

6.4 Mutation and variant interpretation

Name: _____ Class: _____ Date: _____

Total: 23 marks

KEY WORDS variant of uncertain significance

Objective

Classify variants and grade them with the evidence chain.

1 Key knowledge and worked examples

■ The classes

Synonymous / missense / nonsense / frameshift / splice + CNVs; verdicts pathogenic → benign with VUS at the centre ✓.

■ Worked example: the frequency kill

A 1 %-population variant for a 1/10 000 dominant disease: posterior odds $\approx$ 1:100 AGAINST ✓ – Bayes before prediction algorithms.

2 Practice

2.1 Which variant type truncates the protein? [3]

2.2 What does VUS stand for and mean? [3]

2.3 Which variant class deletes whole exons? [3]

3 Exam-style questions

3.1 A nonsense variant early in a haploinsufficiency gene (fictional).

State the likely verdict with reasons (mechanism: one working copy insufficient). Contrast with a dominant-negative gene. State the phenotype-severity expectation. [7]

3.2 A missense VUS in a breast-cancer gene in an affected woman (fictional).

State the counselling (not pathogenic; no cascade on a VUS). List two evidence streams that could upgrade it (segregation in the family; accumulating case data). State one harm of treating it as pathogenic. [7]

Solutions

2.1

- Nonsense (premature stop).

2.2

- Variant of uncertain significance – explicitly unknown.

2.3

- CNV (copy number variant).

3.1

- Likely pathogenic/pathogenic: truncation in a gene where one working copy is insufficient is loss-of-function disease.
- In a dominant-negative gene, missense (poison peptide) variants matter more than truncation.
- Severity tends to track the variant type and position – truncations early are often more severe.

3.2

- ”We found a spelling change; we do not yet know if it means anything” – no cascade testing on a VUS. Upgrades: co-segregation with disease in the family; more affected carriers reported over time (and functional studies).
- Harm: unnecessary prophylactic surgery in relatives treated as carriers.