
27. This table shows the nucleotide sequence in the “Beginning of Allele for Normal Hemoglobin” vs. the “Beginning of Allele for Sickle Cell Hemoglobin”. What is the only difference?

<table>
<thead>
<tr>
<th>Beginning of Allele for Normal Hemoglobin</th>
<th>CACGTAAGACTGAGGACTC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transcription produces:</strong></td>
<td>codon1 codon 2 codon 3 codon 4 codon 5 codon 6</td>
</tr>
<tr>
<td>Beginning of Normal Hemoglobin mRNA</td>
<td></td>
</tr>
<tr>
<td><strong>Translation produces:</strong></td>
<td>amino acid 1 amino acid 2 amino acid 3 amino acid 4 amino acid 5 amino acid 6</td>
</tr>
<tr>
<td>Beginning of Normal Hemoglobin Protein</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Beginning of Allele for Sickle Cell Hemoglobin</th>
<th>CACGTAAGACTGAGGACAC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transcription produces:</strong></td>
<td>codon1 codon 2 codon 3 codon 4 codon 5 codon 6</td>
</tr>
<tr>
<td>Beginning of Sickle Cell Hemoglobin mRNA</td>
<td></td>
</tr>
<tr>
<td><strong>Translation produces:</strong></td>
<td>amino acid 1 amino acid 2 amino acid 3 amino acid 4 amino acid 5 amino acid 6</td>
</tr>
<tr>
<td>Beginning of Sickle Cell Hemoglobin Protein</td>
<td></td>
</tr>
</tbody>
</table>

28. Complete the above table. The table below provides the information you will need for translation.

<table>
<thead>
<tr>
<th>mRNA codon</th>
<th>ACU</th>
<th>CAU</th>
<th>CCU</th>
<th>CUG</th>
<th>GAG</th>
<th>GUG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amino acid</td>
<td>Thr (Threonine)</td>
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<td>Pro (Proline)</td>
<td>Leu (Leucine)</td>
<td>Glu (Glutamic acid)</td>
<td>Val (Valine)</td>
</tr>
</tbody>
</table>

29. Compare the amino acid sequence for the beginning of sickle cell hemoglobin vs. the beginning of normal hemoglobin. What difference do you observe?

Sickle cell hemoglobin and normal hemoglobin differ in only a single amino acid out of more than 100 amino acids in the complete hemoglobin protein. This difference in a single amino acid results in the different properties of sickle cell hemoglobin compared to normal hemoglobin.

Normal hemoglobin dissolves in the watery cytosol of red blood cells. Sickle cell hemoglobin tends to clump in long rods instead of dissolving in the cytosol. One reason why is:
- Valine (Val) is much less water-soluble than glutamic acid (Glu).
- Amino acid 6 is in a crucial location on the outer surface of the hemoglobin protein.
30. Explain how replacing glutamic acid (Glu) with valine (Val) as the sixth amino acid in hemoglobin can result in pain and organ damage.

Each person has more than 20,000 genes that code for the amino acid sequence in different proteins. Proteins have many functions in our bodies, including carrier proteins like hemoglobin, messenger proteins like growth hormone, structural proteins like collagen, and enzymes like RNA polymerase. Our genes act via these proteins to influence our risk of diseases, such as sickle cell anemia, and a broad array of other characteristics, such as our height or the color of our eyes.

31. Considering that we are all made up of the same 4 nucleotides in our DNA, the same 4 nucleotides in our RNA, and the same 20 amino acids in our proteins, why are we so different from each other?

Challenge Questions
The COVID-19 pandemic has been caused by a new type of coronavirus. A coronavirus includes several types of proteins and an mRNA molecule.

A virus cannot reproduce on its own. Instead, the coronavirus enters a person’s cells and uses the cells’ organelles and molecules to produce new viruses. For example, after the virus releases its mRNA inside a cell, the viral mRNA directs the cell’s organelles to make viral proteins that will be used to make new viruses.

What process will the cell use to make viral proteins?
Which of the cell’s organelles will make viral proteins?
Which cell molecules will be used to make viral proteins?

The viral proteins combine with other viral molecules produced by the cell to make multiple new coronaviruses that are released from the cell. What do you think happens to these viruses?