

GENETICS AND CANCER

NOTES

FOURTH EDITION

PRE-SUMMARIZED
READY-TO-STUDY
HIGH-YIELD NOTES

FOR THE TIME-POOR
MEDICAL, PRE-MED,
USMLE OR PA STUDENT



208 PAGES

PDF



A Message From Our Team

Studying medicine or any health-related degree can be stressful; believe us, we know from experience! The human body is an incredibly complex organism, and finding a way to streamline your learning is crucial to succeeding in your exams and future profession. Our goal from the outset has been to create the greatest educational resource for the next generation of medical students, and to make them as affordable as possible.

In this fourth edition of our notes we have made a number of text corrections, formatting updates, and figure updates which we feel will enhance your study experience. We have also endeavoured to use only open-source images and/or provide attribution where possible.

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What's included: Ready-to-study summaries of human genetics, genetic conditions, tumorigenesis and cancer, presented in succinct, intuitive and richly illustrated downloadable PDF documents. Once downloaded, you may choose to either print and bind them, or make annotations digitally on your iPad or tablet PC.

Human Genetics & Cancer Topics:

- **DNA - DEOXYRIBONUCLEIC ACID**
- **GENE EXPRESSION**
- **CHROMOSOMES**
- **CHROMOSOMAL ERRORS**
- **GENE MUTATIONS**
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- **SEX-LINKED & MITOCHONDRIAL INHERITANCE**
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 - **HYPOCHONDROPLASIA**
 - **HUNTINGTONS DISEASE**
 - **MYOTONIC DYSTROPHY**
 - **RETINOBLASTOMA**
 - **NEUROFIBROMATOSIS**
- **CLASSIC CHROMOSOMAL DISORDERS**
 - **47, XY, +18: EDWARD'S SYNDROME**
 - **47, XY, +21: DOWN'S SYNDROME**
 - **KLINEFELTER'S SYNDROME 47, XXY**
 - **DIPLO-Y (SUPER-MALE) 47, XYY**
 - **TURNER'S SYNDROME**
- **CLASSIC X-LINKED DISORDERS**
 - **COLOUR BLINDNESS**
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- **COLON / COLORECTAL CANCER (CRC)**
- **CANCER EPIDEMIOLOGY**
- **BASICS OF CLINICAL ONCOLOGY**

DNA - DEOXYRIBONUCLEIC ACID

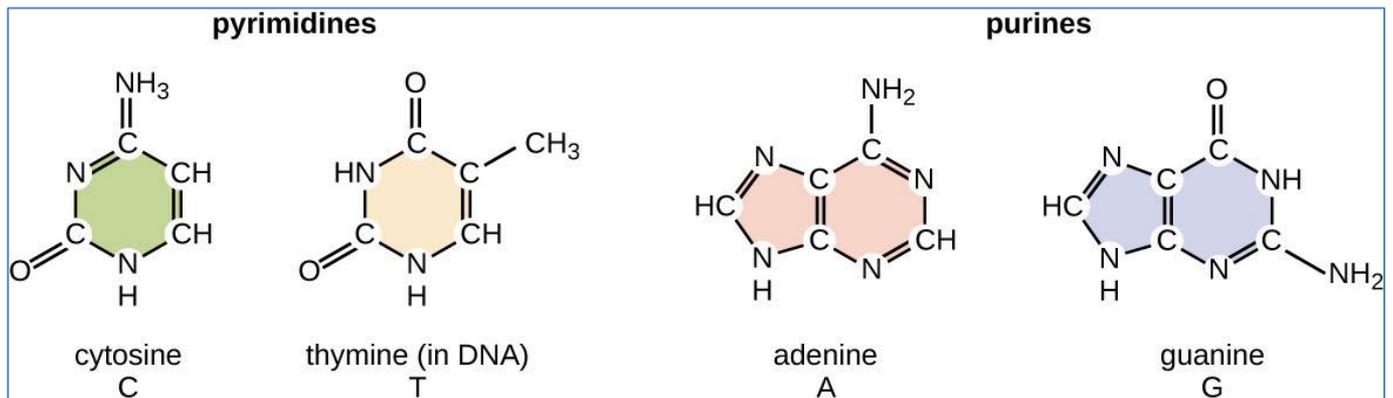
DNA - DEOXYRIBONUCLEIC ACID

DNA – An Overview:

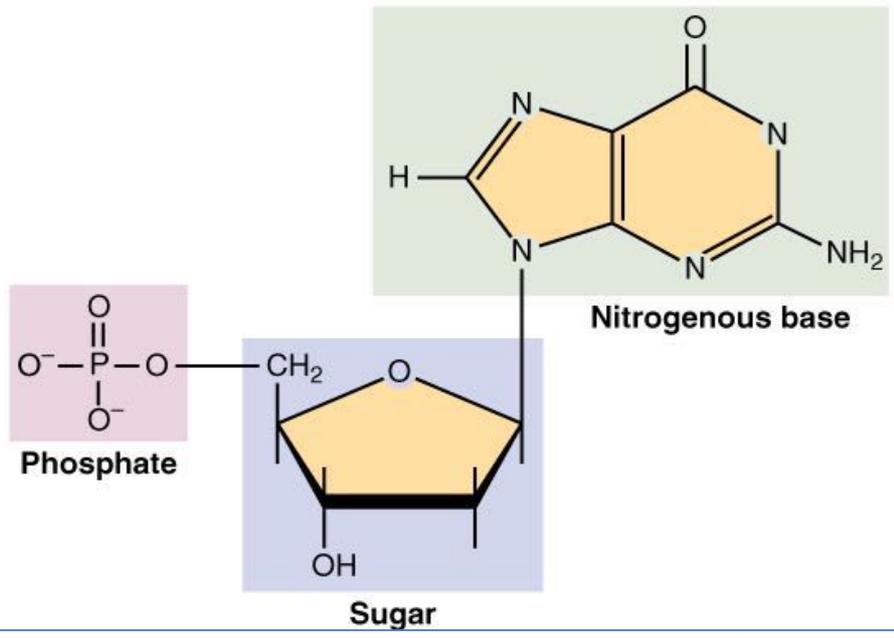
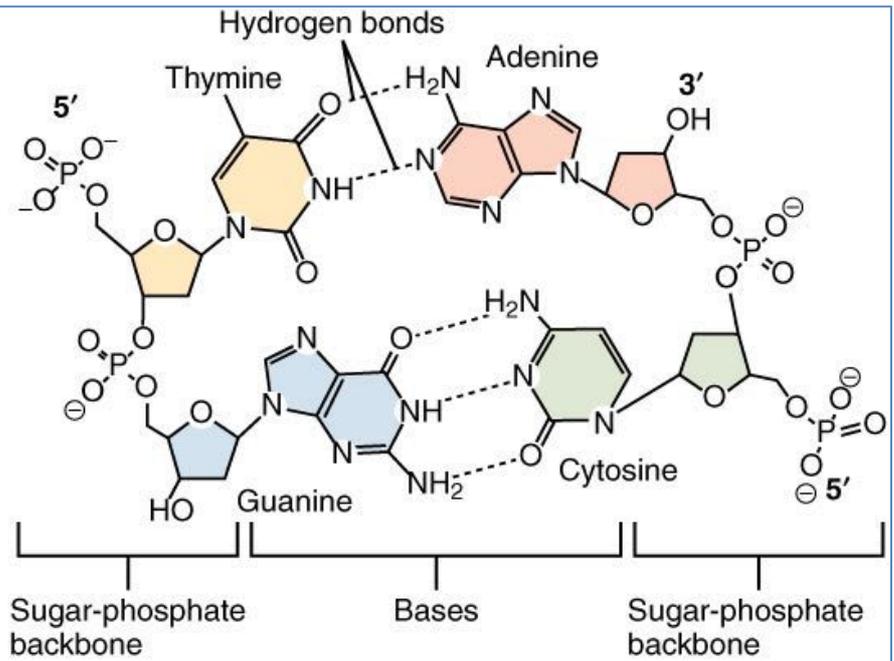
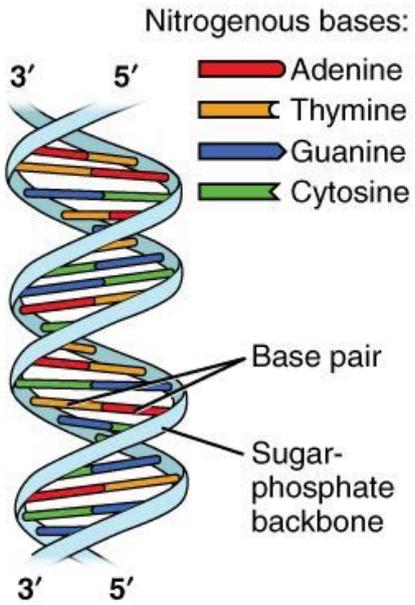
- DNA is contained within the **Nucleus** of the cell; hence ‘nuclear material’ (nothing to do with radioactivity)
- DNA contains all the genetic blueprints for proteins of a cell/organism
- **Think about this:**
 - o The **ONLY** reason DNA exists, is to encode the creation of all the proteins necessary for you to exist
 - o Proteins are created from DNA Transcription and Translation
- DNA must be replicated accurately and completely before a successful cell division
- Genetic blueprints are encoded in the **nucleotide sequence**

