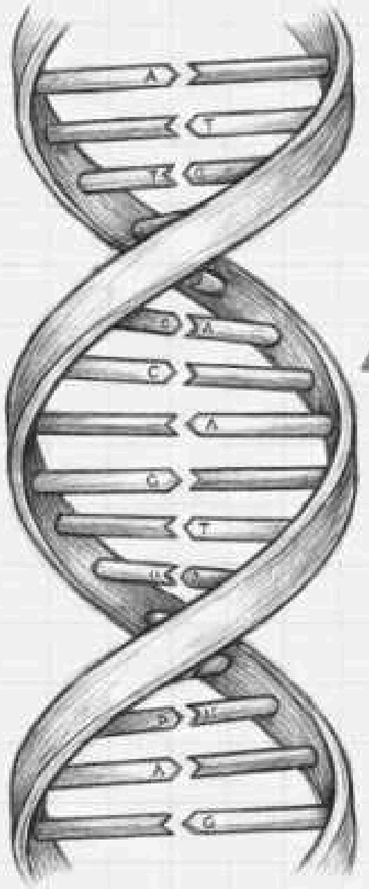
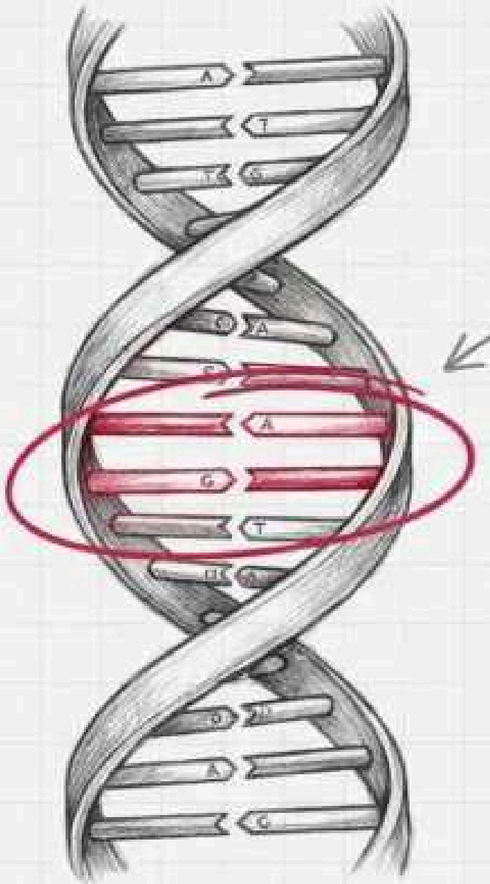
Variation: The Raw Material of Evolution



No two genomes are identical (even identical twins differ slightly).



DNA changes = Variants (formerly ‘Mutations’).

Variation drives uniqueness and evolution, but occasional disruptions cause disease.

The Typography of DNA: Single Letter Substitutions

The smallest change is a single-letter substitution (one base swapped for another). Effect depends on position.

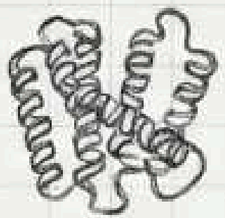
DNA → RNA → Amino Acid

Synonymous

Changed Codon = Same Amino Acid

↓

Protein Unchanged

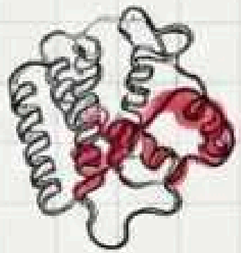


Missense

Changed Codon = Different Amino Acid

↓

Function altered or disrupted

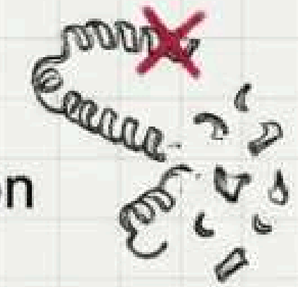


Nonsense

Changed Codon = STOP!

