Activity 2.2.2
A Protein Problem

Break the sequence three ways and watch what survives. Substitution, insertion, deletion. Same starting strand, three changes, three different amounts of damage. Then you read the sequencing report.

DATE	PORTAL DAY	LESSON	TURN IN
Thursday 2026-10-28	**Analyze the mutation**	**Lesson 2.2 Decoding a Diagnosis**	**CER**

Where this sits. Day 2 of 2. Portal calendar label for today: Analyze the mutation.

01 Why today matters

Yesterday you ran protein synthesis the way it is supposed to go. Today you change one base at a time and find out why some changes do nothing at all and one of them destroys everything downstream.

That difference is what a genetics report is actually telling you.

02 What you already know

- You can transcribe DNA to mRNA, set a reading frame from the first AUG, and translate to an amino acid chain. You know one codon means one amino acid and several codons can mean the same one. That last fact is about to matter a great deal.

WHAT THIS SHEET WILL NOT TELL YOU

- This sheet explains how to read a report. It does not tell you what your patient's report says, name the gene, or name the condition.

03 Vocabulary

TERM	WHAT IT MEANS, PLAINLY
Substitution	One base swapped for another. The sequence stays the same length.
Insertion	One or more extra bases added into the sequence. The sequence gets longer.
Deletion	One or more bases removed. The sequence gets shorter.
Frameshift	What an insertion or deletion does when the number of bases is not a multiple of three: every codon from that point on is regrouped, so every amino acid after it is different.
Silent change	A substitution that lands on a codon which still specifies the same amino acid. The DNA changed and the protein did not.
Missense change	A substitution that swaps one amino acid for a different one. Effect ranges from nothing to severe depending on which amino acid and where.

Nonsense change	A substitution that turns a codon into a stop codon. Translation ends early and the protein is truncated.
Truncated protein	A chain that stopped short of its full length. Usually cannot fold into its working shape.
Loss of function	The changed protein does less than it should, or nothing.
Gain of function	The changed protein does more than it should, or does something new. Less common and not automatically better.
Variant	The neutral word laboratories use for a difference from the reference sequence, chosen because most differences are not harmful.
Genetic testing	Sequencing a patient's DNA and comparing it against known healthy sequences to draw a conclusion.
Geneticist	The professional who reads that comparison and interprets it.
Reference sequence	The known healthy version a patient's sequence is compared against. Everything a report calls a change is a change relative to this.
Genetic counseling	A conversation with a trained specialist about what a genetic result means for a person and their family. Recommended on almost every positive report, and a recommendation you can make.
Prognosis	The likely course a condition takes over a lifetime. Answered from the literature and the individual, not from the sequence alone.
Incidence	How often a condition occurs in a population, usually given as one in some number of people.

Every term on this list is flagged for the illustrated glossary, scoped to this activity only. Terms are not shared forward or backward between activities, because a definition from a later activity can hand you an answer you were supposed to derive.

04 How to do the work

You will use the same starting strand for all three mutations. Same strand, three separate runs, so the comparison is fair.

1. Copy the original DNA sequence from yesterday to the top of a clean page. Underneath it, copy yesterday's correct mRNA and amino acid chain. This is your control, and every comparison today is against it.
2. Substitution run. Choose any single base and change it to a different base. Underline the changed base. Transcribe the whole strand again. Find the first AUG. Bracket the codons. Translate to the first stop codon.
3. Compare against your control chain. Write down exactly what changed: which position, which amino acid became which, and how many amino acids after that point are different.
4. Insertion run. Go back to the original strand. Insert one extra base somewhere. Underline it. Transcribe, find AUG, bracket, translate.
5. Compare against the control again. Count how many amino acids are different this time, not just whether any are.
6. Deletion run. Back to the original again. Remove one base. Note which one. Transcribe, find AUG, bracket, translate. Compare.
7. Now put the three results side by side and answer the question this activity is really asking: why do two of these three changes do so much more damage than the third, when all three changed exactly one base?
8. Predict and write down: what would happen if a change landed inside the start codon, and what would happen if it landed inside a stop codon. Two different failures, and both are worth a sentence.
9. Test one more case. Insert three bases together instead of one. Translate and compare. Explain the result using the word frame.
10. Read your patient's sequencing report. Identify what kind of change it describes, and work out from the number of bases involved whether the reading frame survives it.

11 Research the condition the report names. Record its inheritance pattern, how often it occurs, what signs and symptoms appear over a lifetime, what monitoring and care are involved, and what the report itself recommends.

12 Write your response to the family. It has to cover what to expect now, what to expect as the child grows, what care and monitoring will be needed, and what follow-up testing is recommended. Then rewrite it shorter.

READ THE REPORT AS A DOCUMENT, NOT AS AN ANSWER

- A sequencing report has parts and each part does a different job. Find them and label them: what test was ordered, what the result was, what change was found at the level of the DNA, what that does to the protein, how the laboratory interprets it, what it recommends, and what it says about inheritance.
- The interpretation section is the laboratory's reasoning, not raw data. It is well founded and it is still somebody's conclusion. Being able to see the difference between the result and the interpretation is a skill that outlasts this unit.
- The recommendation section usually asks for a conversation with a specialist. That is not a formality. Notice what it implies about the limits of what a sequence alone can tell a family.

05 Where students get stuck

- Assuming every mutation is harmful. Most changes do nothing you would ever notice. Some are silent because the new codon still means the same amino acid. Some swap an amino acid in a place the protein does not care about. The interesting question is never whether the DNA changed, it is whether the protein still works.
- Forgetting that three bases is a special number. Insert or delete one or two bases and the frame shifts and everything downstream is scrambled. Insert or delete three and the frame survives, so you gain or lose one amino acid and the rest of the chain is intact. This is the single most useful fact in the whole activity.
- Not going back to the original strand between runs. If you mutate your already-mutated sequence you are testing two changes at once and your comparison is worthless. Fresh copy of the original for every run.
- Comparing only the first difference. For a substitution, count how many amino acids differ. For a frameshift, count again. The number is the finding. Saying the chains are different is not.
- Confusing the result with the interpretation. The result is what the sequencing found. The interpretation is what the laboratory concludes it means. Quote them separately in your writing, and attribute the second one.
- Leading the family conversation with the diagnosis word. Start with how the child is now. Then what was found and what it means. Then what happens next and who will be involved. A name delivered first is the only thing anybody hears.

06 What you turn in

CER

A claim, evidence, reasoning response, plus your three mutation runs. Claim: what the change described in the report does to the protein. Evidence: all three of your mutation runs laid out against the control, with the number of amino acids affected in each; the specific change quoted from the report; and the number of bases it involves. Reasoning: connect the base count to the reading frame and the reading frame to the protein's ability to do its job. Attach your written response to the family, and be explicit about which parts of it are the report's findings and which are your own research.

07 Check yourself

- [ ] Two patients each have a single-base substitution in the same gene. One has no symptoms at all. Give two different reasons that could be true. (Vocabulary, silent change and missense change)
- [ ] A change deletes two bases and inserts four. Does the reading frame survive? Show the arithmetic. (Vocabulary, frameshift)
- [ ] Why does a stop codon appearing early in a sequence usually cause more trouble than one amino acid being swapped in the middle? (Vocabulary, nonsense change and truncated protein)