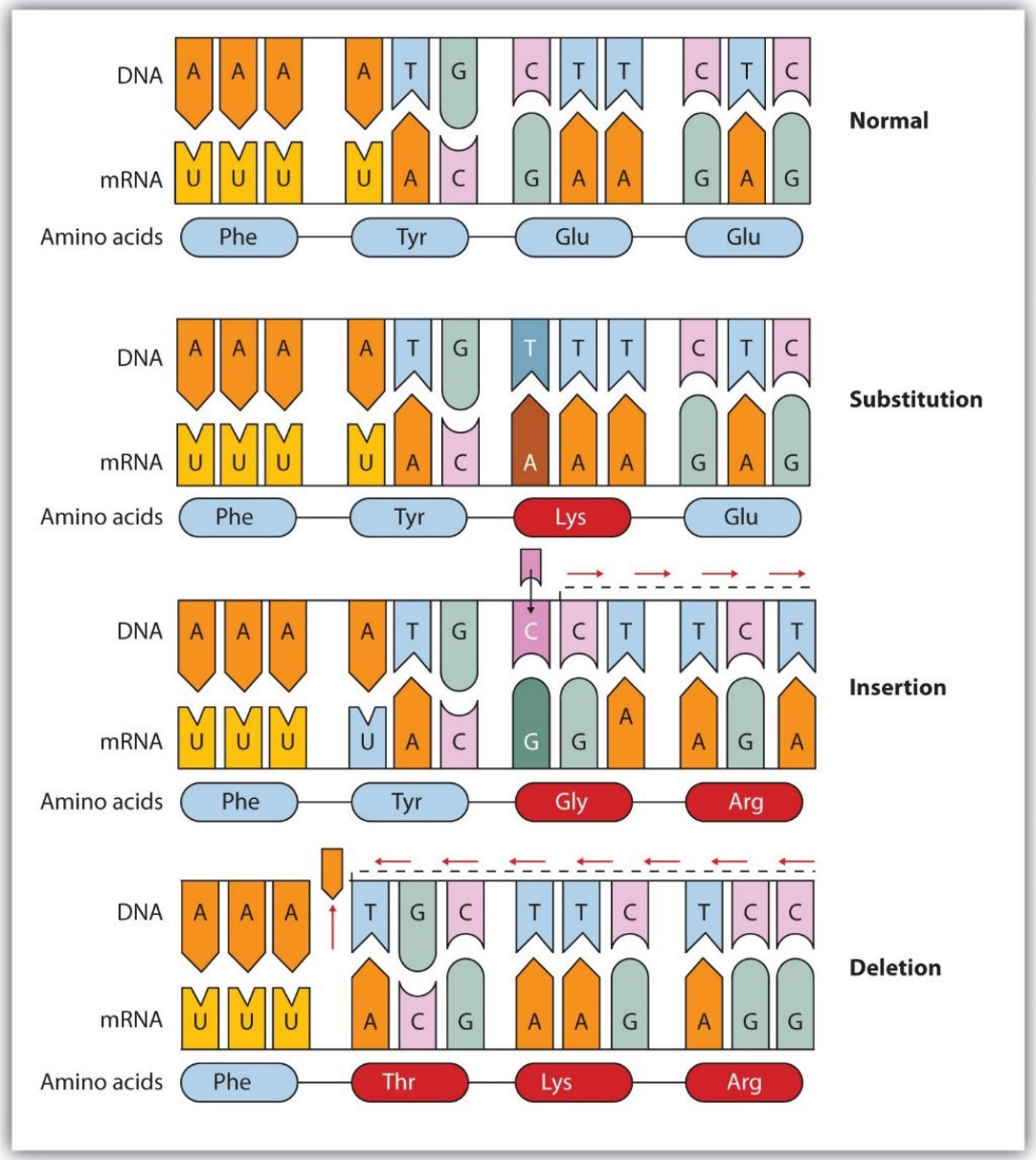
Lesson 13
DNA mutations and their outcome