↓

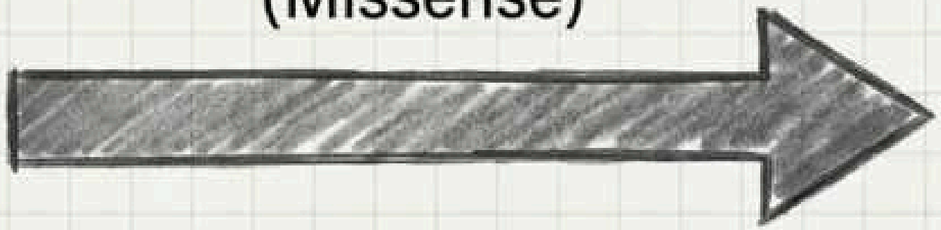
Premature termination; protein function destroyed



Sickle Cell Disease: A Missense Case Study



1 Letter Swaps
1 Amino Acid
(Missense)







Altered haemoglobin clumps when oxygen is low, distorting the cell shape.

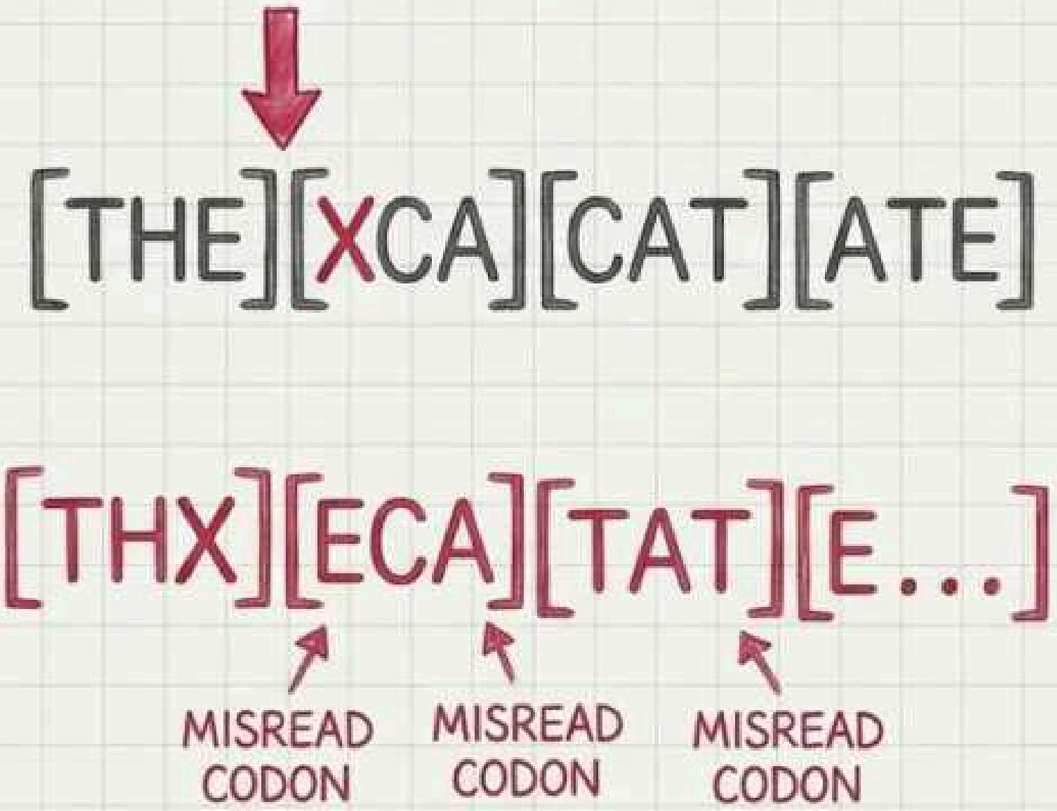


Sickled cells break down early and block small blood vessels. Clinical Impact: Anaemia, pain, organ damage.

One letter, in one gene, explains the whole disease.

Indels and The Reading Frame

Frameshift Insertion



Ruined protein.

In-Frame Deletion

[THE][FAT][CAT][ATE]

Sniped together.

