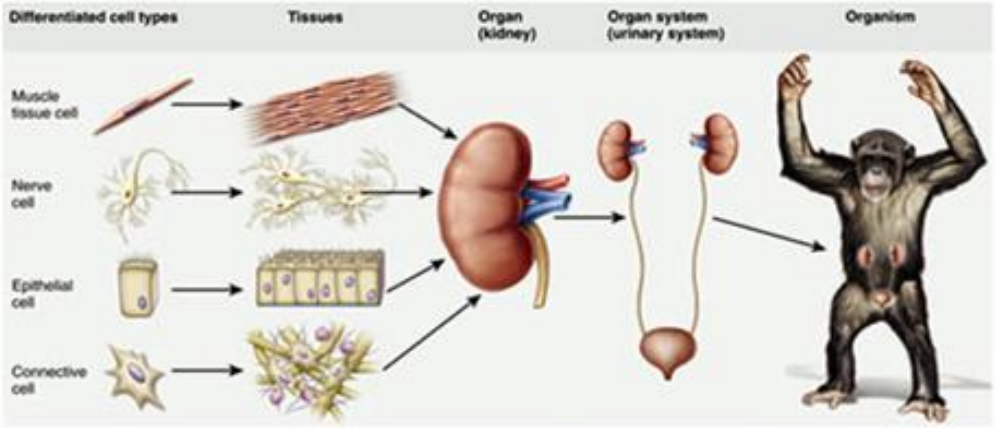
Fundamentals of Molecular Biology

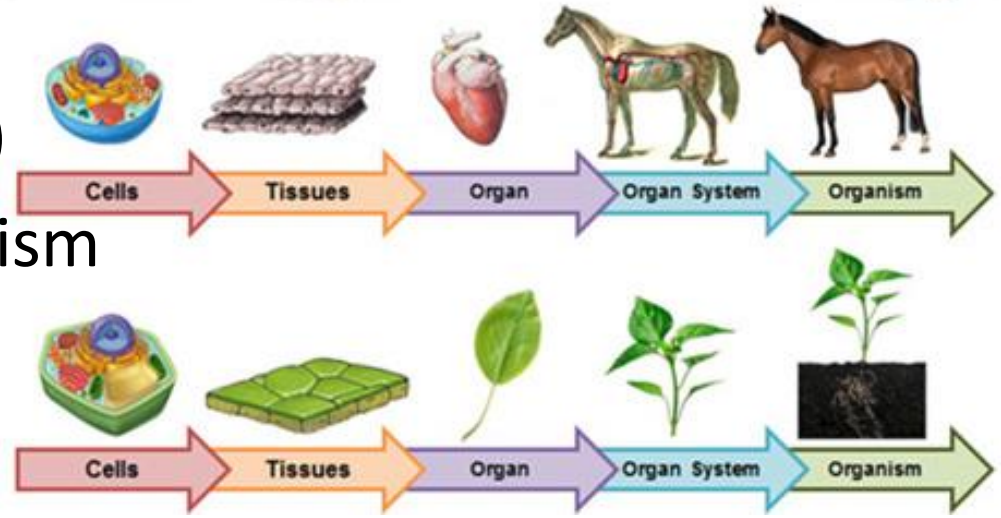
IN-BIOS 5000/9000

1. A guided tour of the (human) genome
2. From DNA to biological function
3. Genomics in biomedical research

Living organisms are built up of cells

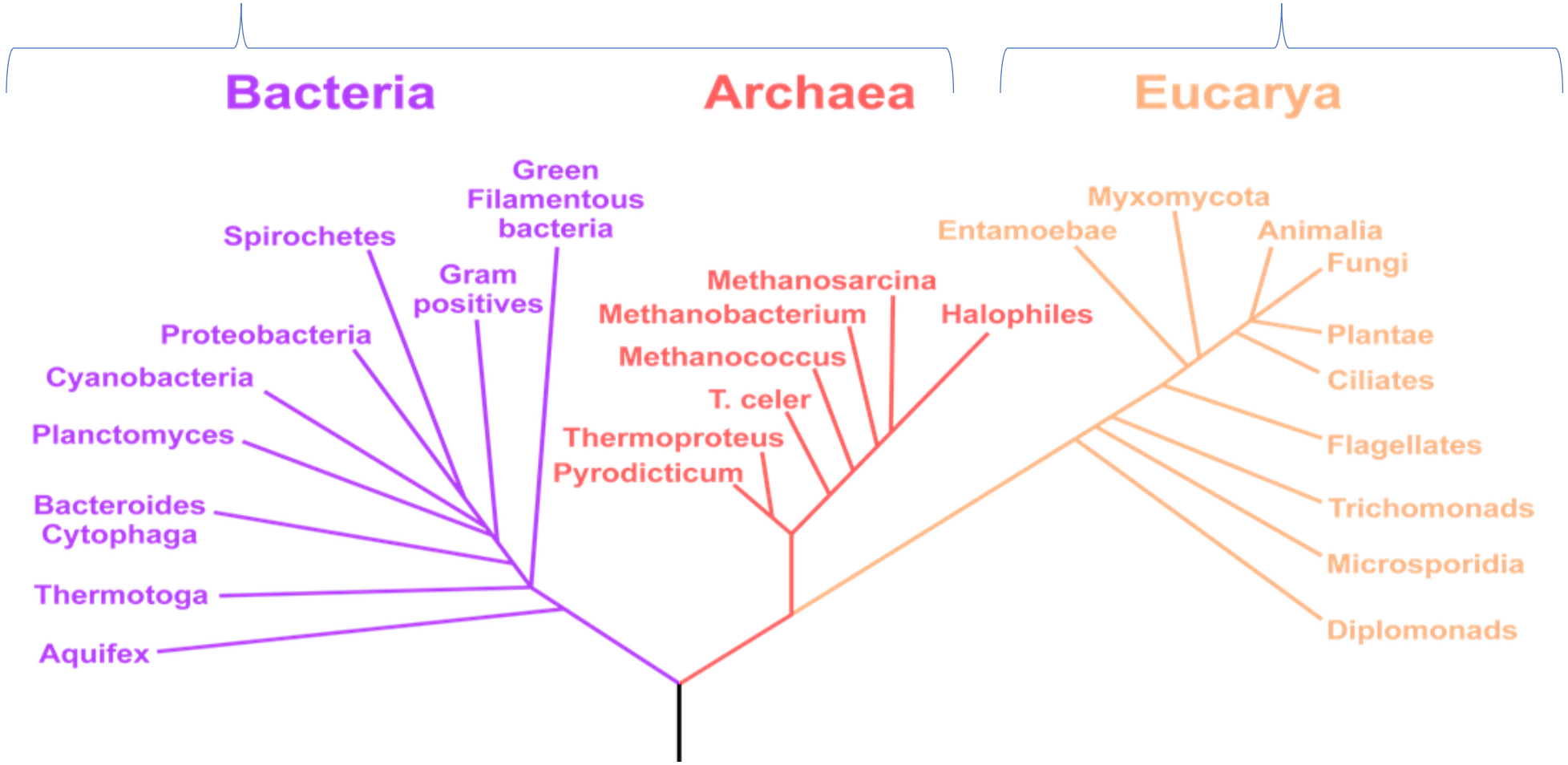
- Unicellular organisms *vs.* multicellular
- Humans, average 5 x 10^{13} cells (50 000 billion)
- Cells > tissues > organ > organ system > organism





