Making Sense of Mutations

Your Approach

Suppose you are a medical geneticist presented with three infant patients, all of whom have a nucleotide-pair substitution in their insulin gene. It is your job to analyze each mutation to figure out the effect of the mutation on the amino acid sequence of the insulin protein. To identify the mutation in each patient, you will compare his or her individual insulin complementary DNA (cDNA) sequence to that of the wild-type cDNA. (cDNA is a double-stranded DNA molecule that is based on the mRNA sequence and thus contains only the portion of a gene that is translated—introns are not included. cDNA sequences are commonly used to compare the coding regions of genes.) Identifying the codons that have been changed will tell you which, if any, amino acids are altered in the patient's insulin protein.

Your Data

You will analyze the cDNA codons for amino acids 35–54 (of the 110 amino acids) of each patient's insulin protein, so the start codon (AUG) is not present. The sequences of the wild-type cDNA and the patients' cDNA are shown below, arranged in codons.

Wild-type cDNA	5′–CTG GTG GAA GCT CTC TAC CTA GTG TGC GGG GAA CGA GGC TTC TTC TAC ACA CCC AAG ACC–3′
Patient 1 cDNA	5′–CTG GTG GAA GCT CTC TAC CTA GTG TGC GGG GAA CGA GGC TGC TTC TAC ACA CCC AAG ACC–3′
Patient 2 cDNA	5′–CTG GTG GAA GCT CTC TAC CTA GTG TGC GGG GAA CGA GGC TCC TTC TAC ACA CCC AAG ACC–3′
Patient 3 cDNA	5′–CTG GTG GAA GCT CTC TAC CTA GTG TGC GGG GAA CGA GGC TTC TCG TAC ACA CCC AAG ACC–3′

Data from N. Nishi and K. Nanjo, Insulin gene mutations and diabetes, *Journal of Diabetes Investigation* 2:92–100 (2011).

Sections:

1) Background - Research **silent, missense and nonsense** mutations. Provide a description that includes the meaning of each type of mutation. Provide specific examples of each type of mutation. (4 marks)

2) Analysis - Write out the provided cDNA sequences (wild type, patients 1,2 and 3) and underneath convert each into the near identical mRNA sequence (just substitute U in for T). Underneath each mRNA sequence, Identify the amino acid sequence that results from each mRNA strand using the genetic code. (4 marks)

3) Discussion - Discuss whether each case demonstrates a **silent, missense or nonsense** mutation. Think about whether each mutation will lead to a **functional**, **partially functional** or **nonfunctional** insulin hormone and explain with potential intermolecular interaction. (4 marks)

Criteria	L1 (50-60%)	L2 (60-70%)	L3 (70-80%)	L4 (80-100%)
Background - Discusses the 3 types of mutation and gives examples				
Analysis - cDNA, mRNA and polypeptide sequences are shown and mutations identified				
Discussion - The three patients' mutations are discussed and classified (silent, missense, nonsense) - Hormone function is predicted and supported by the analysis				
Comments:				