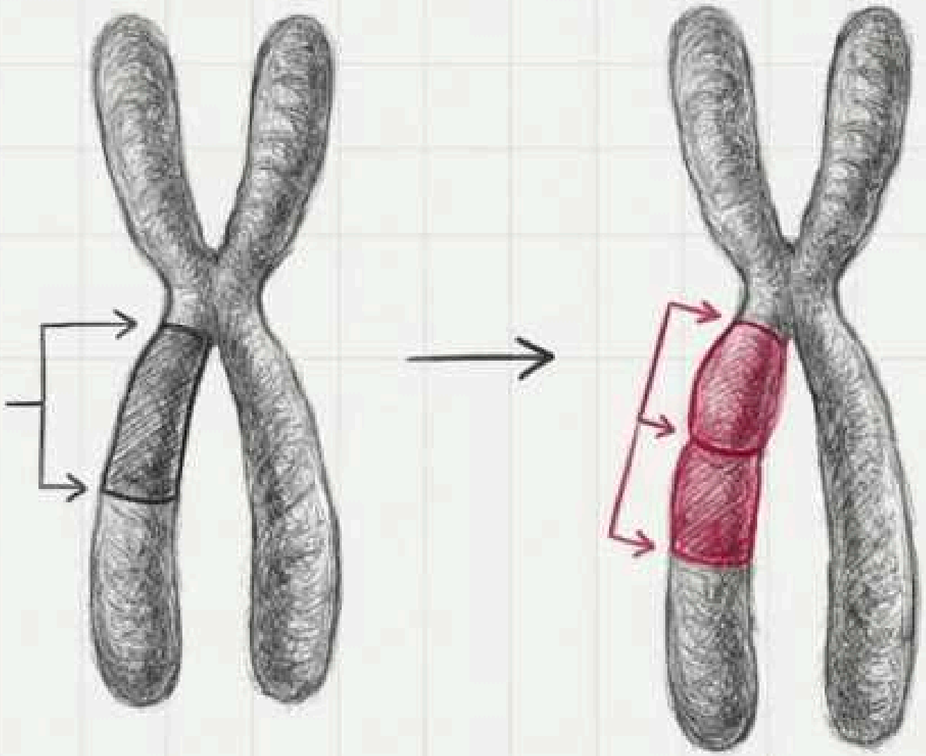
[THE][FAT][CAT][ATE]

[THE][CAT][ATE]

Cystic Fibrosis (Commonest Variant) - Frame intact, but protein still fails to work properly.

