Case study: Malignant hyperthermia

Your role during this case study: Stephanie has woken up after her surgery. Initially, she's lethargic, she complains of muscle pain, and she has difficulty focusing and concentrating on people speaking to her. Sometime later, Stephanie's condition improves enough for her to converse with her family and medical staff. Her parents have ordered a genetic test to identify the mutation in her RYR1 gene. During your shift, you visit Stephanie's room to check in on her. She's got a few questions about her disorder and you're more than happy to answer them.

A. Mutation in a calcium channel: Stephanie's parents have ordered a genetic test to examine the type of mutation in her RYR1 gene. The RYR1 gene codes for ryanodine receptor 1, an active calcium channel in the membrane of the sarcoplasmic reticulum. The gene is approximately 150,000 nucleotides long and codes for a protein that is about 5,000 amino acids long. Presented is a short region in the middle of the transcript:

Normal:	Coding:	
	Template:	
	Transcript:	5′ - G C C A C A A G G G U U G A G C C A - 3′
	Polypeptide:	
Stephanie:	Coding:	
	Template:	
	Transcript:	5′ - G C U A A A A G A G U U G G G C C U - 3′
	Polypeptide:	

Write in the portions of the coding and template strands based on the transcript sequence. Assume the transcript is in frame and translate it using the genetic code. Answer the following questions:

1. How many codons differ between the two transcripts?
2. How many amino acids are different in the resulting polypeptides?
3. Of the amino acids that differ between the transcripts, which nucleotide in their codon is different? Choose one of the following: **first**, **second**, or **third**
4. Of the codons that differ between the transcripts that don't code for different amino acids, which nucleotide is different? Choose one of the following: **first**, **second**, or **third**
5. Can you tell which mutated amino acid in the polypeptide causes Stephanie's symptoms?

B. Anatomy of a muscle cell and the biochemistry of contraction: Part 1: Collect the first image. This image represents a model of a muscle fiber with its arrangement of myofibrils, cellular structures, and organelles. Also pictured is the neuromuscular junction. Identify the following structures: synaptic cleft (**a**), axon terminal (**b**), myelin sheath (**c**), vesicles containing neurotransmitters (**d**), mitochondria (**e**), nucleus (**f**), T-tubule (**g**), terminal cisternae (**h**), triad (**i**), myofibril (**j**), zone of overlap (**k**), Z-line (**m**), H-band (**n**), myofilaments (**o**), and sarcolemma (**p**). Draw an asterisk where you expect to find the endomysium.

Part 2: Collect the ten images representing the steps in muscle contraction. Place them in the order in which they occur. Answer the following questions:

1. What causes the first sodium channels to open?
2. What causes the second sodium channels to open?
3. After contraction, what happens to the calcium in the sarcoplasm?

C. Discussion (12 pts):

Questions:	Answers:
1. a) In part A of this case study, why is there a discrepancy between the numbers you answered in question 1 and 2? (1 pt) b) Which mutations are more severe: those occurring in the first nucleotide of the codon, the second, or the third? (1 pt)	a) b)
2. Once the ryanodine calcium channel in the sarcoplasmic reticulum is open, calcium floods the sarcoplasm. a) Explain how the calcium ultimately causes myosin to cross bridge with actin. (1 pt) b) Where does ATP figure into this process? (1 pt) c) What happens after the cross bridging event? (1 pt)	a) b) c)
3. Stephanie presented a few symptoms on the operating table, most apparent was her elevated body temperature. What is the chemical formula for ATP catabolism? Explain why this reaction would cause Stephanie's elevated body temperature. (2 pts)	Formula: Explanation:
4. An analysis of Stephanie's muscle showed elevated levels of lactic acid and citric acid. Answer the following three questions (3 pts): a) What metabolic processes could cause elevated levels of i) lactic acid and ii) citric acid? b) Which of these two processes could cause elevated CO_2 output? c) What part of Stephanie's treatment could help compensate for lactic acid production? Explain.	a) i: ii: b) Answer: c) Answer: Explanation:
5. Draw a flowchart/concept map illustrating the *mechanism* whereby the mutated ryanodine receptor 1 causes the symptoms of malignant hyperthermia in Stephanie as she underwent surgery. Start at the time the anesthetic was administered and finish with the symptoms presented in the patient's story. (2 pt)