Composition:

- **Nucleic Acids (DNA and RNA):**
 - o Long polymers of individual molecules called **Nucleotides**
 - o A DNA molecule = **2 complimentary polynucleotide chains** (DNA Chains/Strands)
- **Nucleotides; Each is composed of:**
 - o **1x Deoxyribose Sugar Molecule** (5C sugar ring) (has a hydroxyl group on the 3' carbon)
 - o **1x Phosphate Group** (on the 5' carbon of the deoxyribose)
 - o **1x Nitrogen-containing Base - Either:**
 - **'Purine' Bases:**
 - **Adenine (A)** (Only bonds to T)
 - **Guanine (G)** (Only bonds to C)
 - **'Pyrimidine' Bases:**
 - **Thymine (T)** (Only bonds to A)
 - **Cytosine (C)** (Only bonds to G)
 - **(Note: Uracil replaces Thymine in RNA)**
 - o Each chain of DNA is held together by *hydrogen bonds* between the base pairs
- **Genes:**
 - o There are approximately 20-25,000 **genes** in the nuclear genome (which each encode a certain protein)
 - o Each **gene** is made up of a specific sequence of **nucleotides**

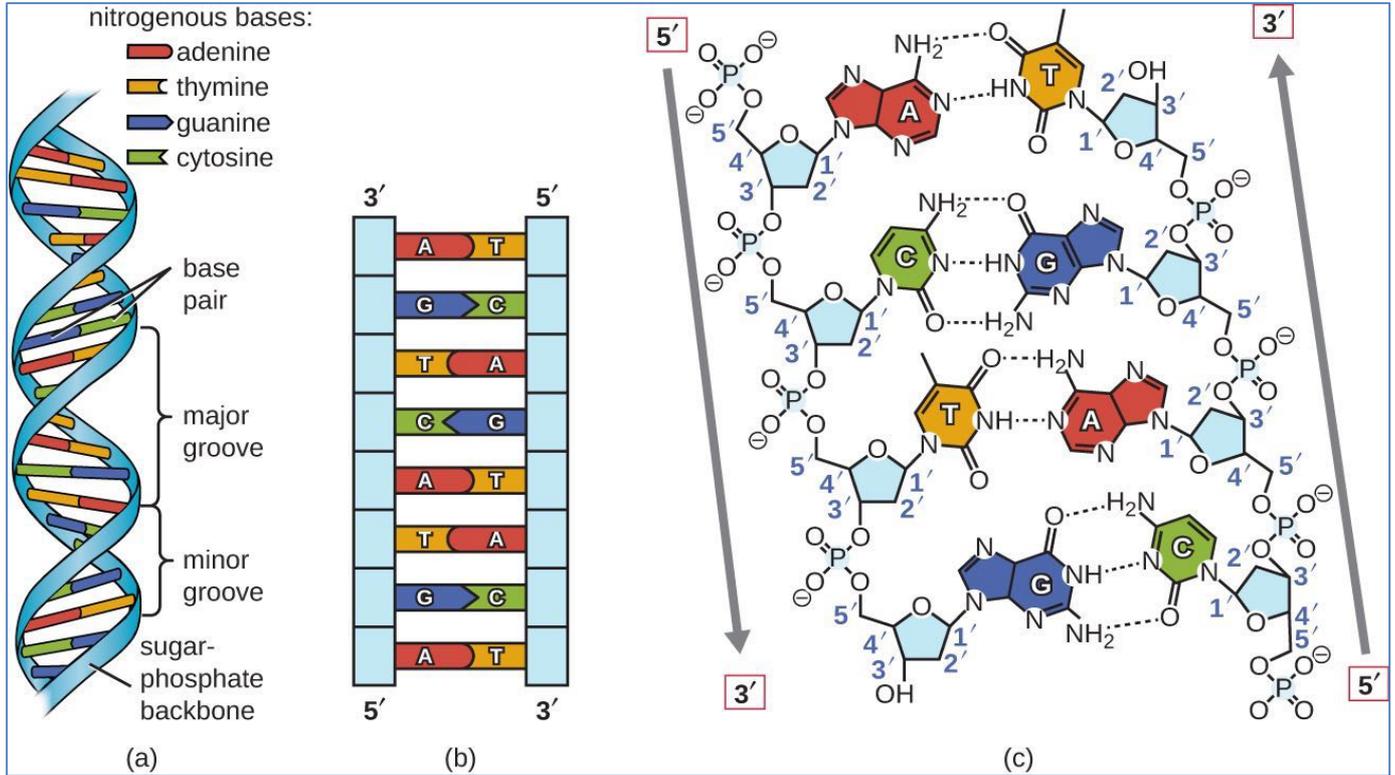


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Polarity & Antiparallel:

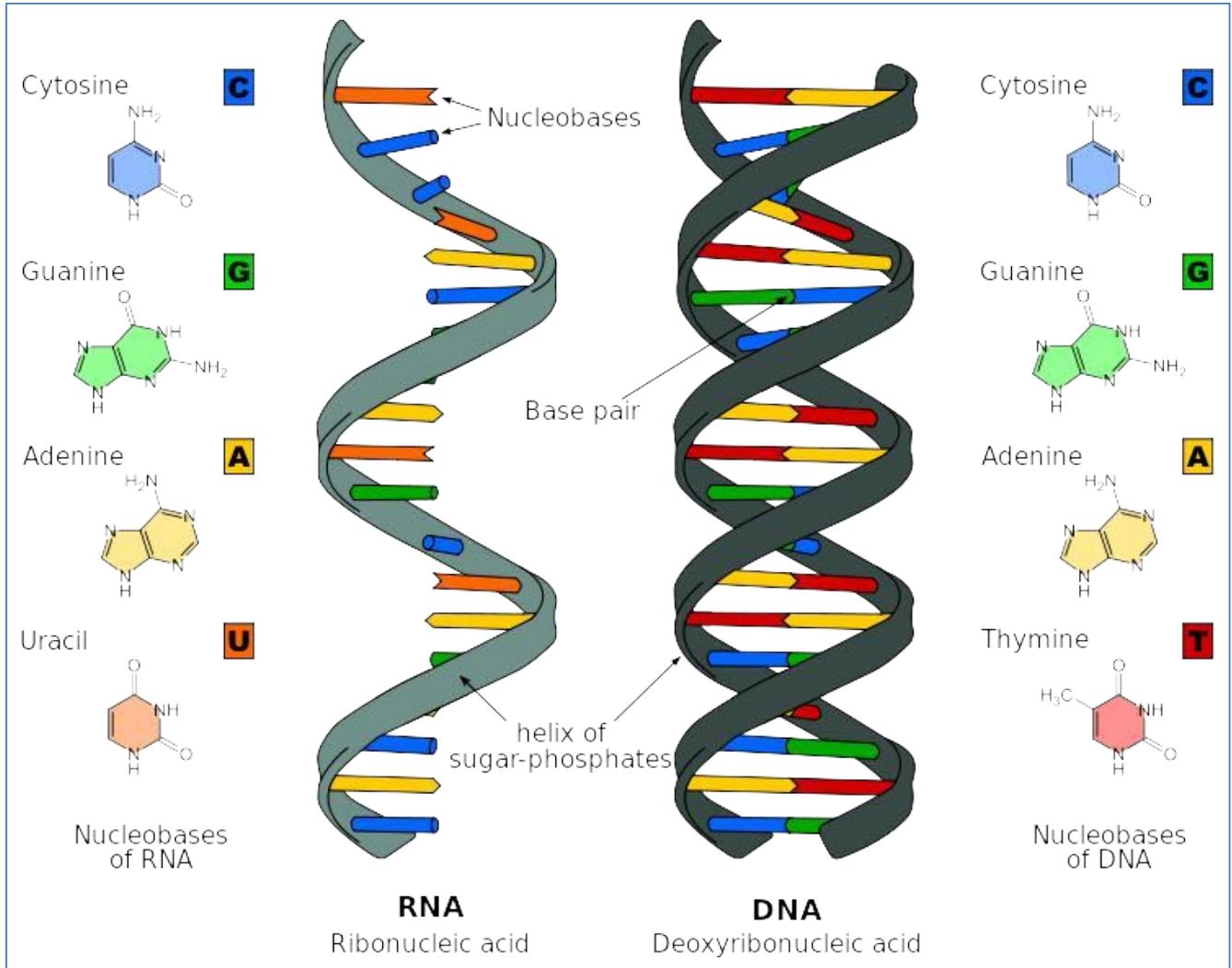
- Every DNA chain has **Polarity**:
 - Has a 5' Phosphate (key)
 - And a 3' Hydroxyl (keyhole)
- The 2 chains in a DNA molecule are **antiparallel (run in opposing directions)**
- Opposing polynucleotide chains are wound into a **double helix**



