

Exercise walk-through

6.4

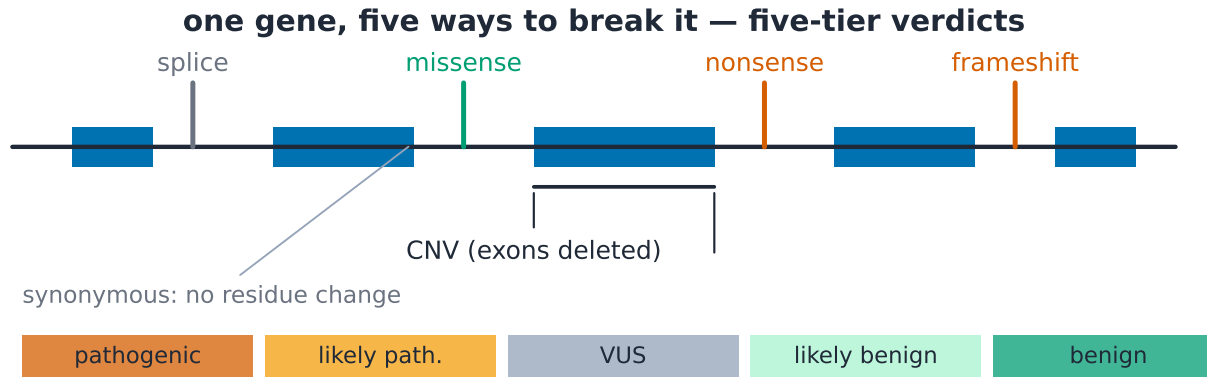
Mutation and variant interpretation

University Medicine

Variant interpretation: five ways, five tiers

- 1 **Types** Synonymous, missense, nonsense (stop/truncation), **frameshift**, splice - plus CNVs (exon/gene deletions).
- 2 **Tiers** Pathogenic / likely pathogenic / VUS / likely benign / benign.
- 3 **Filter** Population frequency first: 1% variant vs 1/10 000 dominant disease → posterior odds 1:100 AGAINST pathogenicity.

Variant interpretation - the figure



A gene model annotated with variant types and verdict tiers.

Exercises 2.1-2.3

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]

Exercises 2.1-2.3

2.1 Which variant type truncates the protein? [3]

2.1

- Nonsense (premature stop).
-

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

2.2

- Variant of uncertain significance – explicitly unknown.
-

2.3 Which variant class deletes whole exons? [3]

2.3

- CNV (copy number variant).

Exercise 3.1

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]

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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.

Exercise 3.2

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]

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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.