Solutions

Marking: **M1** a correct method, **A1** the correct answer, **B1** an independent mark.

Each answer shows the steps, then the **result**.

2.1

TGG (Trp) → TGA (stop): **nonsense**

GAG (Glu) → GTG (Val): **missense**

one base deleted: **frameshift**

2.2

every codon after the change is read in a new frame

a stop codon soon appears, so the mRNA is destroyed or the protein is short

2.3

benign

it is far too common in healthy people to cause such a rare disease

2.4

pathogenic, likely pathogenic

variant of uncertain significance

likely benign, benign

3.1

(a) a variant of uncertain significance: the evidence does not show if it causes disease

(b) no: a result could not be interpreted, so care is based on the family history instead

(c) segregation: does it track the disease in the family; how common it is in large databases, case reports, or lab tests of protein function

(d) the VUS does not follow the cancer in the family, which counts towards benign, although the cousin's cancer could have another cause

3.2

(a) one working copy does not make enough protein for normal function

(b) an early stop codon makes the mRNA be destroyed (nonsense-mediated decay), so that copy makes no protein

(c) the disease needs an abnormal protein that does too much; a variant that stops the protein being made removes it rather than adding the harmful effect

3.3

(a) one codon is lost: an in-frame deletion; one amino acid is missing, and the frame is kept

(b) yes: 7 is not a multiple of 3, so the frame shifts

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(c) the splice donor site is lost, so the exon may be skipped or the intron kept, changing the protein

(d) it can create or break a splice site

(e) each affected person has one variant allele, so disease alleles are at most 1 in 100 000; 40 in 100 000 is far too common, so it is **benign**