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DNA Vs RNA:

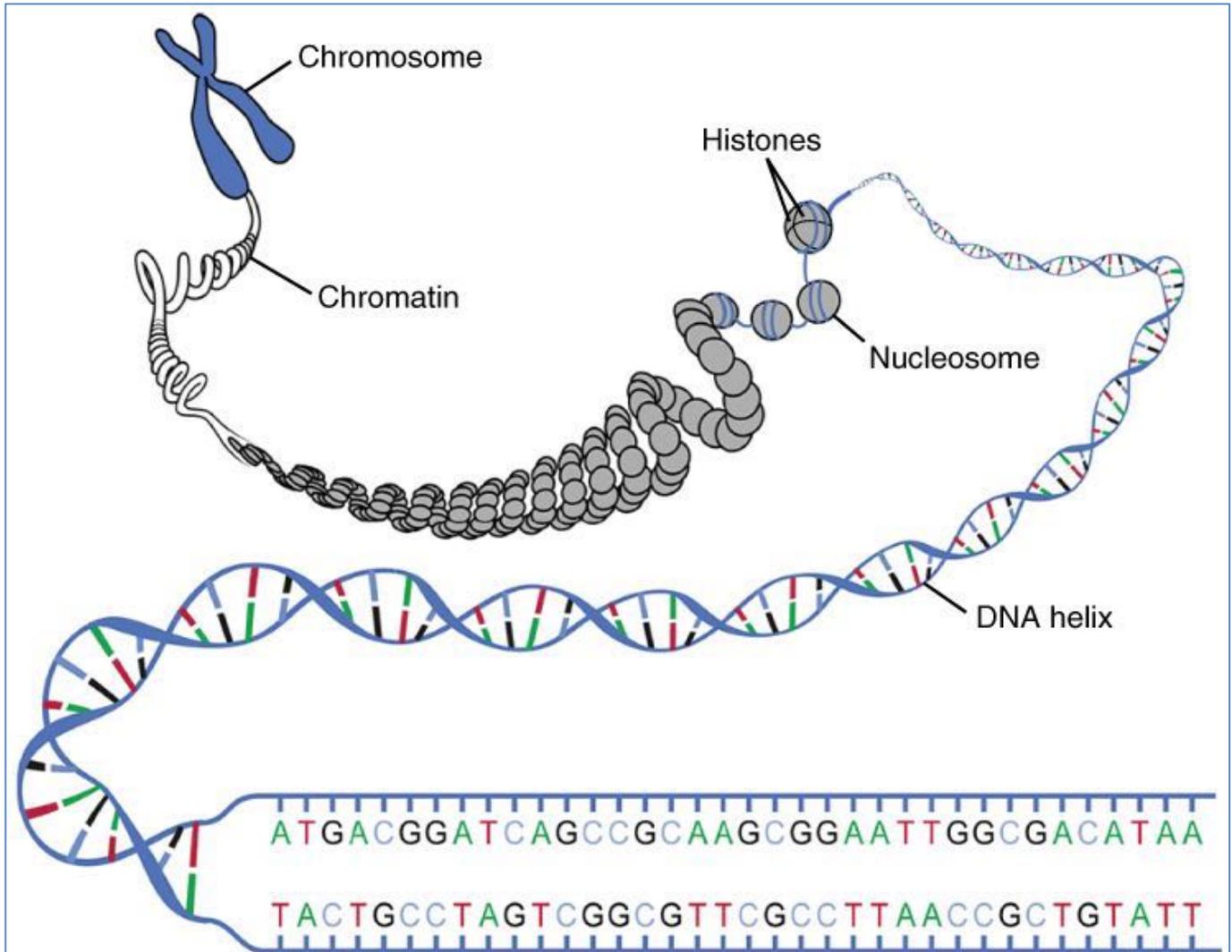
- **DNA:** Deoxyribonucleic Acid
 - The stable genetic code stored in the nucleus of cells
- **RNA:** Ribonucleic Acid
 - The temporary transcription product of DNA
 - Necessary for translation of genetic information from DNA into proteins
 - Acts as a messenger between DNA and the ribosomes (protein synthesis organelles)
 - Has the base **Uracil instead of Thymine**



File: Difference DNA RNA-DE.svg: Sponk / *translation: Sponk, CC BY-SA 3.0
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DNA Packaging into Chromosomes:

- **Why are Chromosomes Important?**
 - o The total length of DNA molecules in a cell would be several meters long if unfurled
 - o Therefore, chromosomes are necessary to condense DNA into manageable packages
- **How is DNA packaged into Chromosomes?**
 - o **Primary Coiling** = The Double Helix of DNA molecules
 - o **Secondary Coiling** = DNA molecules are coiled around **histones**, forming circular **nucleosomes**
 - o **Tertiary Coiling** = **Nucleosomes** are coiled into a **chromatin fibre**
 - o This **chromatin fibre** is then **coiled again and again** into a **Chromosome** seen under light microscope