https://arts2science.wordpress.com/livingthings/celltissueorgansystemorganism/

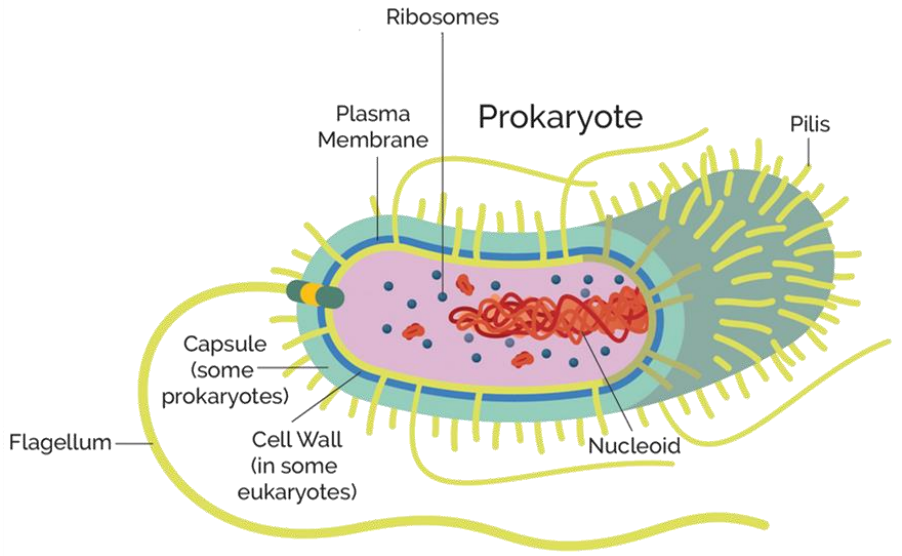
Prokaryots *vs.* eukaryots



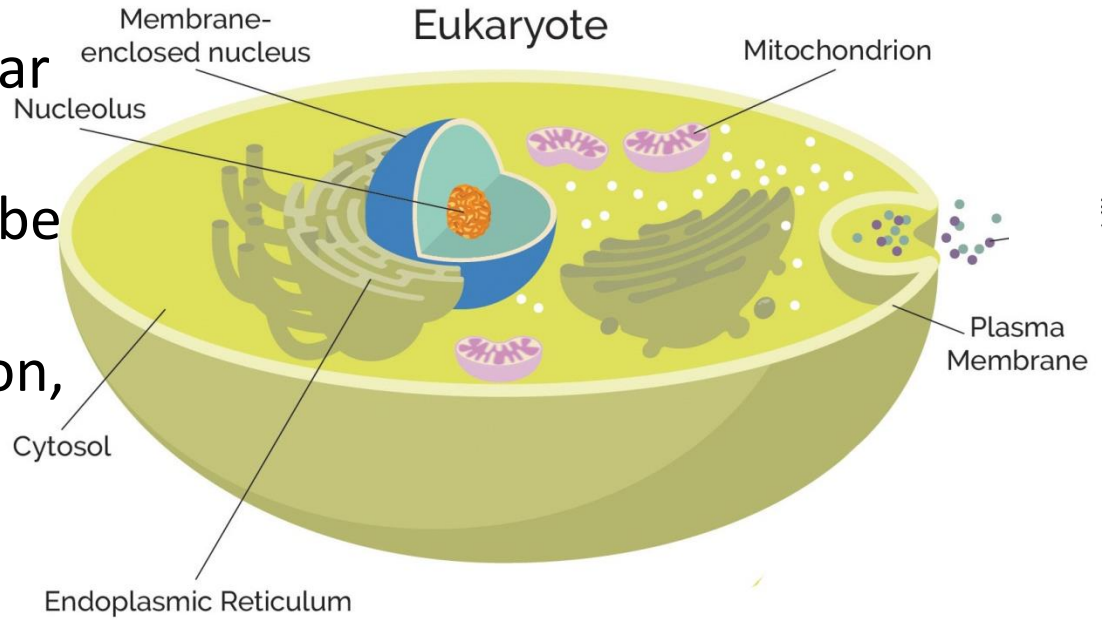
Eric Gaba

Prokaryots *vs.* eukaryots

- Procaryots
  - DNA stored in the cytoplasm, commonly a single circular chromosome
  - Allways unicellular, high-speed selective pressure
- Eukaryots
  - DNA in a cellular nucleus, with several linear chromosomes
  - 100-10000 x larger than procaryotes, may be multicellular
  - Organelles *(e.g.* mitochondria), cytoskeleton, endoplasmatic reticulum, golgi apparatus
- Different histones and ribosomes

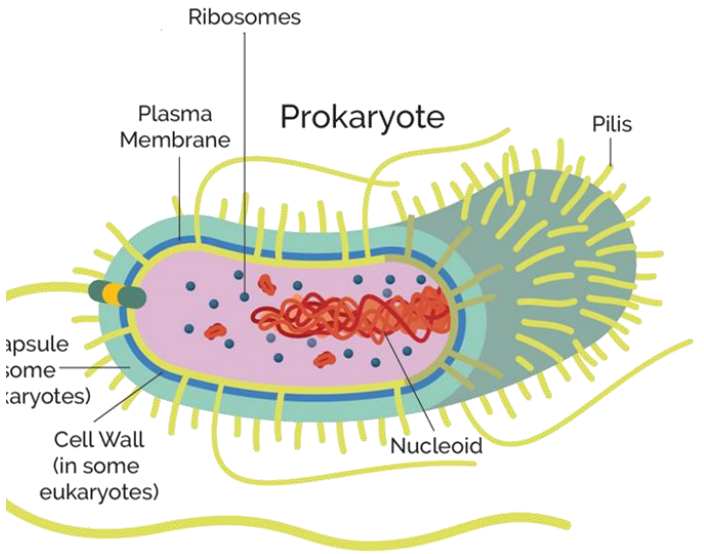


Typically 25 *vs.* 1 μm diameter

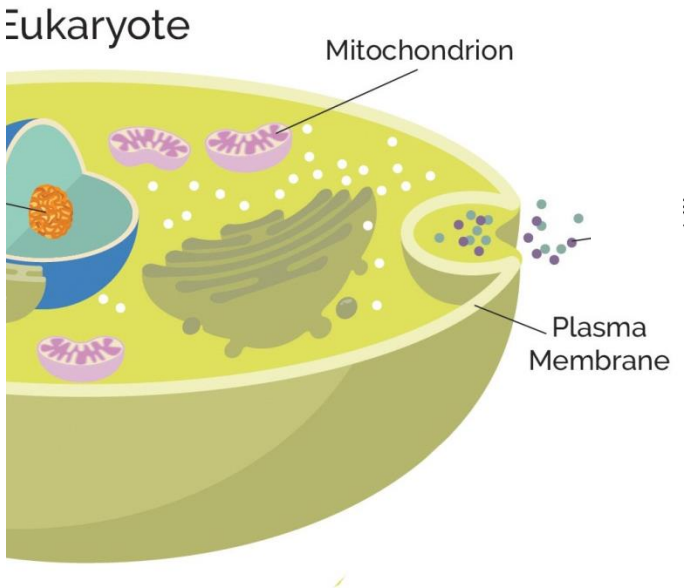


Prokaryots *vs.* eukaryots

	Prokaryote	Eukaryote
Nucleus	Absent	Present
Membrane-bound organelles	Absent	Present
Cell structure	Unicellular	Mostly multicellular; some unicellular
Cell size	Smaller (0.1-5 µm)	Larger (10-100 µm)
Complexity	Simpler	More complex
DNA Form	Circular	Linear
Examples	Bacteria, archaea	Animals, plants, fungi, protists

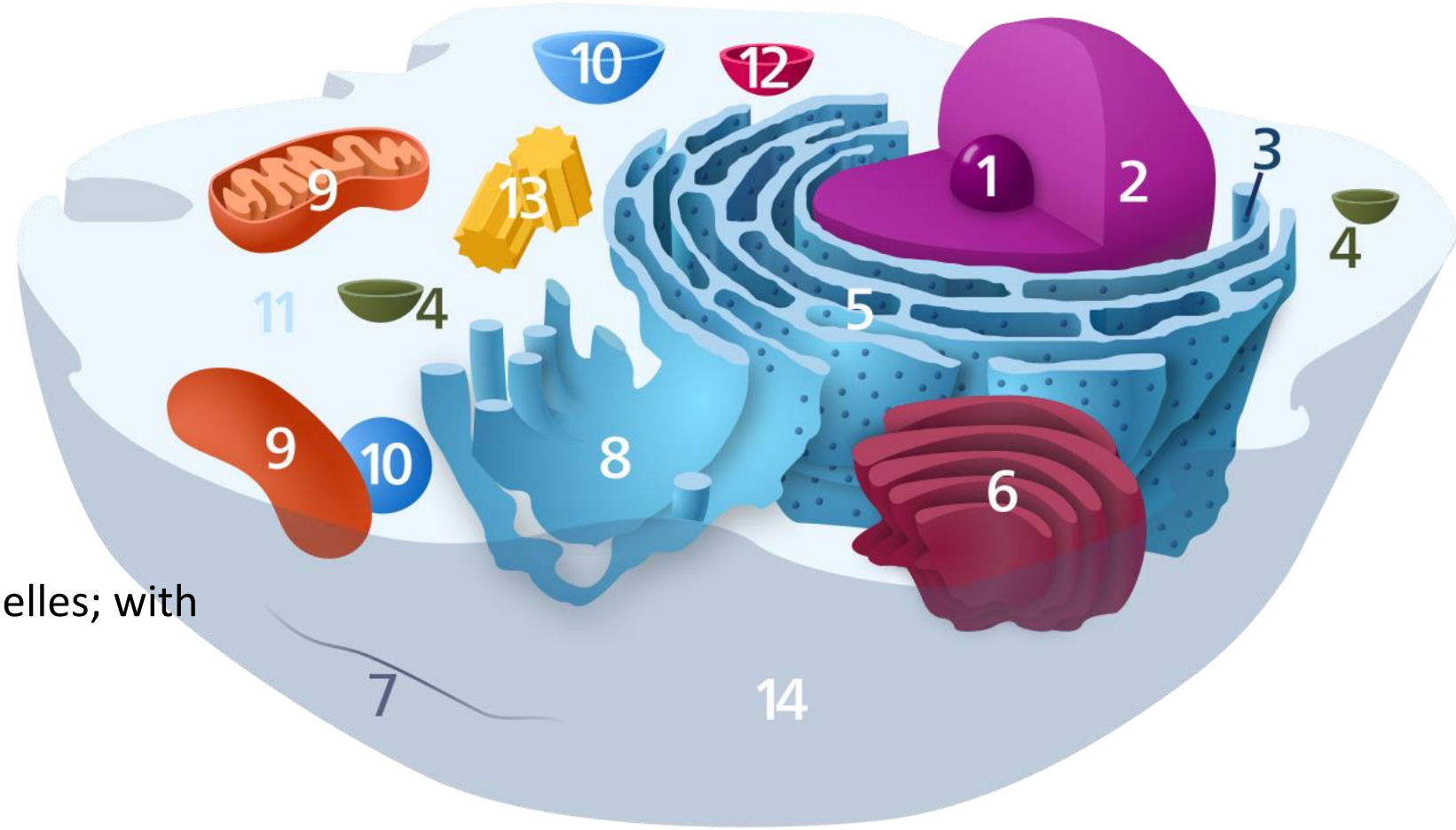


Typically 25 *vs.* 1 µm diameter



Components of a typical eukaryotic cell

1. Nucleolus
2. Nucleus
3. Ribosome (dots as part of 5)
4. Vesicle
5. Rough endoplasmic reticulum
6. Golgi apparatus
7. Cytoskeleton
8. Smooth endoplasmic reticulum
9. Mitochondrion
10. Vacuole
11. Cytosol (fluid surrounding organelles; with which, comprises cytoplasm)
12. Lysosome
13. Centrosome
14. Cell membrane