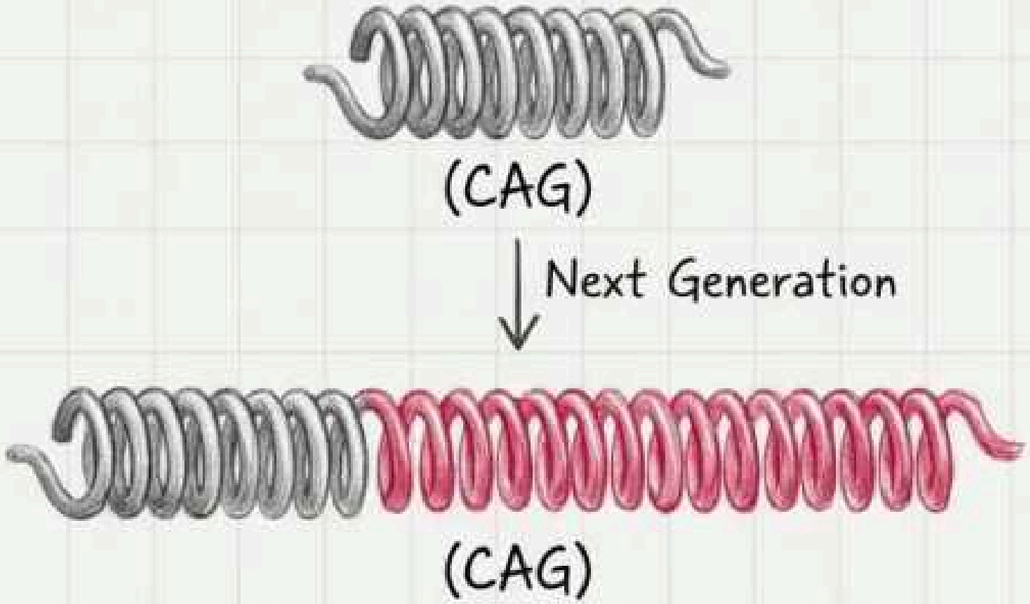
Macro Changes: Sections and Repeats

Deletions/Duplications



Whole sections of a gene (or several) are deleted or duplicated, changing copy numbers.

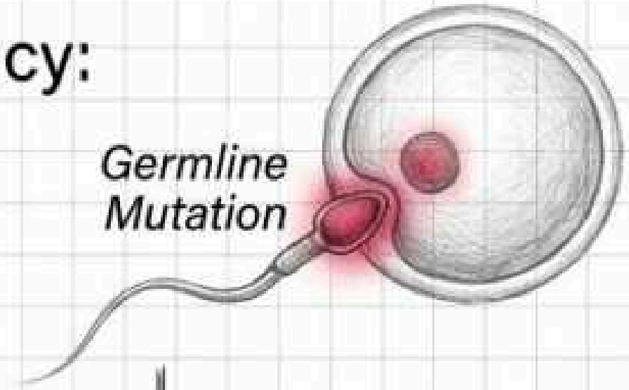
Repeat Expansions

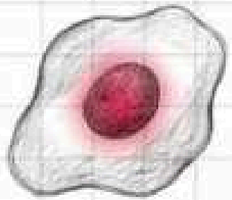


Short 3-letter sequences repeat too many times.

Example: Huntington Disease (repeat grows longer generation to generation, causing earlier disease onset).

Location Dictates Legacy: Germline vs. Somatic

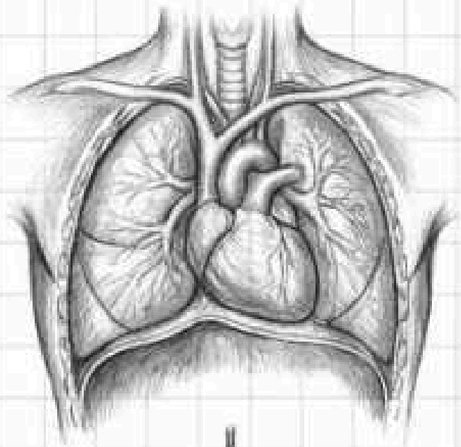


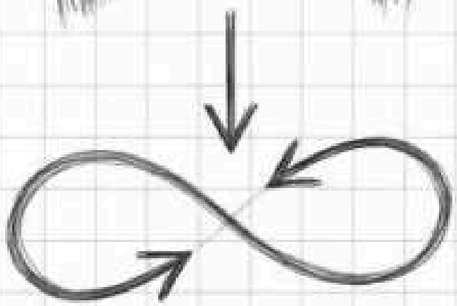


Present in egg/sperm.

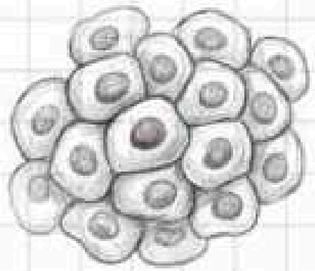
In every cell of the child.

Heritable.