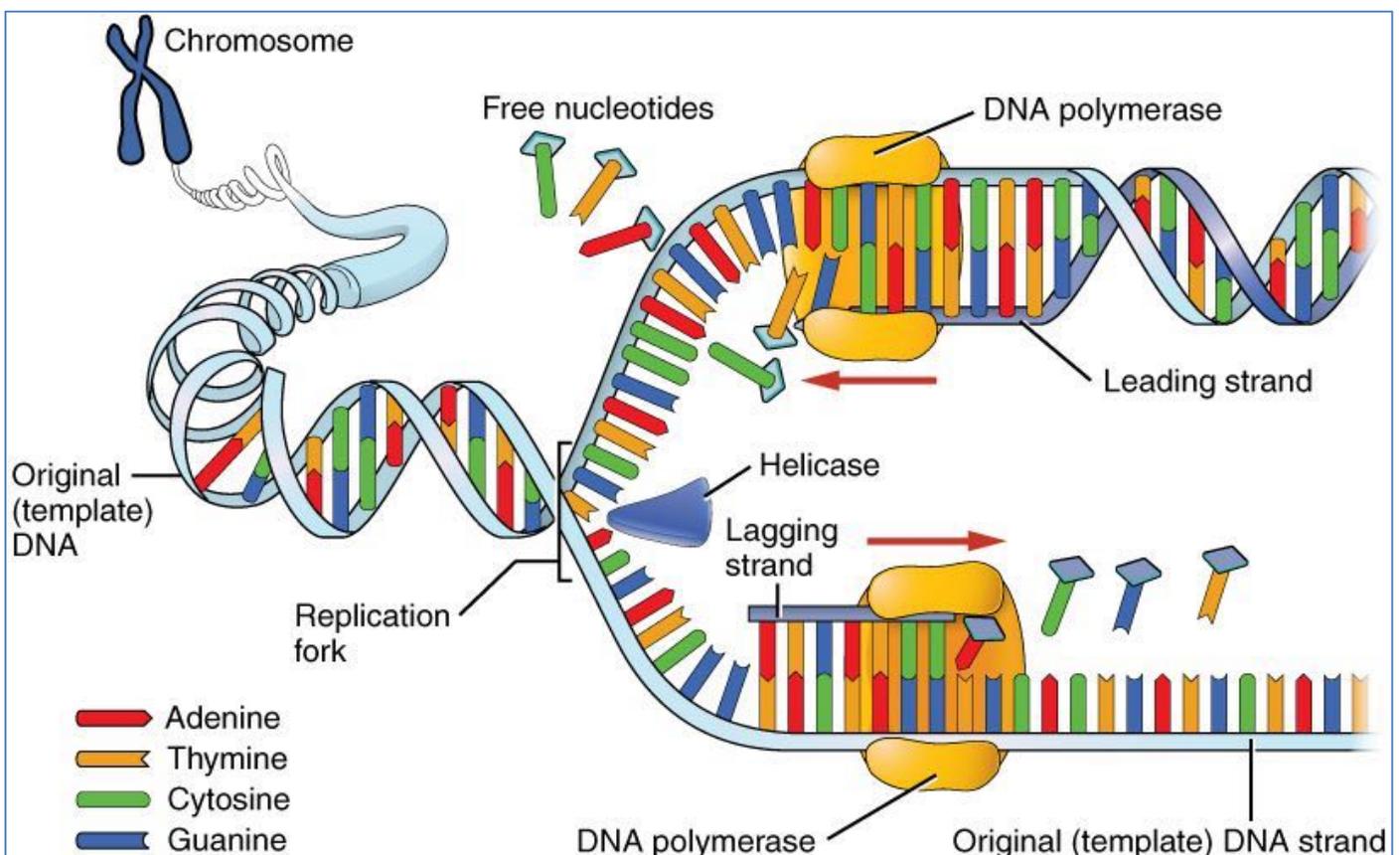


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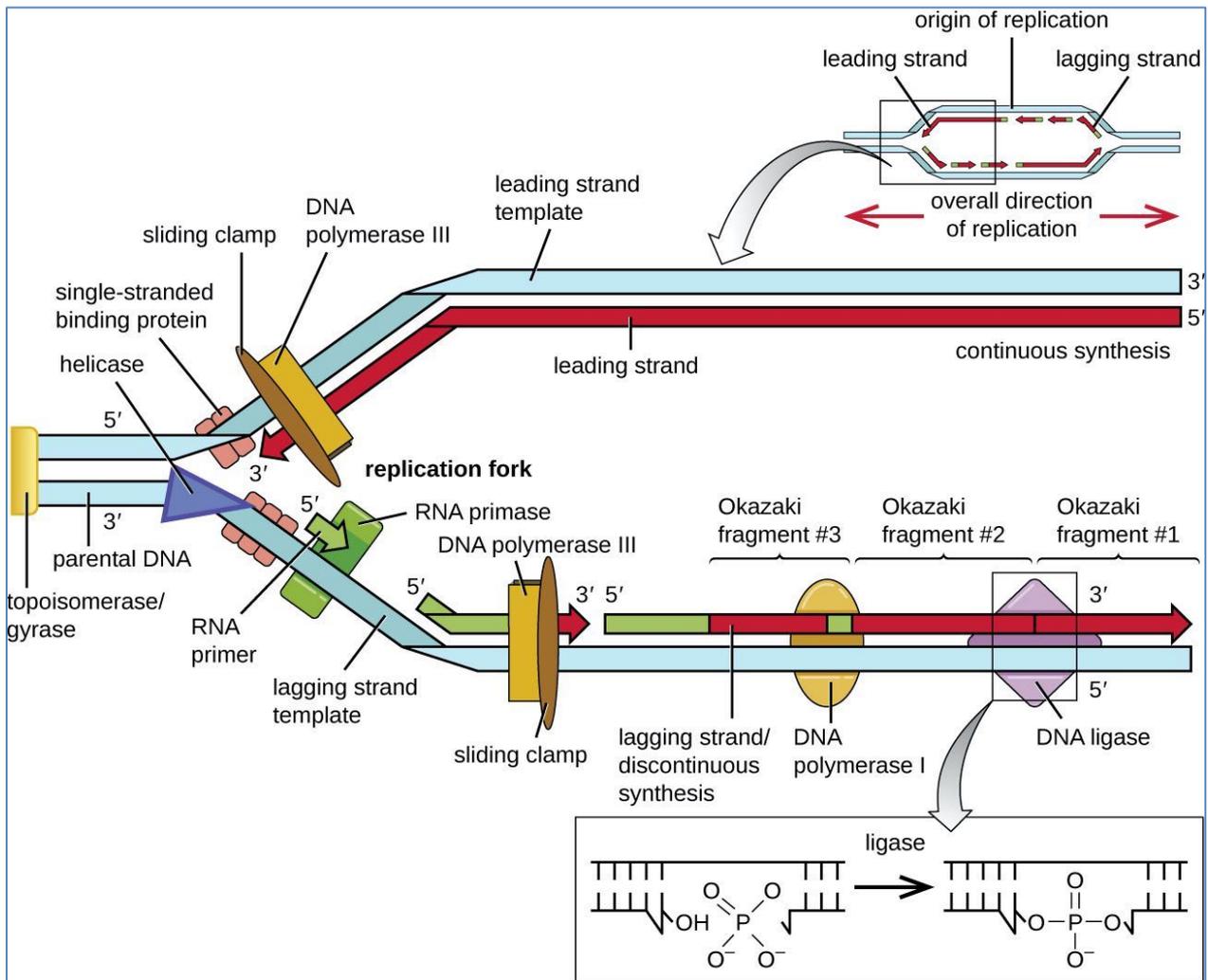
DNA Replication:

- **Why is it necessary?**
 - o Genetic information must be transmitted from one generation of cells to the next
 - o If DNA replication wasn't possible, cells wouldn't be able to replicate
- **What is required?**
 - o Enzymes
 - o Free Nucleotides
- **When does it occur?**
 - o During **Interphase** – when a cell is getting ready to divide
- **What is the process?**
 1. DNA replication occurs at multiple points on a single strand, known as **Origins of Replication (ORI's)**
 2. At each **Origin of Replication**, DNA strands are separated by an enzyme called **DNA Helicase**
 3. This splitting by **DNA Helicase** forms Y-shaped bifurcated structures known as **Replication Forks**
 4. Each exposed nucleotide is then bound by a **Single-Stranded DNA Binding Protein** which keeps the strands from re-annealing (coming back together)

 5. **Leading Strand:** One of the DNA strands encodes the “**leading strand**” (new strand), which is laid down continuously from its 5' to 3' end (towards the Helicase). This is done by an enzyme called **DNA Polymerase III** which moves towards the **helicase**
 6. **Lagging Strand:** The other DNA strand (which runs in the opposite direction) encodes the “**lagging strand**” (other new strand), which must also be laid down from its 5' to 3' end (this time away from the Helicase)
 - a. This is first initiated by **RNA Primase** which lays down an **RNA Primer**
 - b. Another **DNA Polymerase III** then attaches to the **RNA Primer** and lays down a short length of DNA (away from the Helicase) called an **Okazaki Fragment** (100 - 200 Nucleotides long) until it reaches another RNA Primer further down the line. Once the **DNA Polymerase III** reaches the 2nd RNA Primer it dissociates
 - c. **DNA Polymerase I** then **replaces the RNA Primer** (between the 2 Okazaki fragments) **with DNA**
 - d. **DNA Ligase** then links the 2 Okazaki fragments together