Wikipedia

Components of a typical eukaryotic cell

Nucleus: Stores the genetic information in chromatin form (DNA twined around proteins [histones])

Nucleolus: The part of eukaryotic cells where ribosomal RNA is produced; found inside of the nucleus

Plasma membrane: A phospholipid bilayer surrounding the cell and encompassing the organelles within

Cytoskeleton or cell wall: Provides structure, allows for cell movement, and plays a role in cell division

Ribosomes: Carrying out protein synthesis

Mitochondria: Sites for energy production

Cytoplasm: The region of the cell between the nuclear envelope and plasma membrane

Cytosol: A gel-like substance within the cell that contains the organelles

Endoplasmic reticulum: An organelle dedicated to protein maturation and transportation

Vesicles and vacuoles: Membrane-bound sacs involved in transportation and storage

Other common organelles in many eukaryotes include the **Golgi apparatus**, **chloroplasts** and **lysosomes**

Biological macromolecules

Large molecules, necessary for life, built from smaller organic molecules

The majority of a cell's dry mass

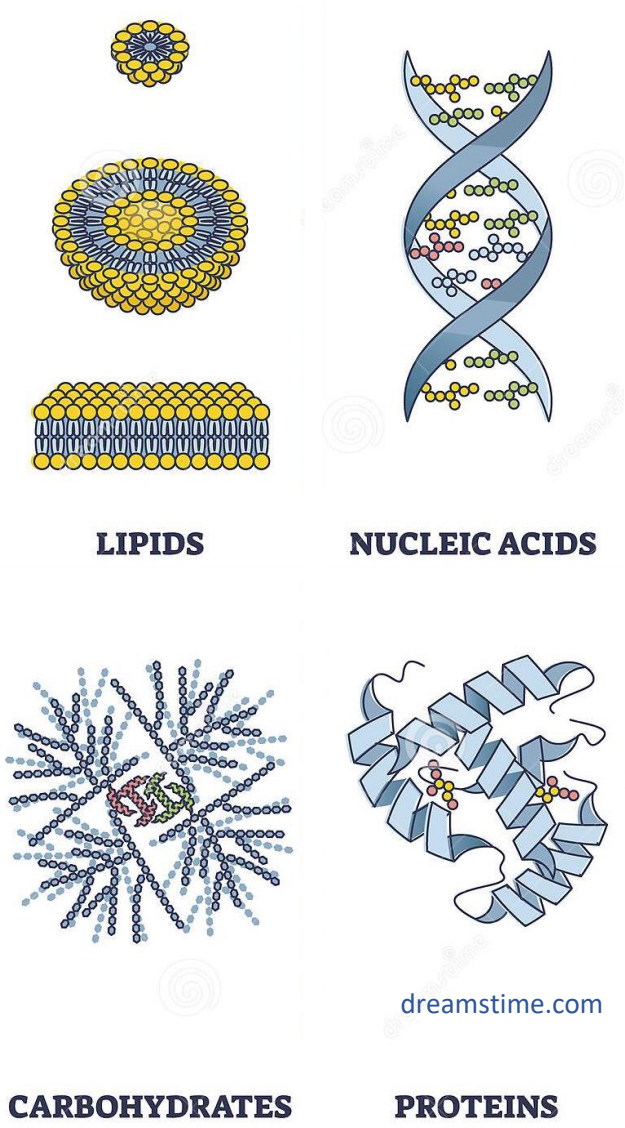
Four main types and functions

Nucleic acids (DNA & RNA): Information storage and transfer, ribozymes

Proteins: Structure, enzymes, signalling

Lipids: Membranes, energy storage, signalling, insulation

Carbohydrates: Energy storage, structure

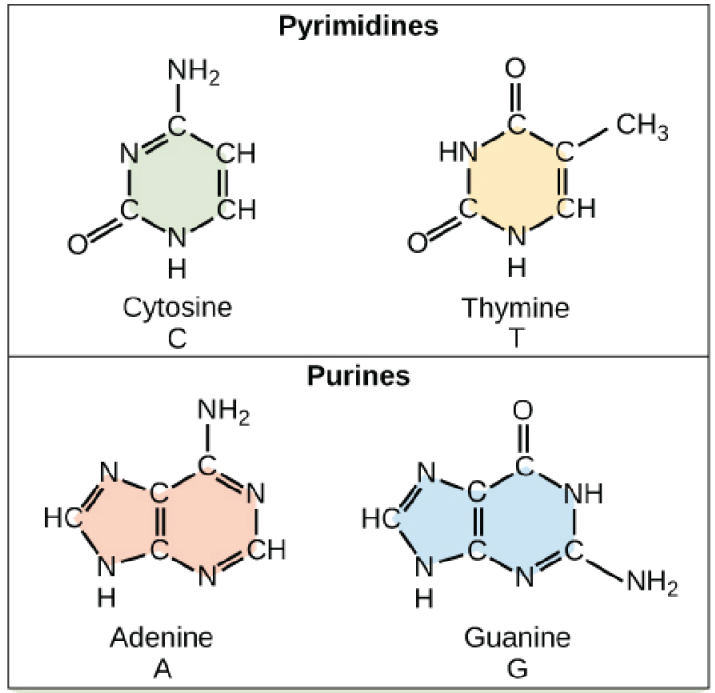


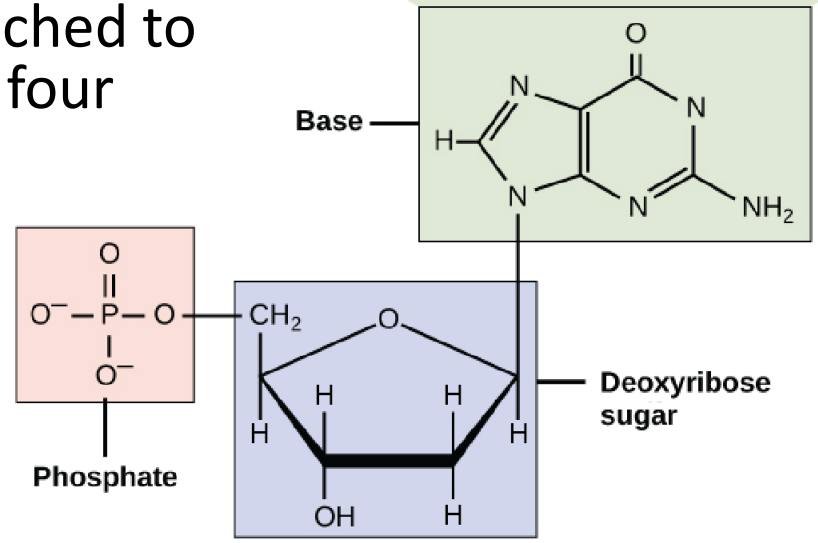
DNA

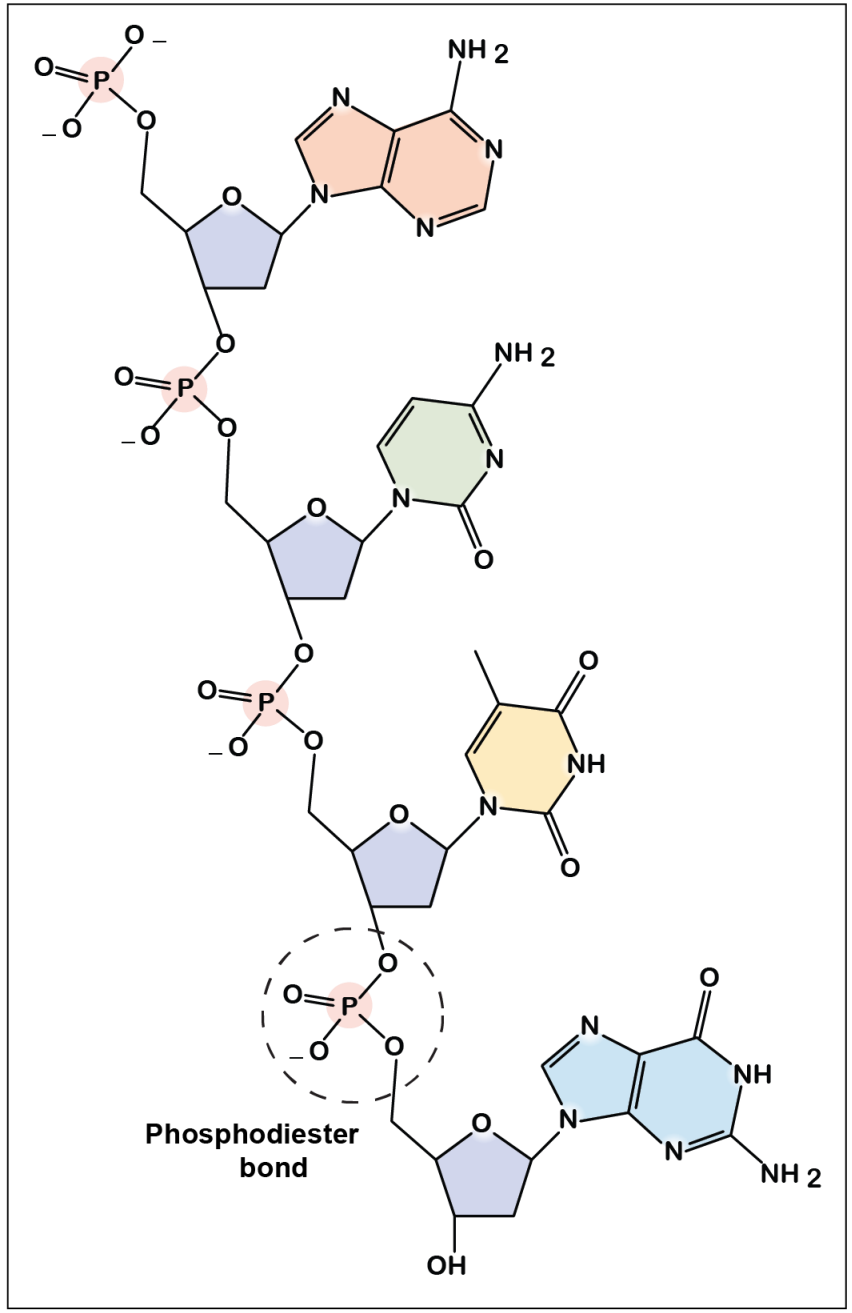
Deoxyribonucleic acid

Nucleotides = phoshate + sugar + base

The DNA-strand has a sugar-phosphate backbone where bases attached to the sugars are of four types