Passed to next generation





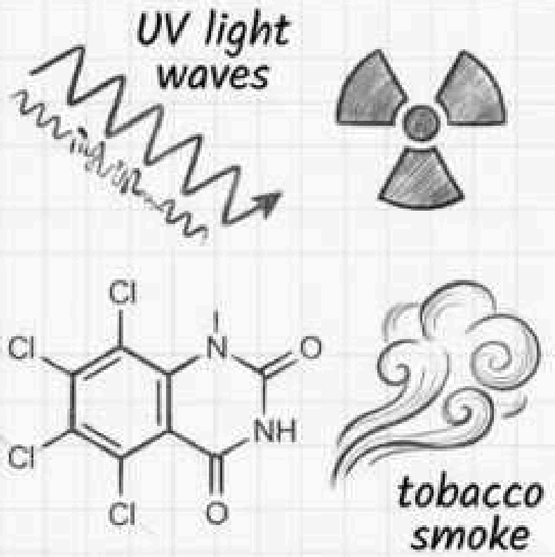
Arises in a single body cell during life.

Passed only to descendants of that cell.

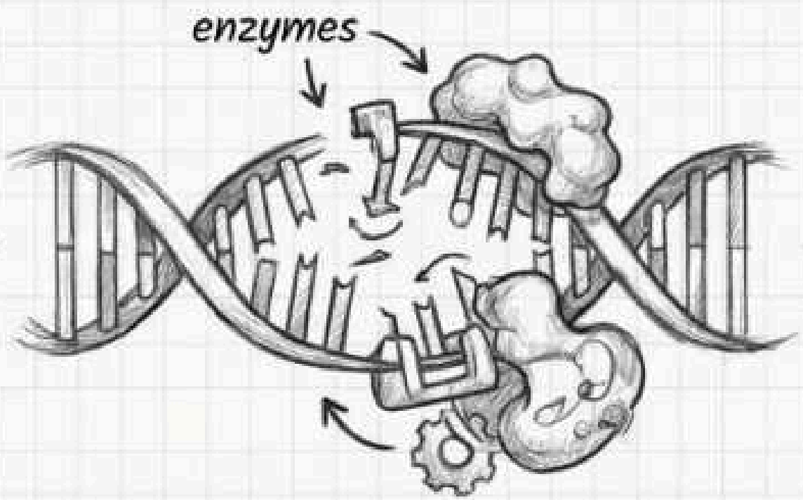
Not heritable by children.

Main cause of cancer.

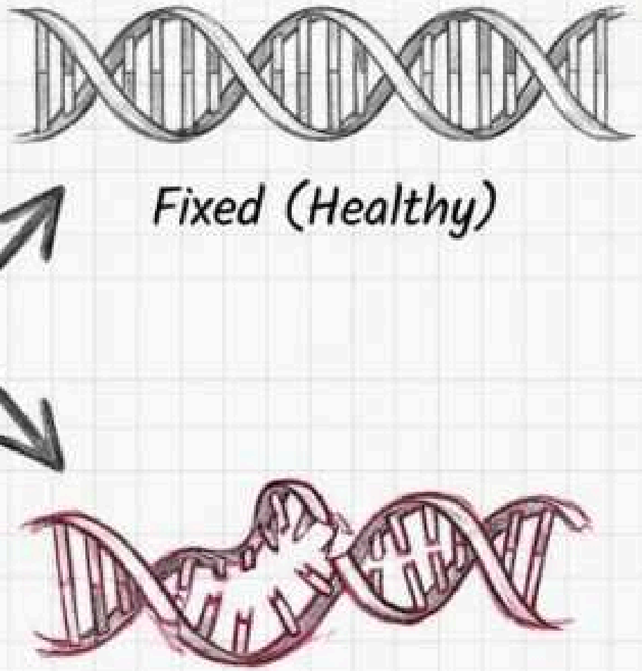
Origins of Damage and The Repair Machinery



Mistakes happen.
Damage is caused by UV light, tobacco, chemicals, and radiation.



Elaborate repair systems fix most damage.