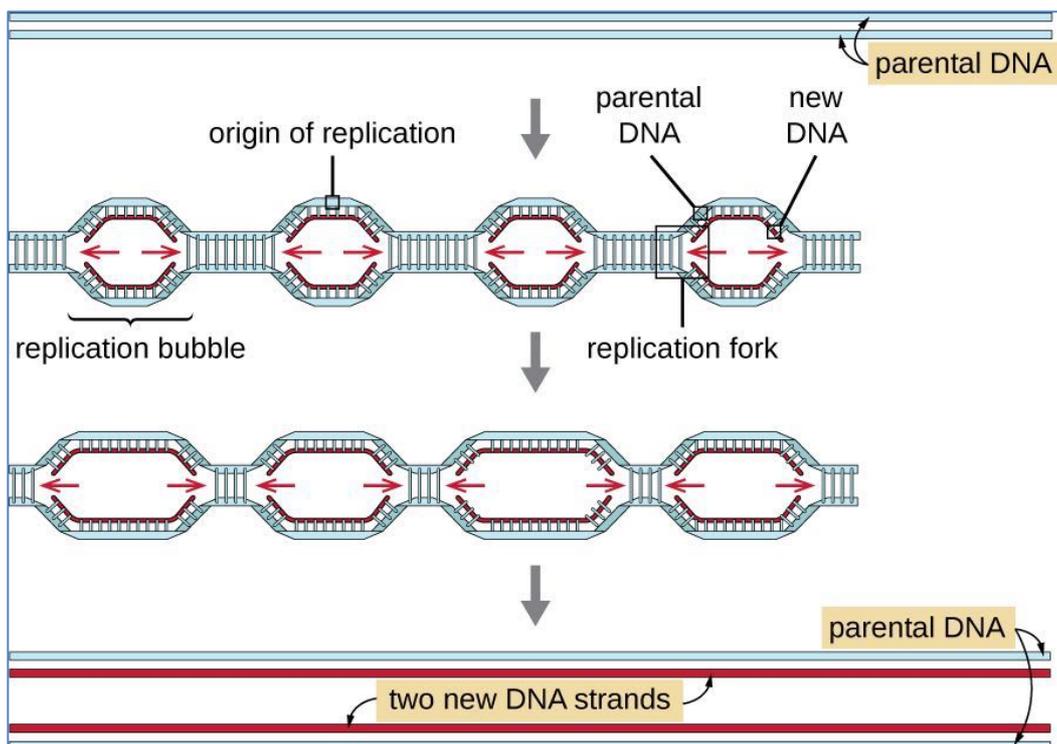


****2x Helicases can bind at one ORI and unzip the DNA in both directions, forming a 'replication bubble'****



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****There can be multiple ORIs, and therefore multiple replication bubbles (increases replication rate)****



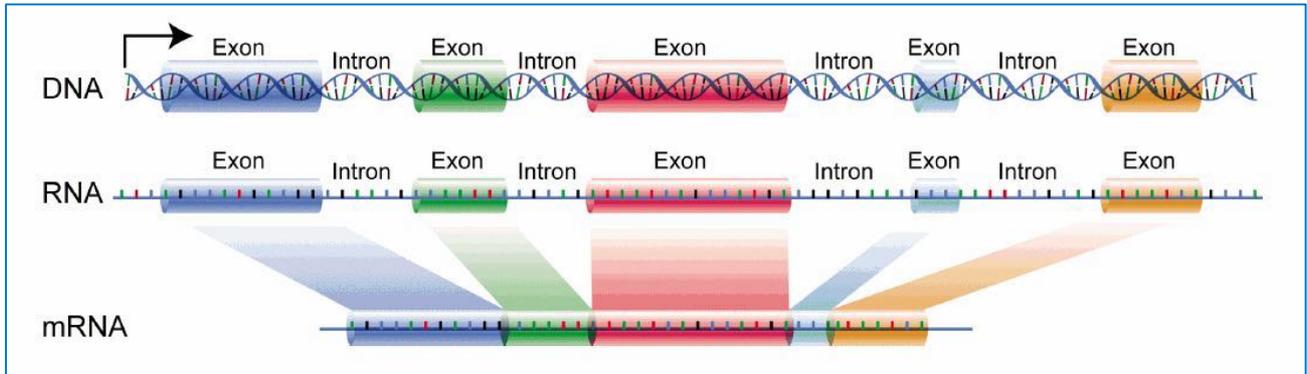
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GENE EXPRESSION

GENE EXPRESSION

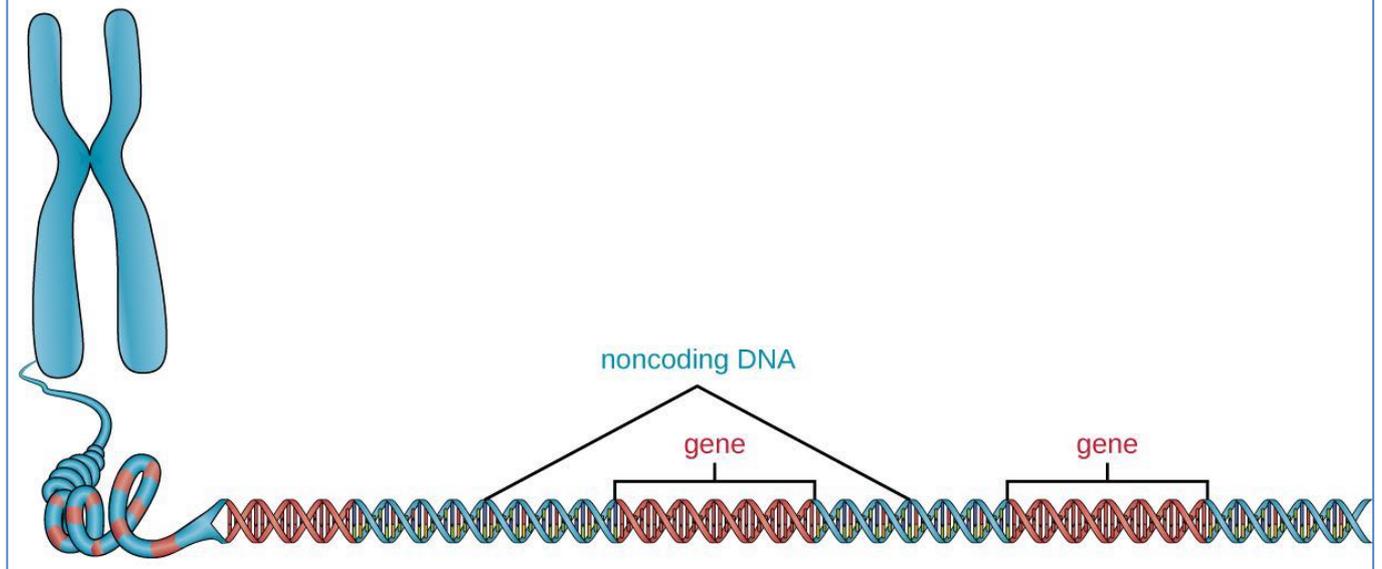
What is a Gene?