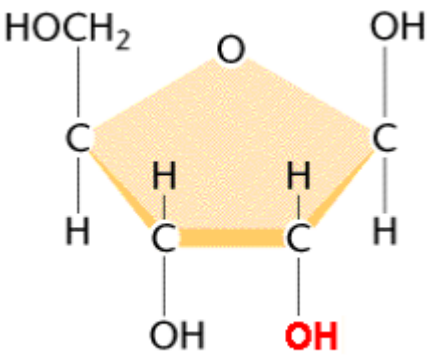




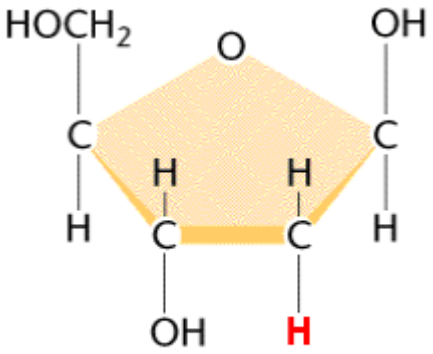


(Deoxy)ribonucleic acids, DNA & RNA

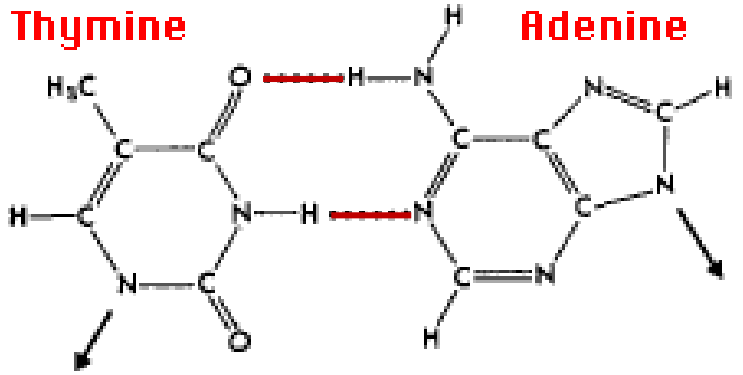
- Four bases or nucleotides: A, C, G, T (or U)
  - Thymine is exchanged for Uracil in RNA
- Double strand and base pairing, A::T & C:::G
- Directionality 5’ to 3’ (synthesis and reading)
- RNA: ribose instead of deoxyribose