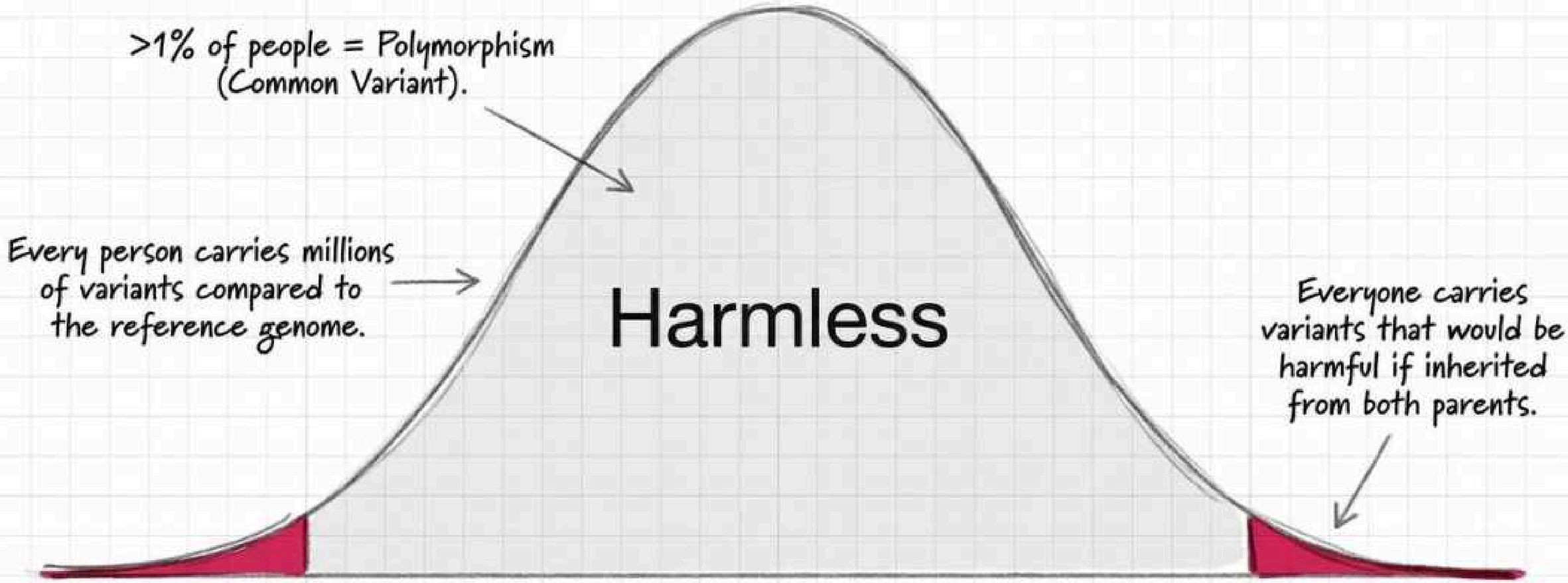


Fixed (Healthy)

Faulty Repair

When repair systems are faulty, changes accumulate rapidly → Causes inherited cancer syndromes.

Variation is the Norm

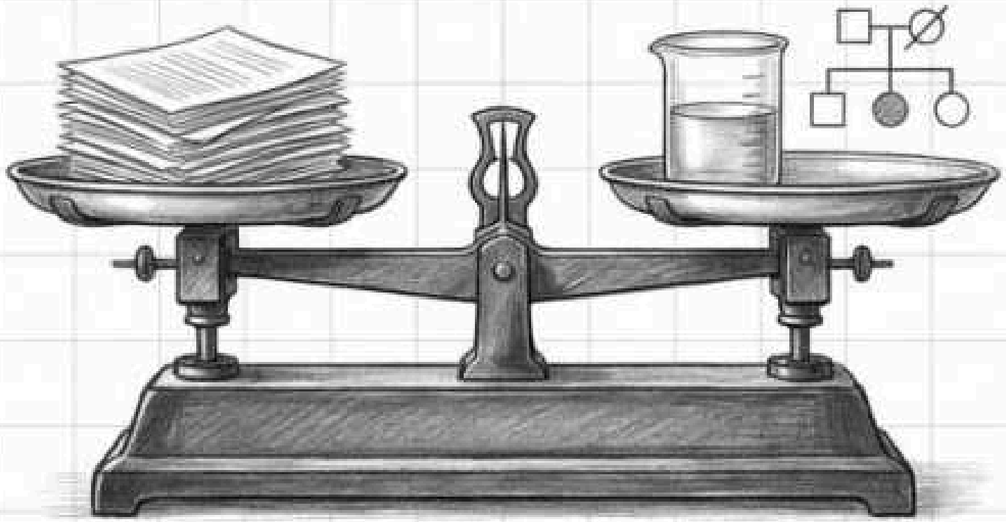


Variation is normal; disease is the exception.