- The section of DNA code which encodes the synthesis of a specific protein (polypeptide chain)
- **Includes both coding & non-coding sequences:**
 - o **Exons:** Coding sequences
 - Forms part of the mature mRNA and therefore influences the resultant protein structure
 - o **Introns:** Non-coding sequences (Function to separate the coding sequences from each other)
 - Note: The RNA that is generated by an Intron is spliced out during transcription and does not form the mature mRNA and therefore does not influence the resultant protein



Available from: https://www.researchgate.net/figure/Exon-Intron-regions-for-eukaryotic-DNA_fig2_236034669

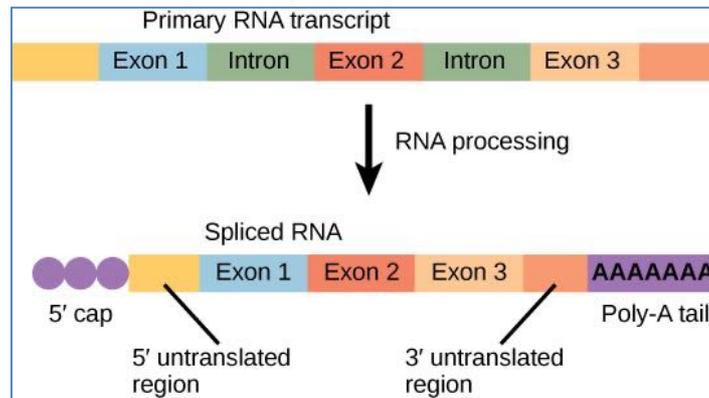
chromosome



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Genes To Proteins:

- **Protein synthesis from a gene happens through 2 processes:**
- **1: Transcription:**
 - The process of **making RNA from a DNA** template (specifically, **hnRNA [heteronuclear]**)
 - Occurs in the **Nucleus**
 - Before entering the cytosol, the **hnRNA is processed** by nuclear enzymes:
 - **Introns Removed** (non-coding regions of the hnRNA)
 - **Splicing Exons Together** (coding regions)
 - **Addition of a GTP-Cap (Gcap) and a Poly-A-Tail**
 - → Produces **mRNA** (messenger RNA) which then leaves the nucleus into the cytosol

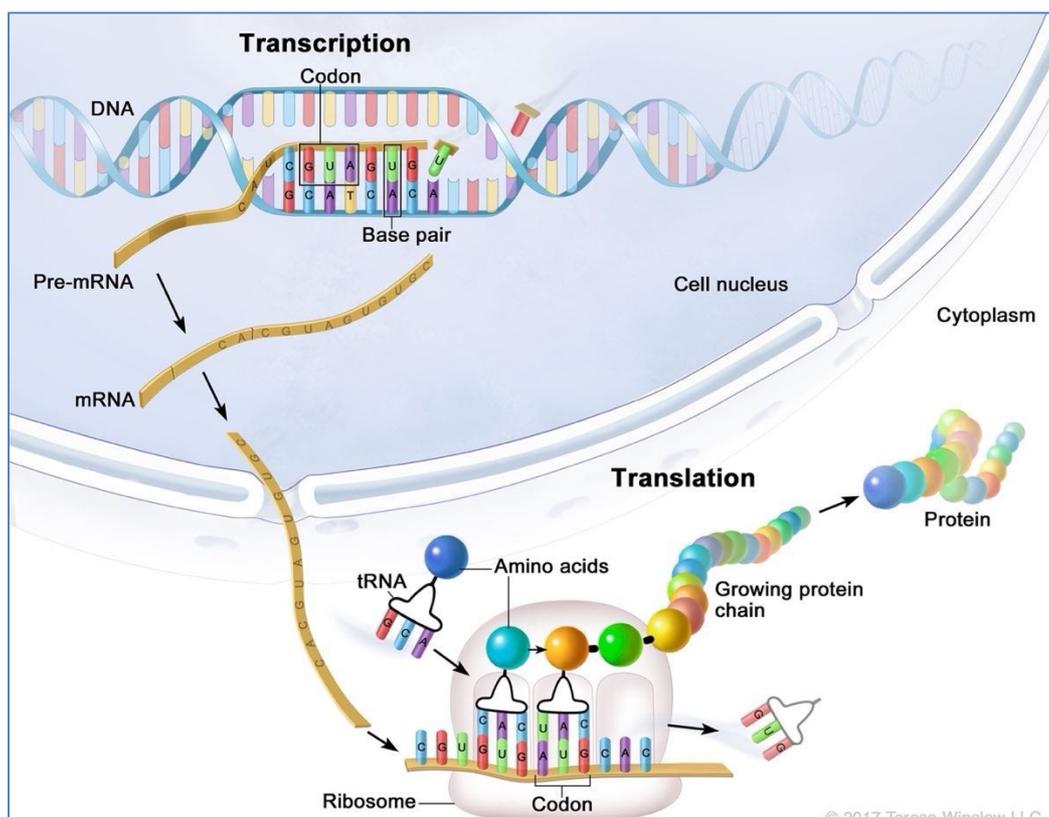


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- **2: Translation:**
 - The process of **making a protein from an mRNA transcript**
 - Occurs in the **Cytosol**
 - Carried out by a **Ribosome** on the **Rough Endoplasmic Reticulum**
 - **Ribosome** → converts **mRNA into an Amino Acid Sequence** (polypeptide/protein)
 - Each amino acid in the protein is determined by a triplet of mRNA bases (a **Codon**)



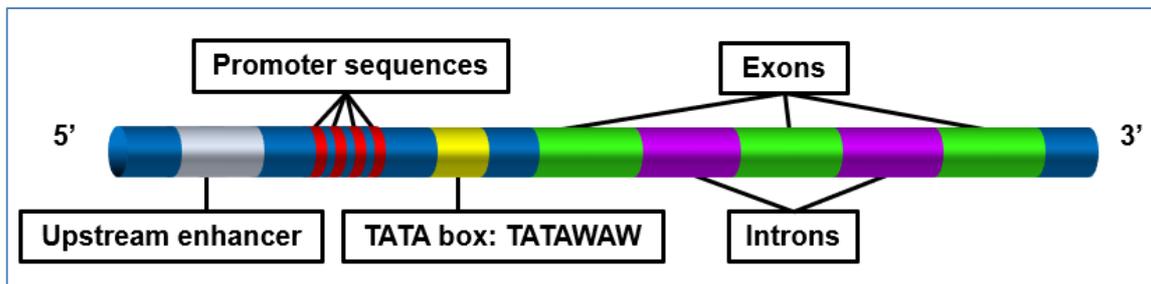
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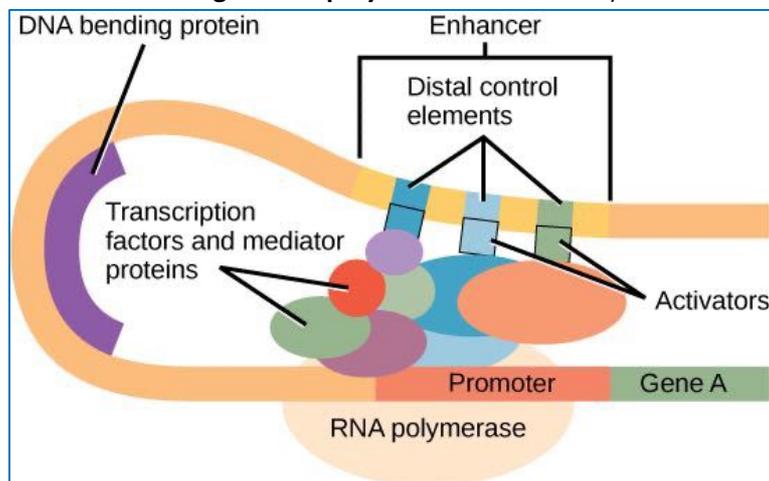
GENE TRANSCRIPTION:

- **Why is it necessary?**
 - Gene Transcription is a critical step in unpacking the condensed genetic code in a chromosome
 - **What is required?**
 - **DNA** (containing a particular **gene**, aka **transcription unit**)
 - **Transcription Factors**
 - **RNA polymerase**
 - **ATP**
 - **When does it occur?**
 - Whenever the body needs to produce/replace any protein required for life/homeostasis
 - **What is the process?**
1. **Begins with a strand of DNA (made up of different important regions)**
 - a. **Transcription unit** (The gene/length of DNA for the desired protein)
 - b. **TATA box** - a DNA sequence found in the **promoter region** of a gene