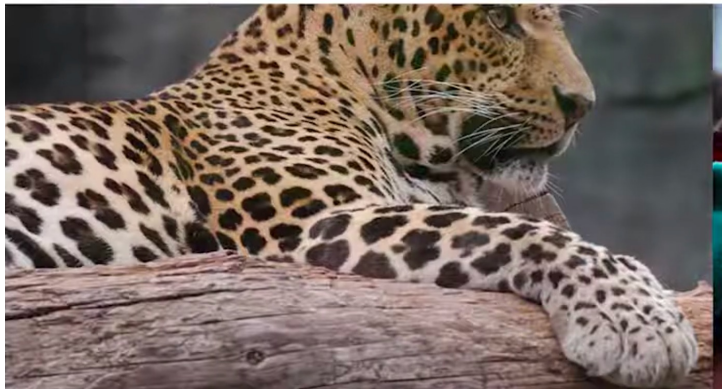


Phenotype

- Changes in genes (DNA) govern the outcome for the organism
- How does a DNA sequence connect with a trait?
  - Trait = something that you can see, an observable characteristic
  - *E.g.*, your eye color, your hair color, your height, ….
- The composite observable characteristics or traits of an organism is called a **PHENOTYPE**

Gene ←→ phenotype

How does DNA sequence connect with a trait? (phenotype)
May alter protein sequence (and therefore function)
or amount of protein made…..



Mutations

- DNA (gene) $\xrightarrow{\text{transcription}}$ RNA $\xrightarrow{\text{translation}}$ protein $\xrightarrow{\text{function}}$ trait
- Trait = observable characteristic = **phenotype**

Mutations

- DNA (gene) transcription RNA translation protein function trait
- Trait = observable characteristic = **phenotype**

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Mutations

- DNA (gene) transcription RNA translation protein function trait
- Trait = observable characteristic = **phenotype**

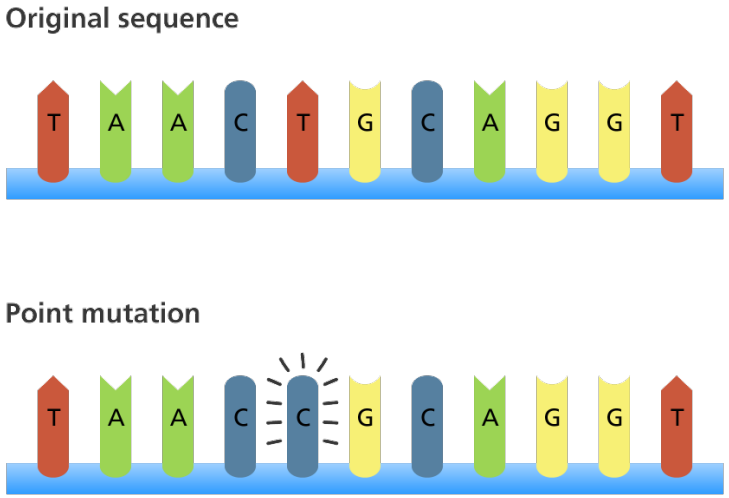
- DNA (gene) transcription RNA translation protein function trait

- Changes in DNA nucleotide sequences = **MUTATIONS**
- Mutated DNA generally:
  - Mutated RNA –> Mutated protein → mutated trait

