Mutations and gene editing

D1.3 · SL

One changed base can have several different outcomes

Follow the sequence, then test the consequence

D1.3 shared: substitutions, insertions/deletions, mutagens and spontaneous errors, randomness, inheritance and genetic variation.

Sequences and numerical examples are invented unless a published study is named.

Distinguish DNA sequence, damage and gene activity

Observation	**Interpretation**
Established sequence change	Mutation; may pass to descendant cells
Damage repaired to original sequence	No lasting mutation at that position
More transcript from unchanged DNA	Changed expression; not automatically mutation
Gene editing	A deliberate change at a chosen DNA sequence

Compare three substitutions in the same coding frame

Coding DNA	Initial polypeptide / signal
Original ATG GAA GCT TAA	→ Met – Glu – Ala; stop
Synonymous ATG GAG GCT TAA	→ Met – Glu – Ala; stop
Replacement ATG GTA GCT TAA	→ Met – Val – Ala; stop
Early stop ATG TAA GCT TAA	→ Met; stop

A substituted base can preserve, replace or stop a codon instruction.

Convert the coding strand before using an RNA codon table

1. **Coding DNA.** ATG GAA GCT TAA, in the stated direction and frame.
2. **mRNA.** AUG GAA GCU UAA: Met–Glu–Ala, then stop.
3. **Interpretation.** Four codons produce three residues here. UAA supplies no amino acid; this is coding DNA, not the complementary template.

Do not infer function from the size of a change alone

New coding triplet	Meaning and limits
GAG → mRNA GAG	Glu remains Glu: synonymous at this codon
GTA → mRNA GUA	Glu becomes Val; function depends on the residue's role
TAA → mRNA UAA	Early stop; observed RNA/product amounts can also change
All three	No length change; no downstream frameshift from the **substitution** itself

A SNP identifies variation at one nucleotide position

Separate sequence variation from a disease claim

An observed nucleotide variant is not automatically harmful. Compare sequence, molecular effect and trait evidence.

Degeneracy allows different codons to specify one amino acid. Synonymous describes that coding outcome.

An unchanged amino acid does not by itself prove every aspect of processing, expression and cell function is unchanged.

Regroup from the same start after deleting base 4

1. **Original mRNA.** AUG GAA GCU UAA: Met–Glu–Ala, then stop.
2. **Remove the first G after AUG.** AUG AAG CUU AA: Met–Lys–Leu and an incomplete group.
3. **Conclusion.** The downstream **reading frame** changes. No complete stop is shown; additional sequence is required to locate termination.

Compare a whole-codon deletion with a frameshift

1. **Remove GAA.** AUG GCU UAA: Met–Ala, then stop; one residue missing.
2. **Frame rule.** A coding insertion/deletion not divisible by three shifts subsequent grouping. Three or six bases preserve the downstream frame; large changes can still disrupt a functional domain.
3. **Limits.** A boundary-crossing deletion can alter the joined codon. A preserved frame does not guarantee normal function; a shifted frame need not change every later residue.

A non-coding change can still alter protein production

Name the region and test a proposed mechanism

A promoter change can reduce transcription initiation without altering the coding triplets.

A splice-related change can alter which RNA sequence is retained. Non-coding does not mean biologically irrelevant.

Measure DNA sequence, transcript and protein separately. Lower protein abundance can also reflect altered breakdown or later regulation.

Connect a cause to damage, copying and repair

Source	Possible route to a sequence change
Spontaneous errors	Replication or repair can establish a new base sequence
Ultraviolet	Damage involving neighbouring pyrimidines can disrupt normal copying
Ionizing radiation	Direct DNA damage or reactive products can lead to changes
Benzo[a]pyrene metabolites	Can bind DNA and disrupt copying/repair; tobacco smoke is one source

Calculate a final resistant fraction without calling it a rate

1. **Invented sample.** 24 resistant colonies among 12,000 viable colonies.
2. **Fraction.** $24/12000 = 0.002 = 0.20\%$.
3. **Limit.** This is a final phenotype fraction. Survival, selection, generations and expansion of early mutants affect it; new mutation events per copying event were not counted.

Antibiotic exposure can select variants already present

Selection changes representation; it does not specify the needed base

A resistant lineage may arise before exposure. Removal of susceptible competitors increases its representation.