The Clinical Classification Scale

The Hardest Task: Deciding whether a particular variant causes disease requires weighing many kinds of evidence.

Population Data +
Protein Predictions



Family History +
Lab Experiments

Benign

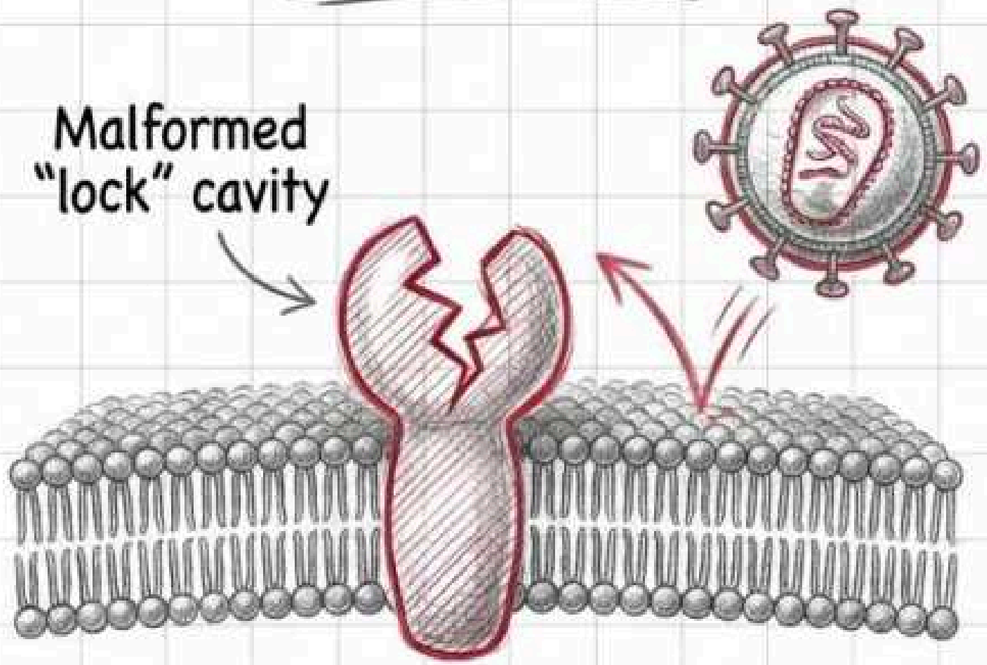
VUS
(Variant of Uncertain Significance)

Pathogenic
(Disease-causing)

Clinical Rule: A VUS is exactly that—uncertain.
It should not be treated as a diagnosis.