Mutation main types

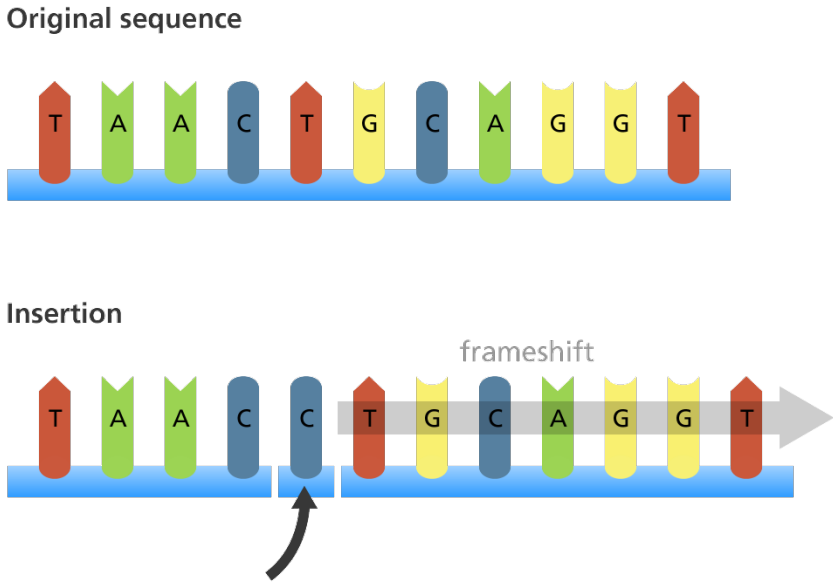
- Point mutations: change 1 nucleotide of one type with another nucleotide of another type in the original sequence
  - *e.g.*, TAAC**T**T… → TAAC**C**T…
- This may change, destroy, or have no effect on the resulting protein
- 🛠️ Engineering Analogy:
- Point Mutation = A typo in a software code
  - Example: Print(“Hello”) → Print(“Hollo”)

  ❌ Some typos crash the program, while others have no effect



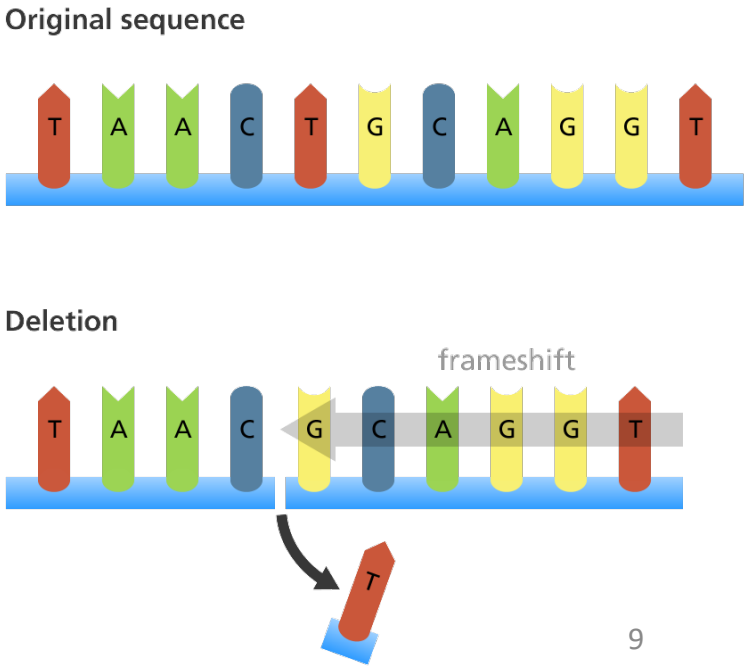
Mutation main types

- Point mutations: change 1 nucleotide of one type with another nucleotide of another type in the original sequence
  - *e.g.*, TAACTT… → TAACCT…
- Insertion: one or more nucleotides are added to the original sequence
  - *e.g.*, TAACT… → TAACCT…