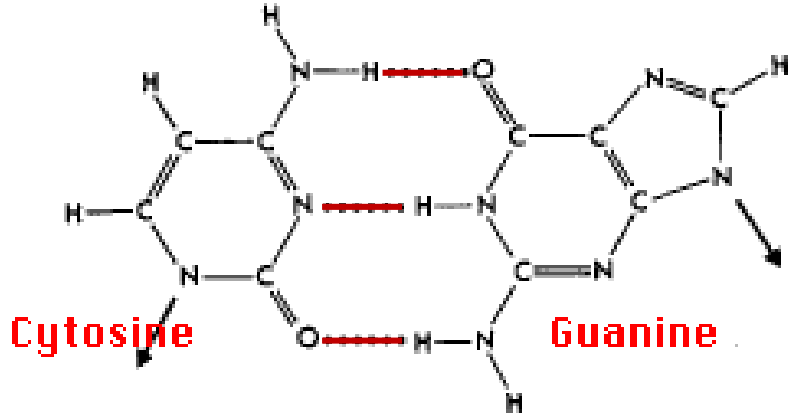


Ribose



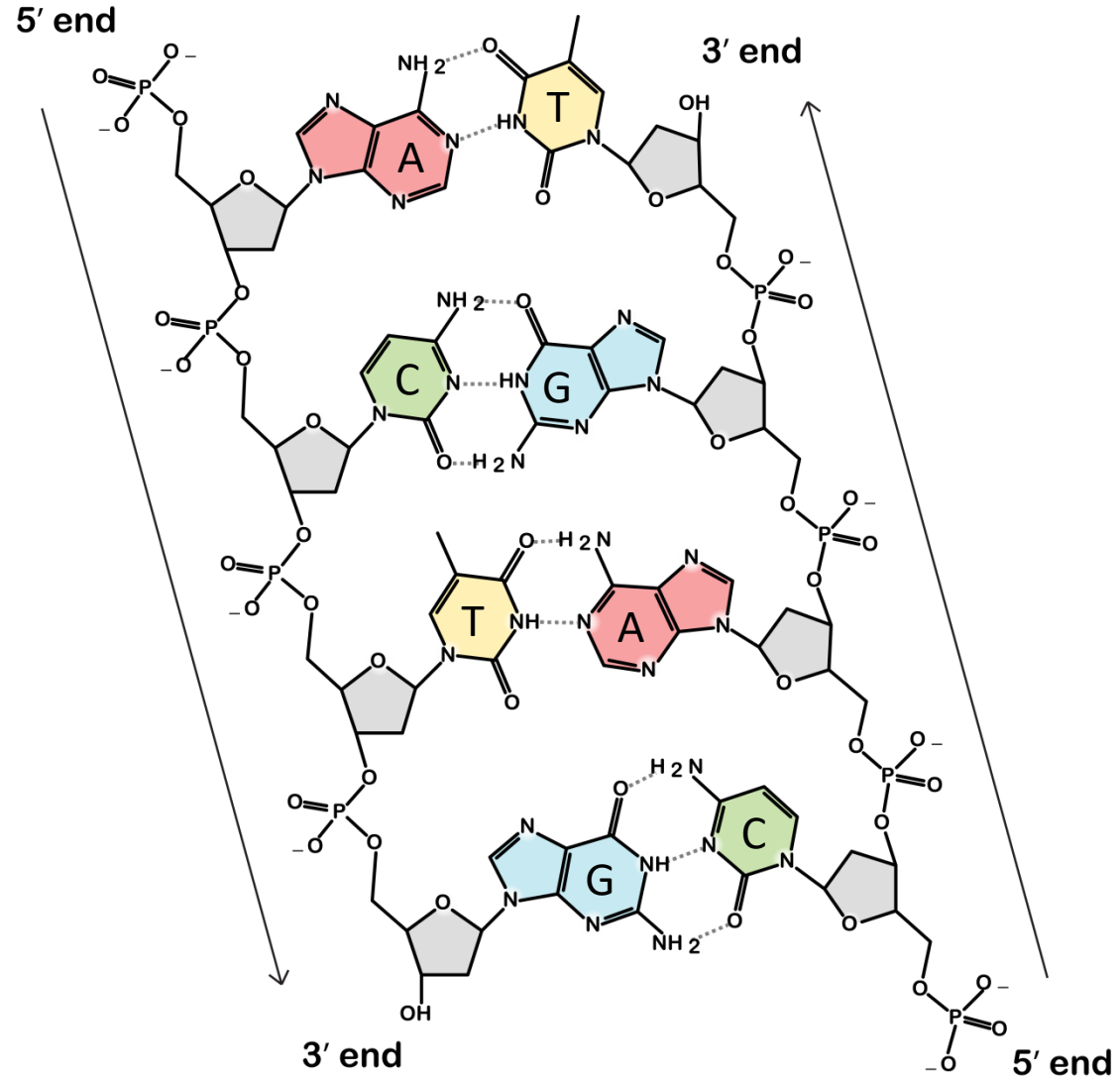
2-Deoxyribose

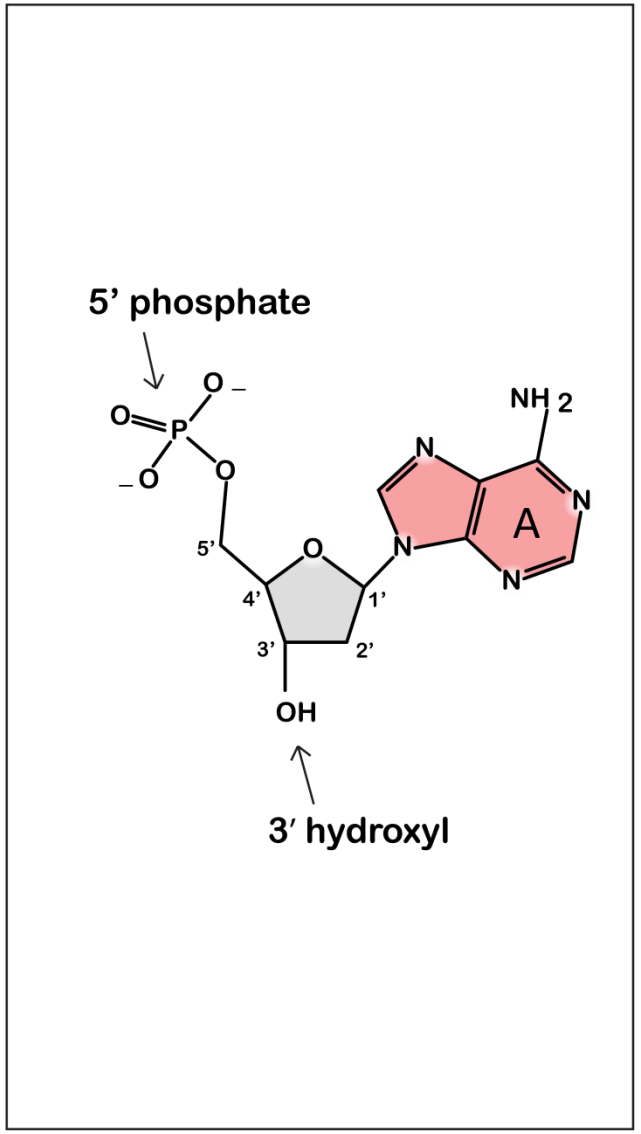




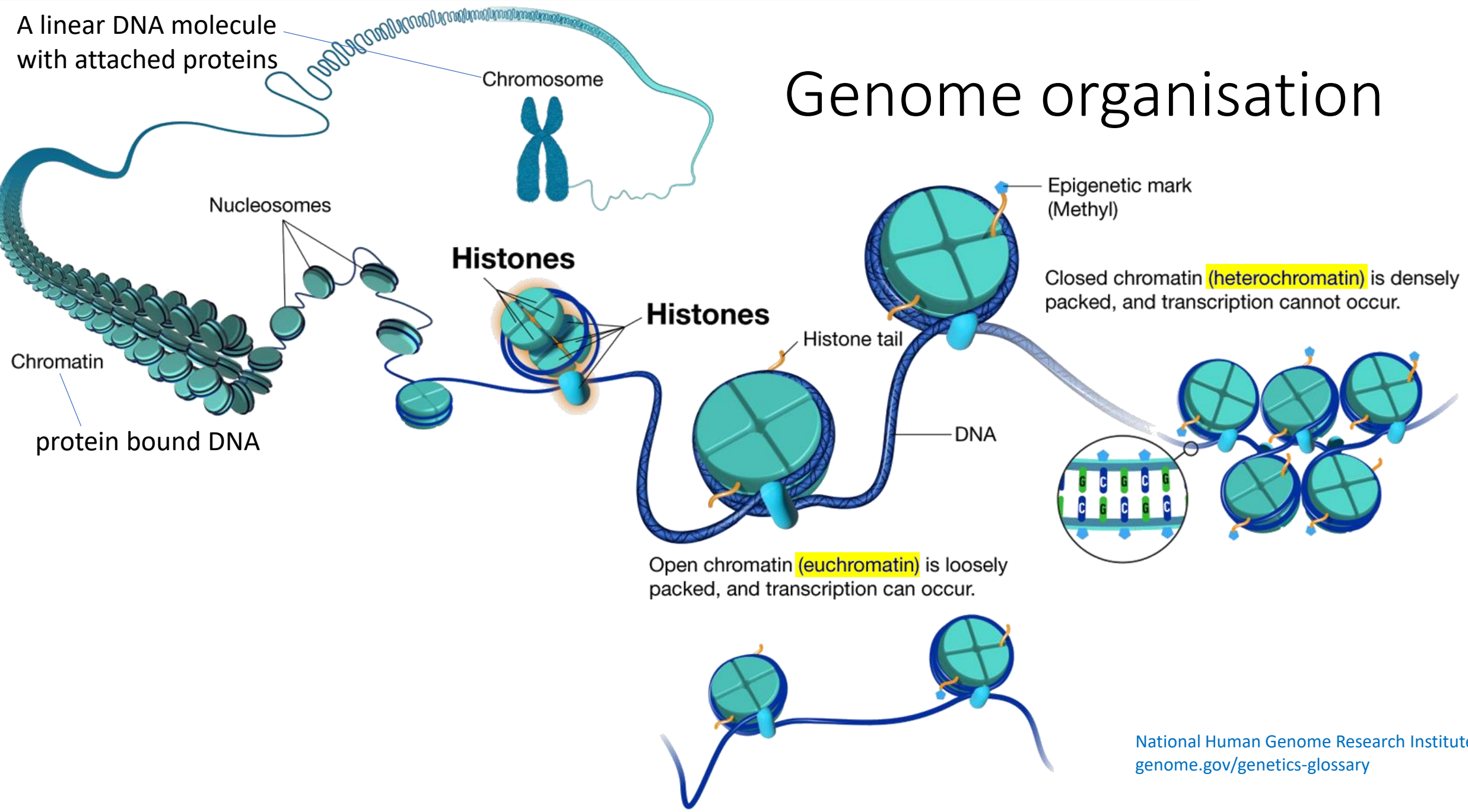
Hydrogen bonds

DNA helix, antiparallel orientation





Genome organisation



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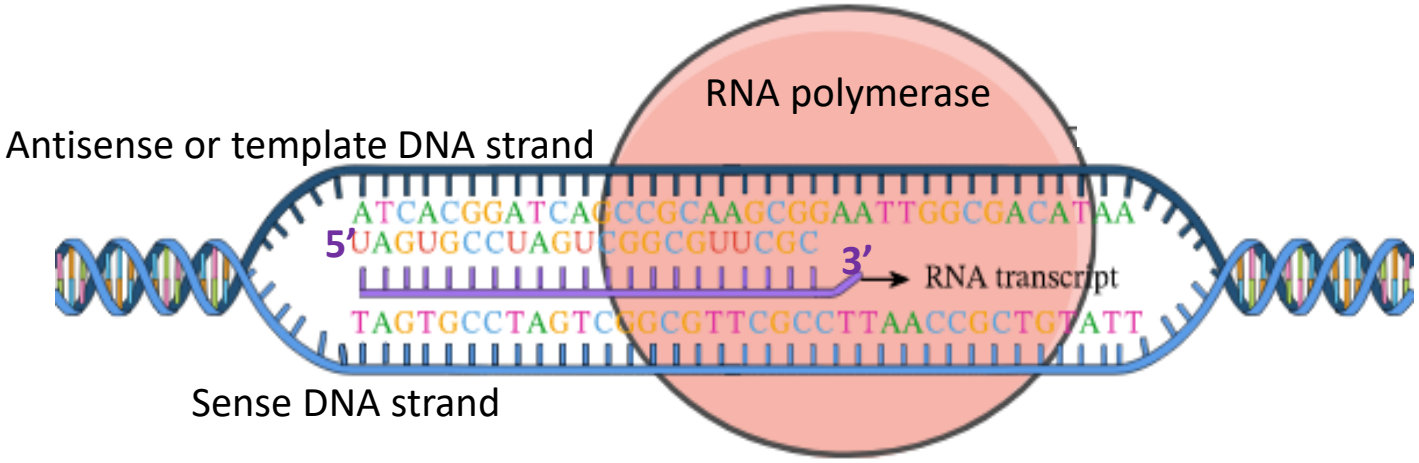
Transcription

- The synthesis of an RNA molecule, based on converting the base-order sequence information from a DNA template into an RNA



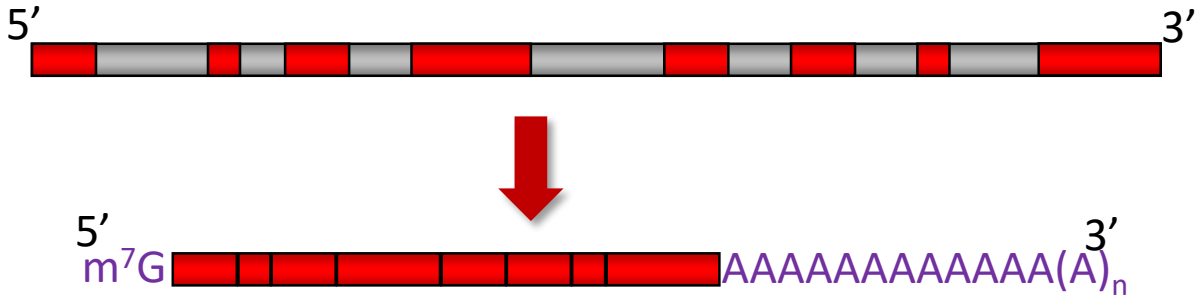
Three (human) RNA polymerases, each primarily synthesising:
Pol I - ribosomal RNA (45S rRNA)
Pol II - messenger RNA (mRNA), microRNA (miRNA), long noncoding RNA (lncRNA)
Pol III - transfer RNA (tRNA), rRNA, other small RNAs