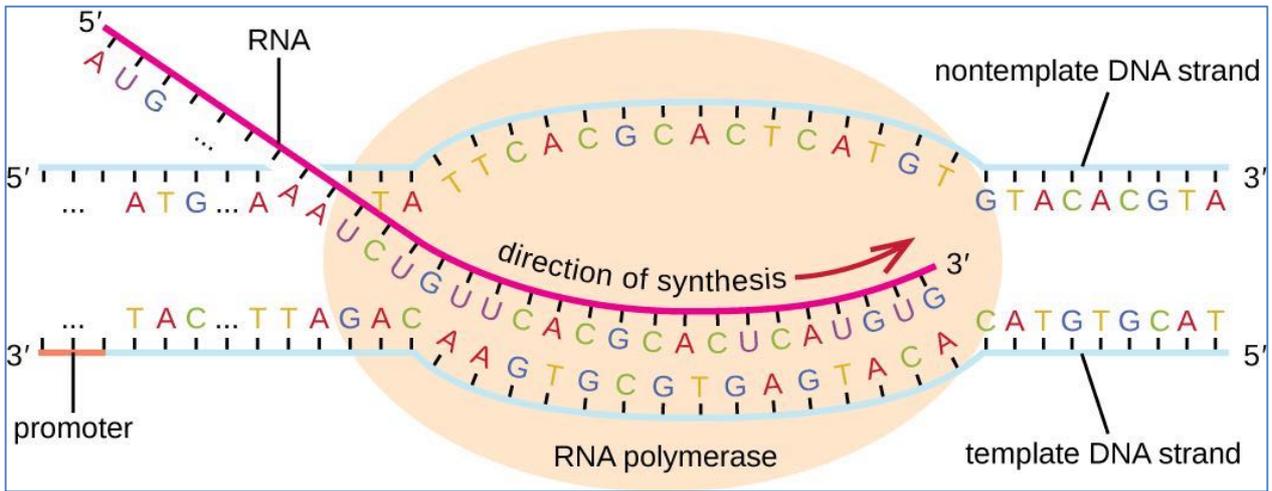
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2. Several **complexes** known as **transcription factors** bind to the TATA box
 - a. (allow the successful **binding of RNA polymerase** to the DNA)