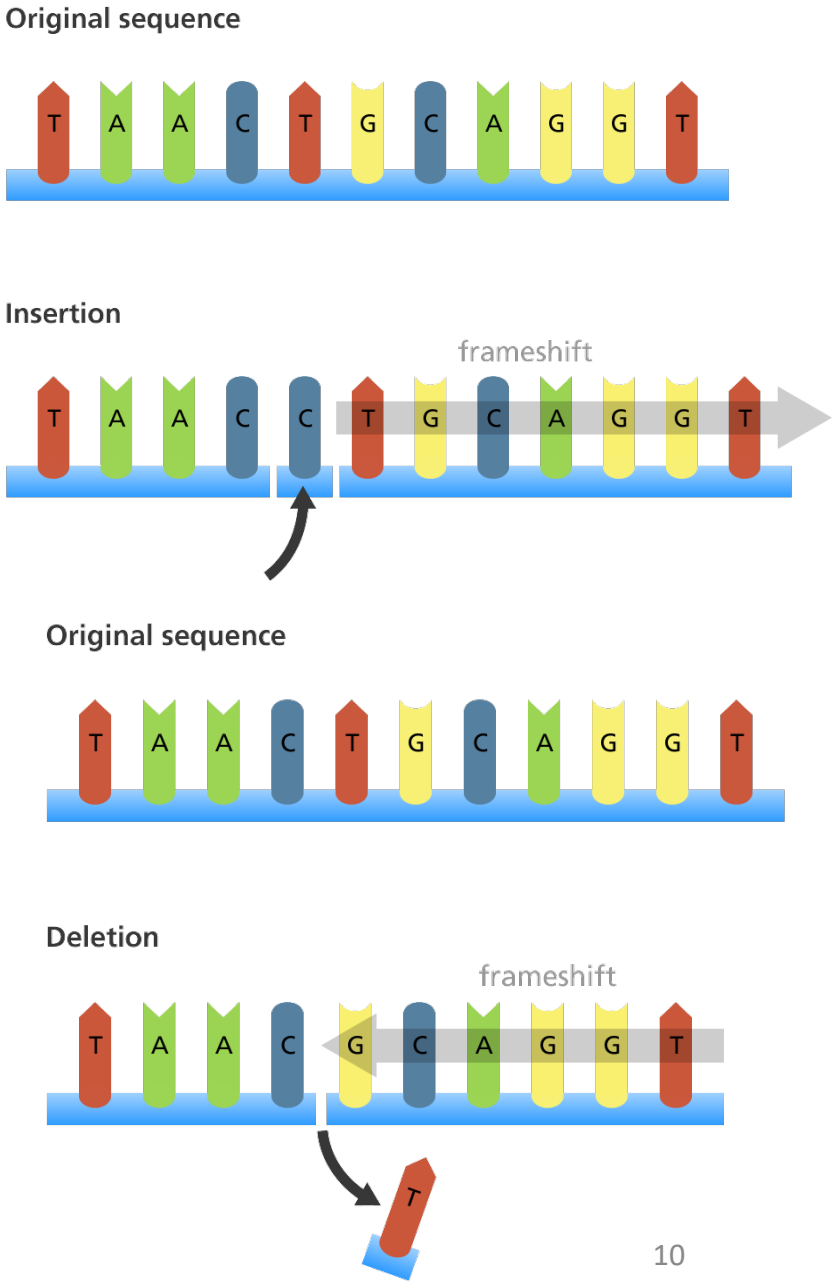
Mutation main types

- Point mutations: change 1 nucleotide of one type with another nucleotide of another type in the original sequence
  - *e.g.*, TAAC**T**T… → TAAC**C**T…
- Insertion: one or more nucleotides are added to the original sequence
  - *e.g.*, TAACT… → TAAC**C**T…
- Deletion: one or more nucleotides are removed from the original sequence
  - *e.g.*, TAAC**T**GC…→ TAACGC



Mutation main types

- Both insertions and deletions **shift the reading frame**, affecting **all codons after the mutation**
- 🛠️ Engineering Analogy
  - Insertion = Accidentally adding an extra command in a software script
  - Deletion = Removing an essential command, breaking the code
- Example:
  ✅ Correct code: "The cat rans fast”
- ✅ Correct reading : "The cat ran sfa st”
- ❌ Insertion: "The xca tra nsf ast" (reading frame is shifted to the right)
- ❌ Deletion: "The catr ans fas t" (reading frame is shifted to the left
- ➡️ When the code shifts, the entire program (protein) may break (being something completely different structure and function)