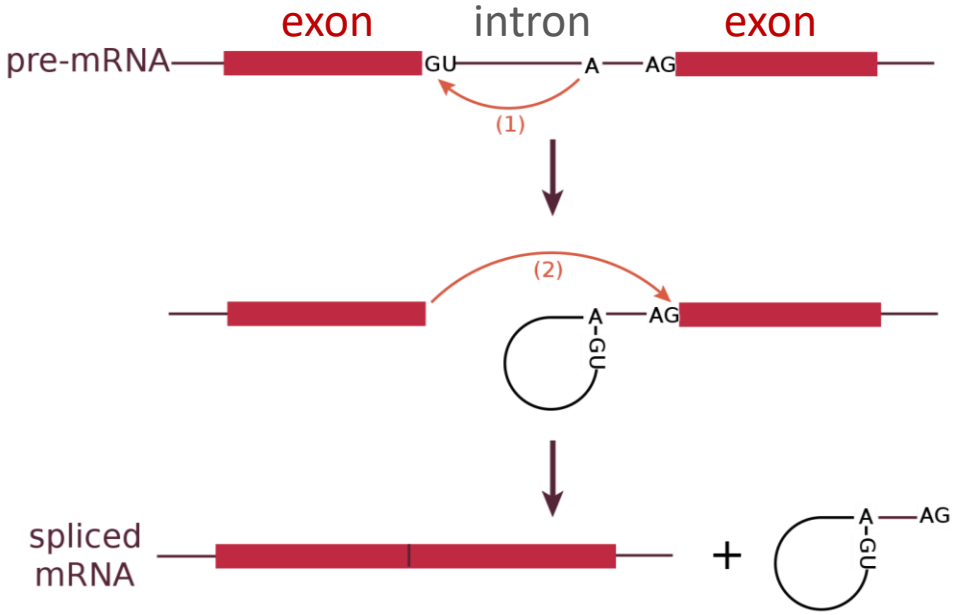
Post/co-transcriptional modification

Chemical altering of the primary mRNA transcript to produce a mature, functional mRNA molecule

Pre-mRNA to mature mRNA:

- 5’ capping (m^7G to 5’-end)
- 3’ poly-adenylation $(A)_n$
- Pre-mRNA splicing (removal of introns)

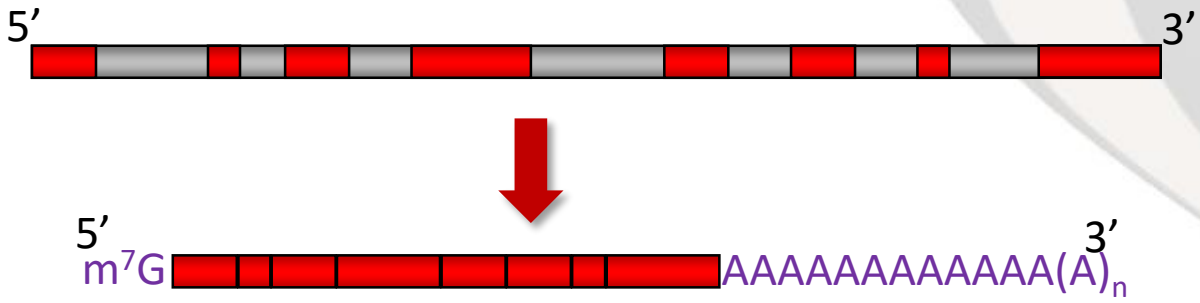


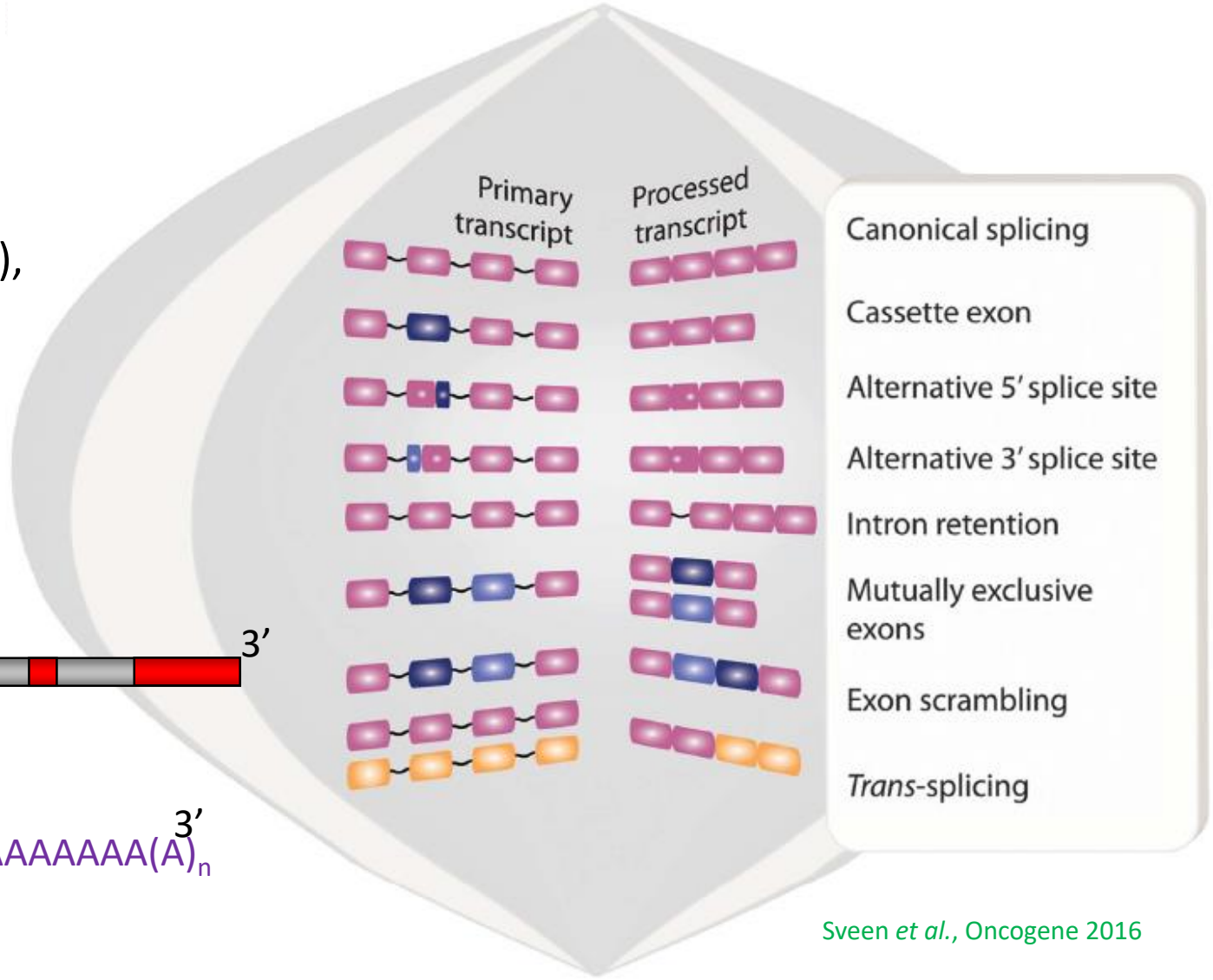


RNA transcript variation - Alternative splicing

Virtually all genes can produce many different transcript variants

In addition to alternative splicing (figure), **transcript variation** are caused by alternative promoters and polyadenylation sites (alternative first and last exons)