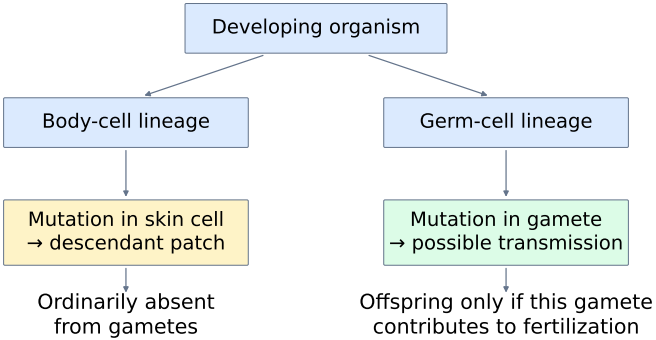
An early mutation can leave many descendants; a late mutation fewer. Independent cultures can therefore vary in resistant counts.

Random with respect to need does not require equal mutation probabilities at all genome sites. Hotspots, repair and exposure can bias rates.

Design the comparison before interpreting the resistant count

1. **Match.** Starting population, medium, exposure, generations and detection method.
2. **Repeat.** Use independent cultures and measure survival as well as the final resistant fraction.
3. **Infer carefully.** More resistant cells after exposure alone cannot distinguish newly induced mutation from selection and multiplication of earlier variants.

Follow mutation through the body or through a gamete



Cell ancestry determines the route of transmission.

Separate cell lineage, transmission and effect

Case	Supported conclusion
Skin-cell mutation	Can pass to descendant skin cells; ordinarily absent from gametes
Germ-cell lineage	May enter a gamete; inheritance requires that gamete to contribute
Later embryonic change	Can create mosaicism across descendant tissues
Growth-control changes	Can contribute to cancer; one mutation is not automatically sufficient

Inherited does not mean beneficial; acquired does not always mean somatic

Identify where the mutation arose

A harmful variant can be somatic or germline. A germline variant can have no detectable effect in the stated conditions.

A change arising during one person's life may occur in a germ-cell lineage, so timing alone does not establish inheritance.

In ordinary sexual reproduction, a mutation restricted to skin cells does not enter an offspring through those skin cells.

Assign each process its actual contribution

Process	Contribution
Mutation	Creates new sequence variants / alleles
Recombination	Rearranges existing alleles into new combinations
Selection	Frequency changes associated with reproductive-success differences
Genetic drift	Chance sampling changes allele frequencies

A useful variant in one environment can carry a cost in another

Fitness describes performance under stated conditions

A resistance variant may help during antibiotic exposure yet have a cost without the antibiotic.

Many changes are neutral in a particular context; changes disrupting important functions are often harmful. No single percentage applies universally.

Heritable variation supplies material for evolution across generations. This does not mean an individual needs a damaging mutation to stay healthy.

Evaluate a commercial genetic-test risk statement

1. **Invented comparison.** Risk rises from 2 in 1,000 to 4 in 1,000.
2. **Two descriptions.** Doubles, a 100% relative increase; absolute increase $= 0.4\% - 0.2\% = 0.2$ percentage points.
3. **Limits.** Association is not a complete individual prediction. Check tested variants, population evidence, effect size and environmental influences; a negative limited panel excludes neither all variants nor all risk.

Attempt the handout questions before revealing answers

Explain the sequence, lineage and evidence separately

Translate and regroup the stated coding sequences. Explain synonymous, replacement, stop and frame-changing effects.

Calculate resistant fractions and absolute/relative risks; explain mutation, inheritance, selection and drift.

Check the shared quantitative practice independently

1. **Resistant fraction.** $36/18000 = 0.002 = 0.20\%$; a final phenotype fraction, not automatically a mutation rate.
2. **Risk.** $3/1000 = 0.3\%$ and $6/1000 = 0.6\%$: doubles; 0.3 percentage-point absolute increase.
3. **Interpretation.** A panel tests specified variants, not every possible cause. A sequence association is not a complete individual prediction.

Check yourself

State what the evidence supports and what remains uncertain

Name DNA region and codon frame. Non-coding changes can affect expression or processing; a frame-preserving change need not be harmless.

Separate new variants, their inheritance and later changes in frequency. Need does not specify the useful new base.