Point mutations

Coding strand → 5’ ATGTGGCTCCTGGATTAA 3’

Template strand → 3’TACACCGAGGACCTAATT5’

DNA

mRNA → 5’ AUGUGGCUCCUGGAUUAA 3’

protein → N-Met-Trp-Leu-Leu-Asp-C (stop)

Point mutations

Coding strand → 5’ ATGTGGCTCCTGGATTAA 3’

Template strand → 3’TACACCGAGGACCTAATT5’

DNA

mRNA → 5’ AUGUGGCUCCUGGAUUAA 3’

protein → N-Met-Trp-Leu-Leu-Asp-C (stop)

Point mutation (**MISSENSE**)

Coding strand → 5’ ATGTGGCTCCTGGTTTAA 3’

Template strand → 3’ TACACCGAGGACC**A**AATT5’

mRNA → 5’ AUGUGGCUCCUGG**U**UUAA 3’

protein → N-Met-Trp-Leu-Leu**-Val-C** (stop)

Point mutations

Coding strand	→	5’ ATGTGGCTCCTGGATTAA 3’
Template strand	→	3’ TACACCGAGGACCTAATT5’
mRNA	→	5’ AUGUGGCUCCUGGAUUAA 3’
protein	→	N-Met-Trp-Leu-Leu-Asp-C (stop)

DNA

Point mutation (**NONSENSE**)

Coding strand	→	5’ ATGT**A**GCTCCTGGATTAA 3’
Template strand	→	3’ TAC**T**CGAGGACCTAATT5’
mRNA	→	5’ AUGU**A**GCUCCUGGAUUAA 3’
protein	→	N-Met-**Stop**

Point mutations

Coding strand	→	5’ ATGTGGCTCCTGGATTAA 3’	DNA
Template strand	→	3’ TACACCGAGGACCTAATT5’	
mRNA	→	5’ AUGUGGCUCCUGGAUUAA 3’	
protein	→	N-Met-Trp-Leu-Leu-Asp-C (stop)	

Point mutation (**SILENT**)

Coding strand	→	5’ ATGTGGCTCCTGGACTAA 3’
Template strand	→	3’ TACACCGAGGACCT**G**ATT5’
mRNA	→	5’ AUGUGGCUCCUGGA**C**UAA 3’
protein	→	N-Met-Trp-Leu-Leu-**Asp-C** (stop)

Insertions

Coding strand → 5’ ATGTGGCTCCTGGATTAA 3’

Template strand → 3’ TACACCGAGGACCTAATT5’

DNA

mRNA → 5’ AUGUGGCUCCUGGAUUAA 3’

protein → N-Met-Trp-Leu-Leu-Asp-C (stop)

Insertion (reading frame shift)

Coding strand → 5’ ATGTGG**A**CTCCTGGATTAA 3’

Template strand → 3’ TACACC**T**GAGGACCTAATT5’

Reading frame shift

mRNA → 5’ AUGUGG**A**CUCCUGGAUUAA 3’

protein → N-Met-Trp-**Thr-Pro-Gly-Leu-C**

Deletions

Coding strand → 5’ ATGTGGCTCCTGGATTAA 3’

Template strand → 3’ TACACCGAGGACCTAATT5’

DNA

mRNA → 3’ AUGUGGCUCCUGGAUUAA 5’

protein → N-Met-Trp-Leu-Leu-Asp-C (stop)

Deletion (reading frame shift)

Coding strand → 5’ ATGTGCTCCTGGATTAA 3’

Template strand → 3’ TACACGAGGACCTAATT5’