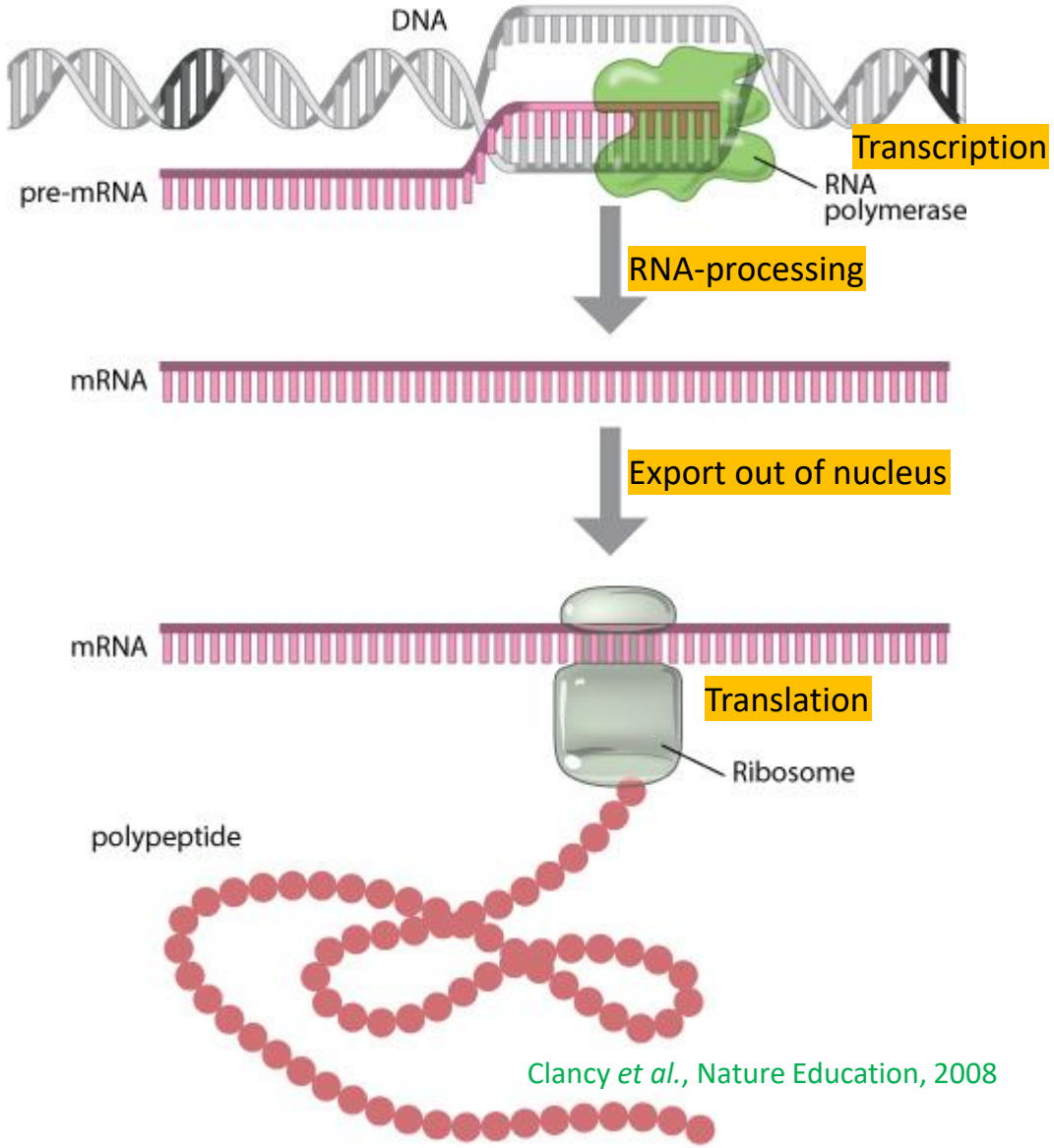


Sveen *et al.*, Oncogene 2016

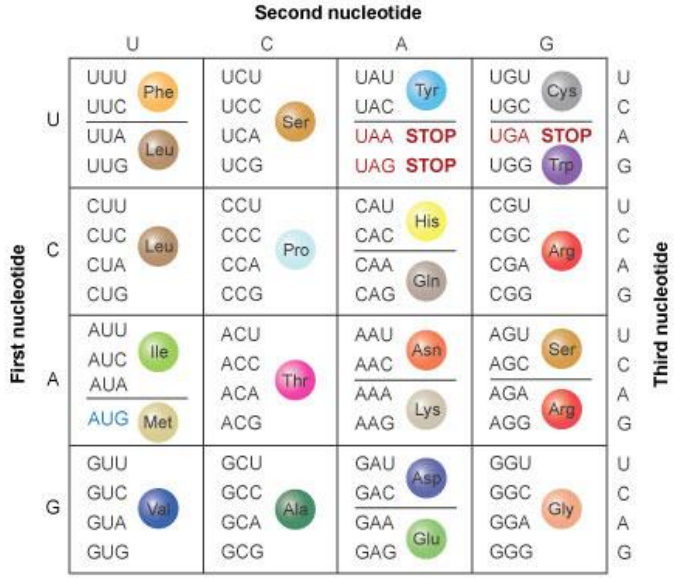
Three main types of RNA

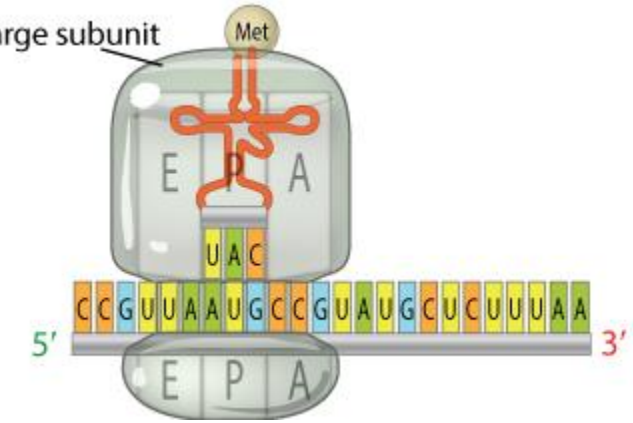
- Coding RNA
  - Messenger RNA, mRNA: Template for protein synthesis, ~5 % of all RNA
- Noncoding RNA
  - Ribosomal RNA, rRNA: Parts of ribosomes, ~90% of all RNA
  - Transfer RNA, tRNA: Translate the DNA/RNA-code into protein-code
- Other types (selected)
  - Long noncoding-RNA, lncRNA: Miscellaneous functions
  - Small nuclear RNA, snRNA: Splicing factors
  - Micro-RNA, miRNA: Regulates translation
  - Ribozymes: Biological catalysts

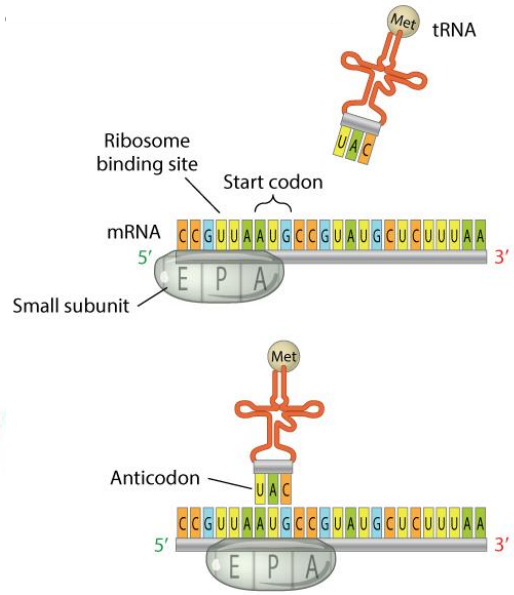
Translation: RNA to protein



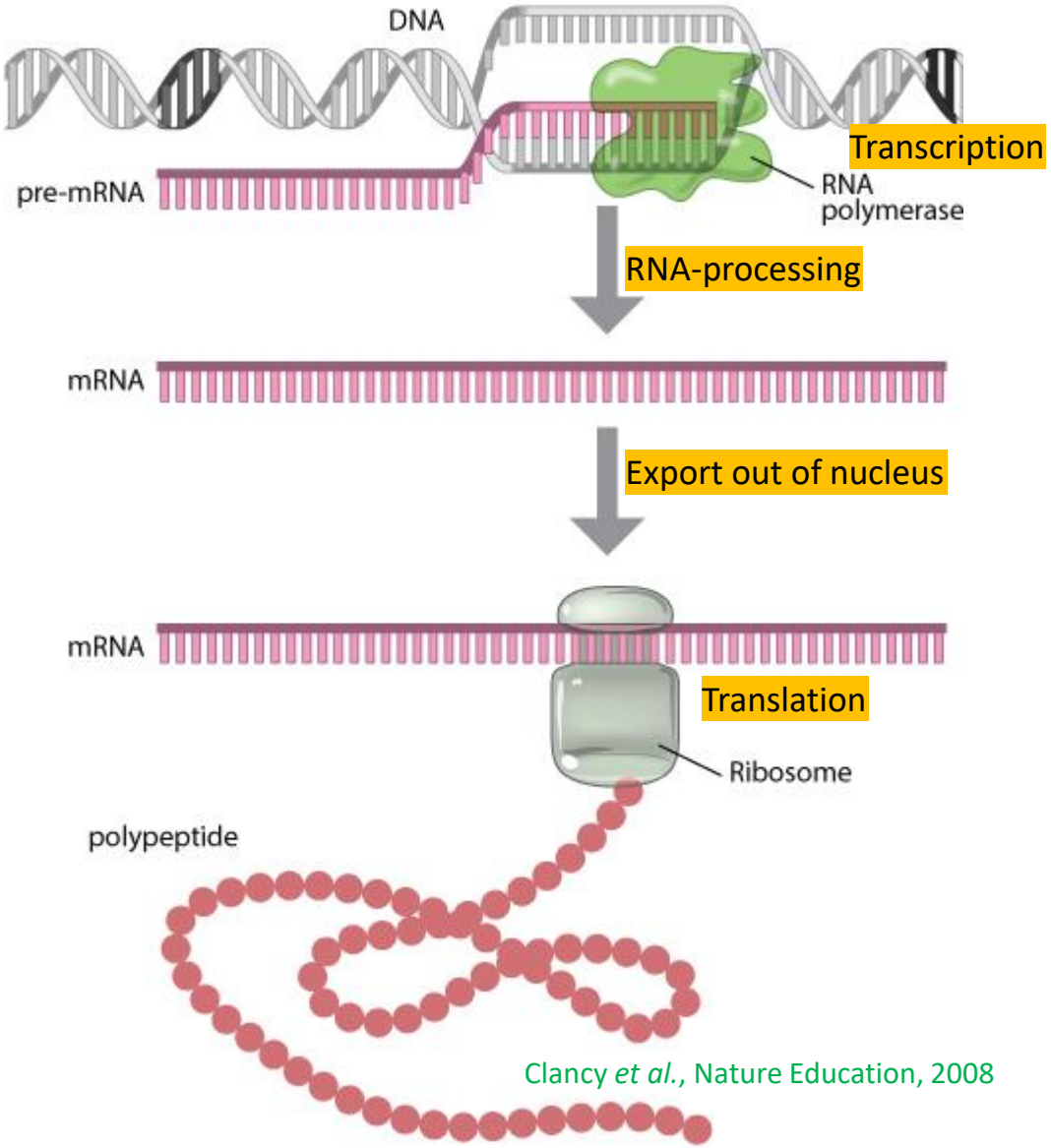
Clancy *et al.*, Nature Education, 2008







Gene regulation at many levels

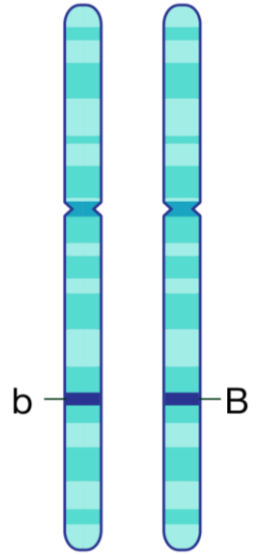


Clancy *et al.*, Nature Education, 2008

- DNA
  - DNA copy numbers
  - Promoter and enhancer sequences
  - Epigenetics: DNA modifications, e.g. methylation at promoters
  - Epigenetics: Histone modifications (hetero *vs.* euchromatin)
- Transcription
  - Alternative transcription start site
  - Transcription factors expression levels
- RNA
  - Alternative splicing
  - RNA editing
  - Stability/degradation
- Translation
- Protein
  - Post-tranlational modification (acetylation, phosphorylation, ubiquitination, *etc.*)
  - Folding
  - Stability/degradation

Genomics concepts

- Ploidy, allele, polymorphism (SNP, STRP, CNP), homo/hetero/hemizygous



Single nucleotide polymorphism (SNP)

Individual 1

Maternal . . . CGATATTCCTATCGAATGTC . . .