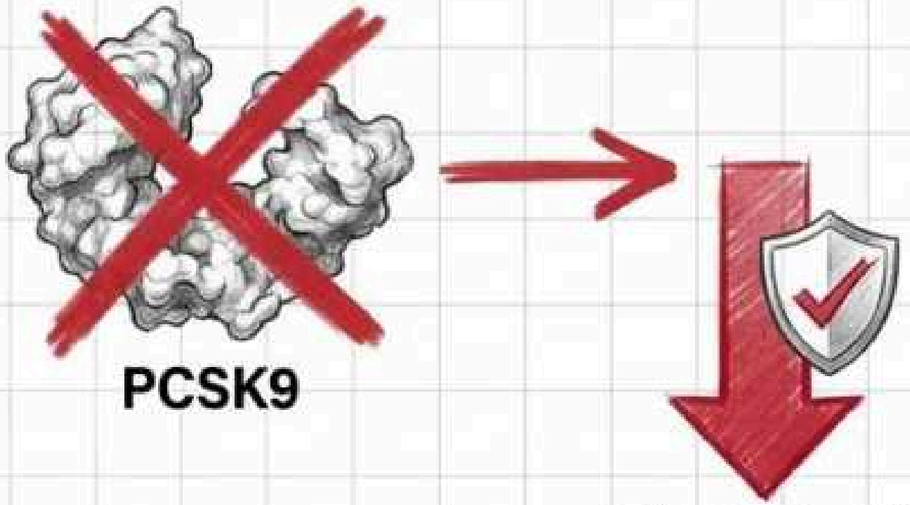
The Protective Power of Variants

HIV Resistance



A variant disables the receptor used by HIV. Carrying two copies makes a person highly resistant to the virus.

Heart Disease Protection



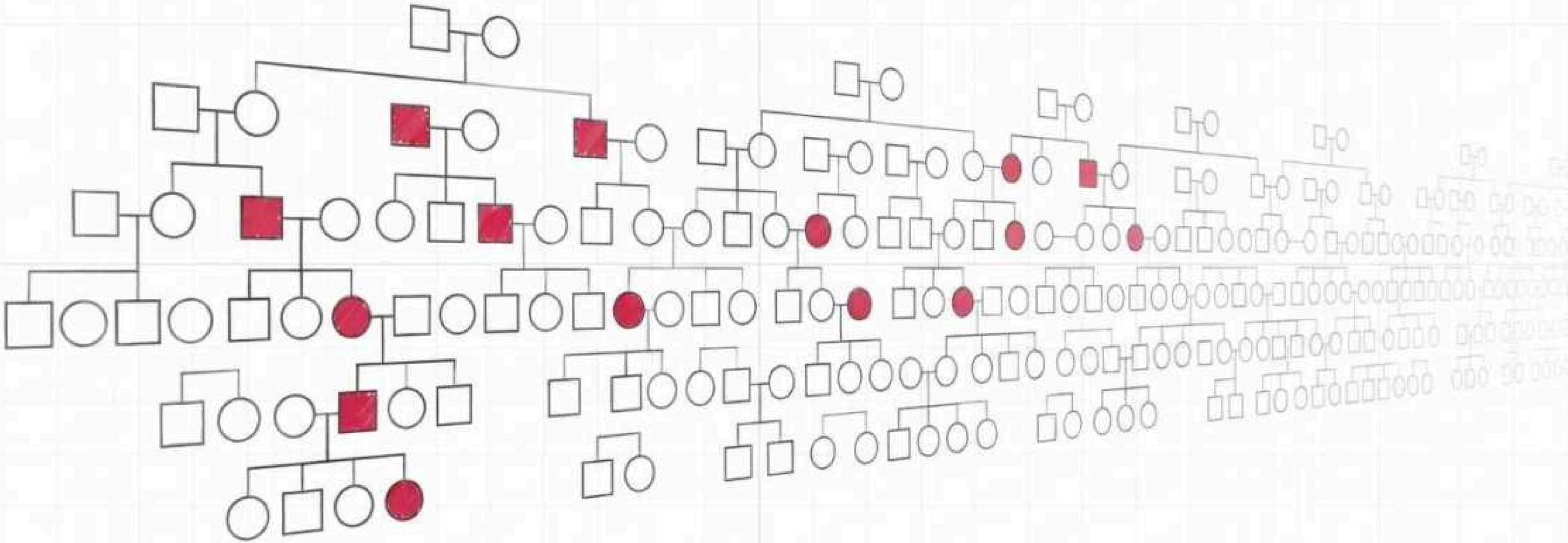
PCSK9 variants lower cholesterol and protect against heart disease (led directly to new medicines).

Takeaway: Studying natural variation is one of the most powerful ways to find new drug targets.

Q: Why does a change that adds one letter to a gene usually do more damage than a change that swaps one letter for another?

Use the idea of the reading frame to explain.

Looking Ahead: Inheritance



Next in Lecture 3: Classic patterns of inheritance.

Preview: How variants pass through families.