Reading frame shift

mRNA → 5’ AUGUGCUGGUGGAUUAA 3’

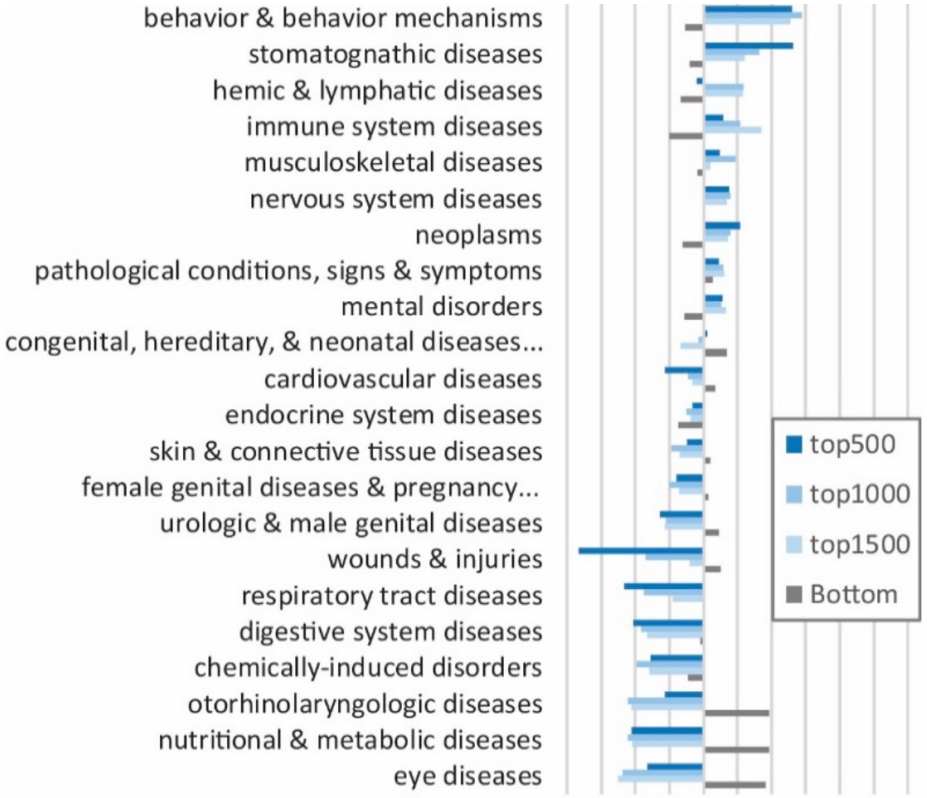
protein → N-Met-**Cys-Trp-Trp-Ile-C**

Mutations - recap

- **Missense mutation** → Changes one protein into another
- **Nonsense mutation** → Prematurely stops mRNA translation resulting in a truncated protein
- **Silent mutation** → The results of the translation is again the wild-type protein
  - This is because of the "redundancy" of the genetic code (more codons codify for the same amino acid – see The codon chart)
- **Insertion/deletion** → Change the reading frame and the protein that is encoded in the mutated gene

Mutations - recap

- Proteins resulting from any of these gene mutations (except from silent mutations) may:
  - Be non-functional (**loss of function**)
    - Protein does not work or is missing
  - Be over-functional (**gain of function**)
    - Protein works too well or at the wrong time
  - Have a **new function**
    - Protein does something completely different
- All these aspects may result in **important human pathologies**



Other mutations

- Some mutations do not change the protein itself but affect how much of it is made
- These mutations occur in the so-called **DNA regulatory (control) regions**
- 🛠️ Engineering Analogy: Regulatory DNA = The volume knob controlling how loud the sound is made by a radio
- Mutation in this region = Making the music too loud (too much protein) or too quiet (too little protein)
- Example: Overproduction of a protein → Cancer (cells grow uncontrollably)
- Reduced protein production → Anemia (low red blood cell count)