Paternal . . . CGATATTCCCATCGAATGTC . . .

Individual 2

Maternal . . . CGATATTCCCATCGAATGTC . . .

Paternal . . . CGATATTCCCATCGAATGTC . . .

Short tandem repeat polymorphism (STRP)

Individual 3

Maternal . . . CGATATTCCCAGCAGCAGATCGAATGTC . . .

Paternal . . . CGATATTCCCAGCAGCAGCAGCAGATCGAATGTC . . .

Individual 4

Maternal . . . CGATATTCCCAGCAGCAGCAGCAGATCGAATGTC . . .

Paternal . . . CGATATTCCCAGCAGCAGCAGCAGCAGCAGATCGAATGTC . . .

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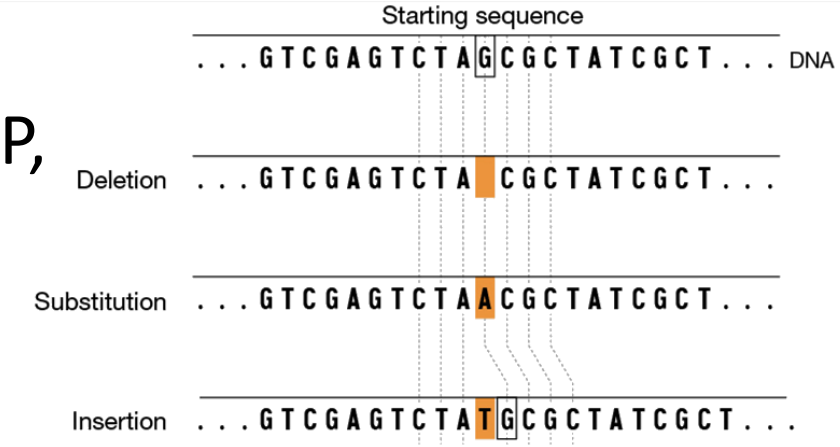
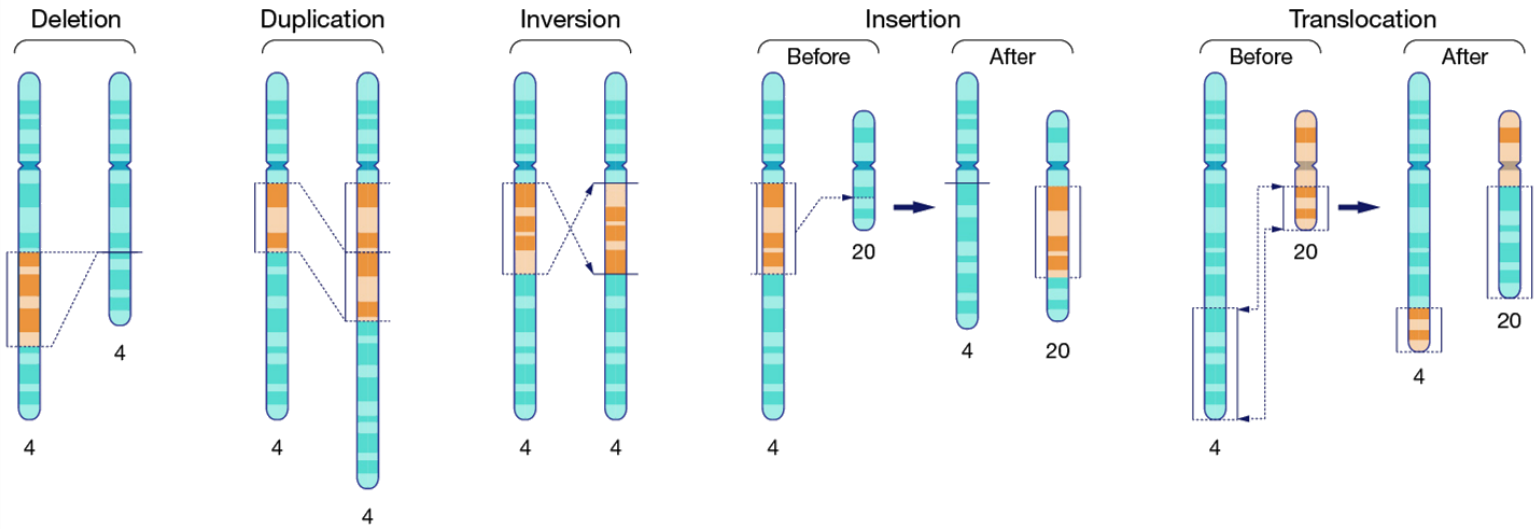
Genomics concepts

- Ploidy, allele, polymorphism (SNP, STRP, CNP), homo/hetero/hemizygous
- Mutation, variants, polymorphisms
  - Germline *vs.* somatic
  - Large *vs.* base-level
  - Silent, missense, nonsense
  - Numeric *vs.* structural
    - DNA copy number changes (amplifications, deletions)
    - Fusion genes
  - Driver *vs.* passenger





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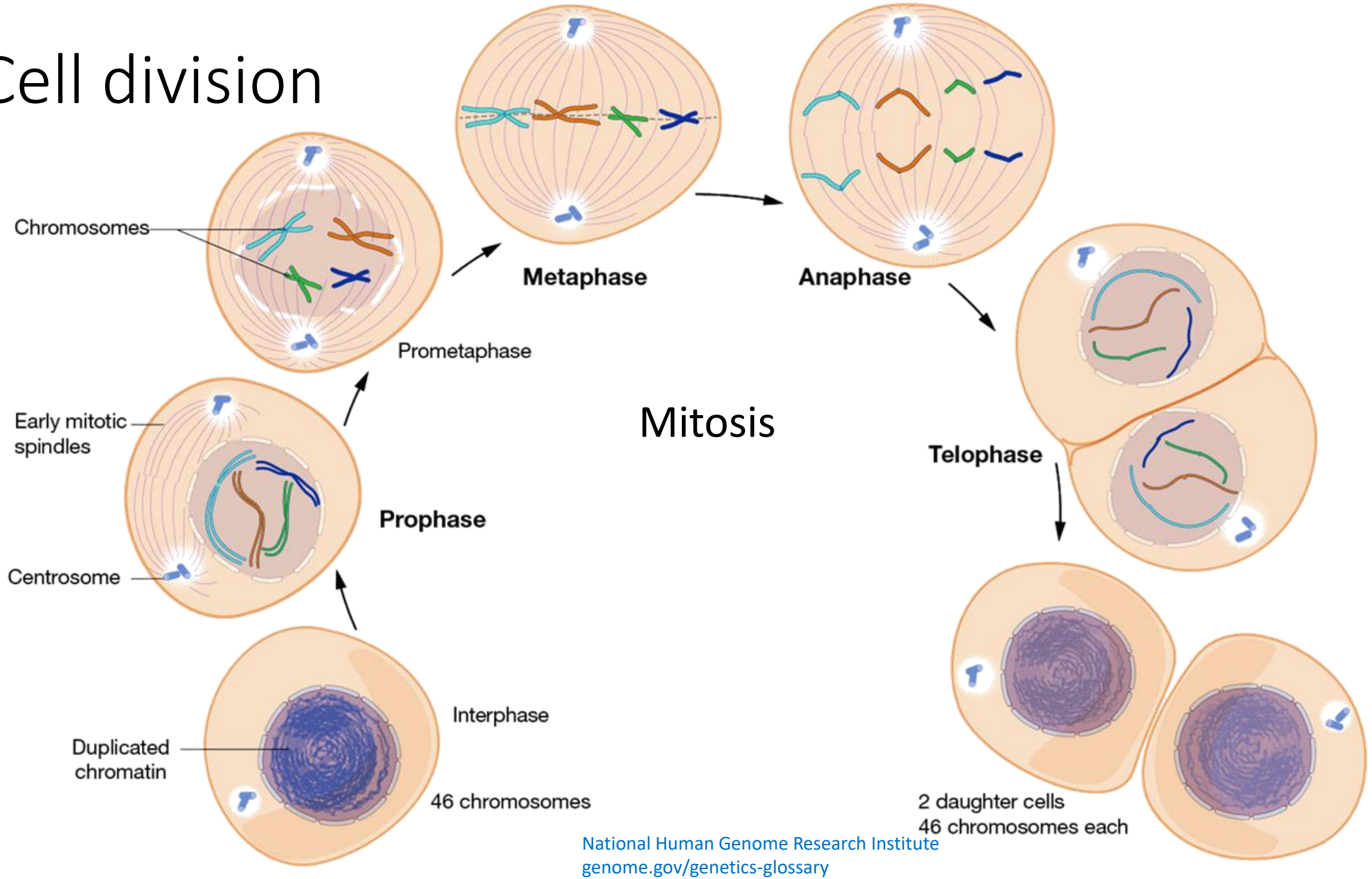
Cell division



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