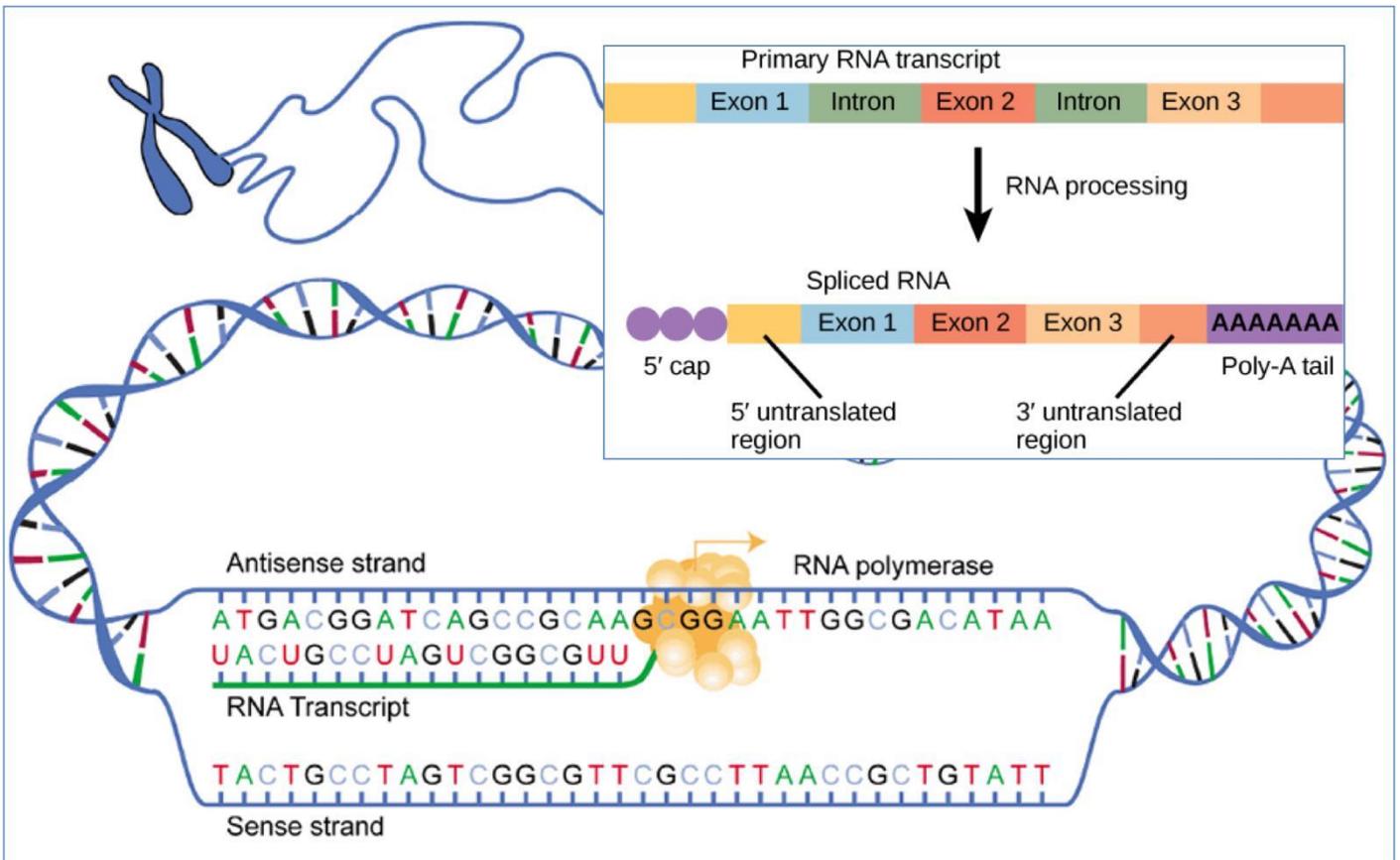


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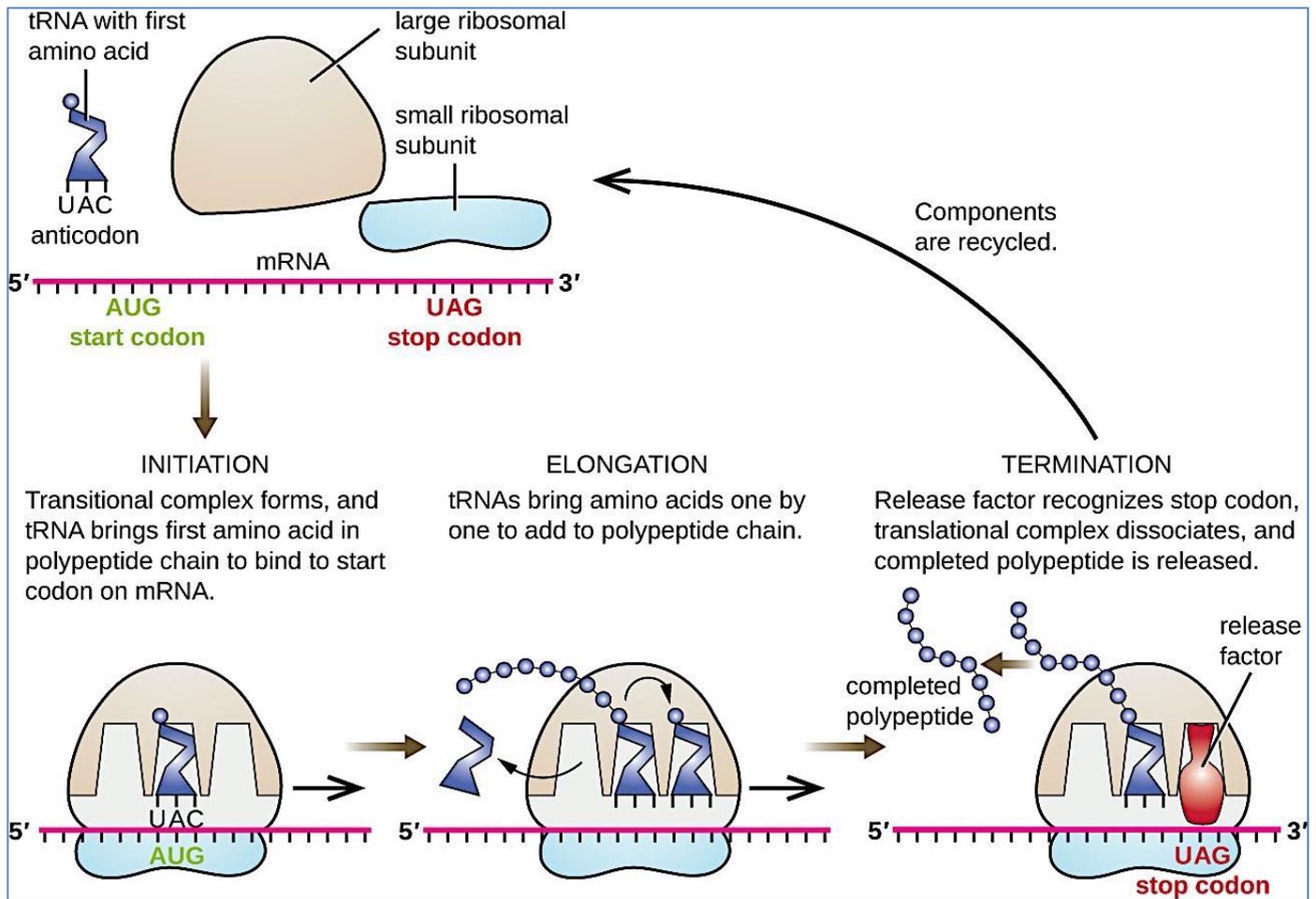
3. **Initiation Phase:** RNA polymerase binds to the DNA @ the *promoter* & other transcription factors complete the mature transcription complex
 - a. **Energy** must be **added** to the system (**Via ATP**) for transcription to begin
 - b. **RNA polymerase** then **splits** the **DNA** into 2 strands **along its own length** (most transcription factors are released after transcription has begun)
4. **Elongation Phase:**
 - a. **RNA polymerase** then moves along the transcription unit, **synthesising an RNA Template** from the strand of DNA
 - b. As it moves along, it **constantly unzips** forward DNA and **rezipts** DNA strands left behind
5. **Termination Phase:**
 - a. When the **terminator region** is reached, the **RNA Polymerase dissociates** from the DNA and the newly formed **strand of RNA is released**



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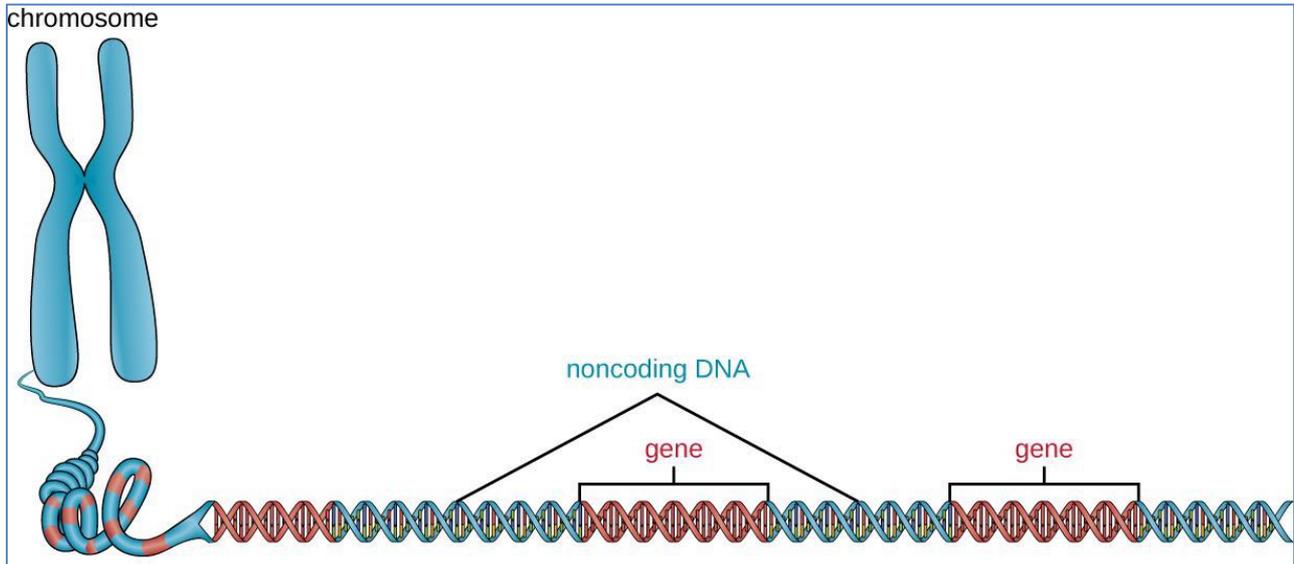
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CHROMOSOMES

CHROMOSOMES

Human Chromosomes:

- **What are they?**
 - Highly compacted **linear** pieces of DNA
 - Contain many different genes
 - Only visible during M-Phase once the replicated chromosomes have condensed
 - Vary in size; 50-250Mbase-pairs

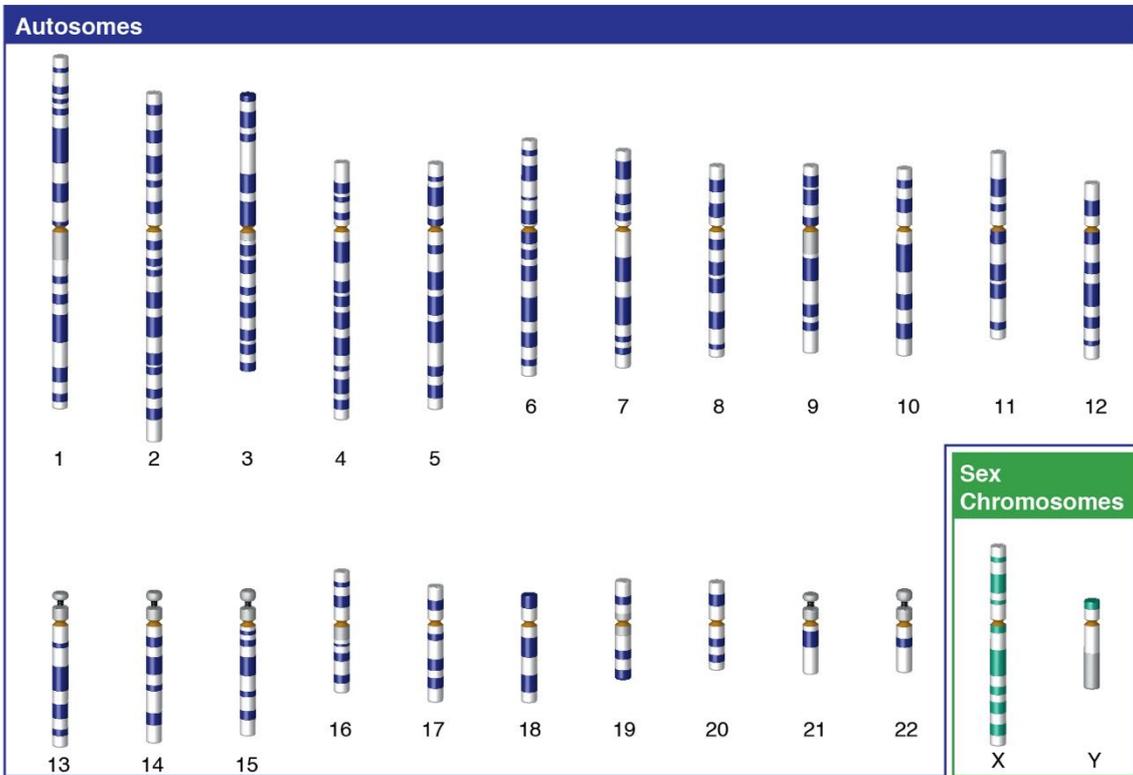


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- **Chromosome Number:**
 - Normal people are born with 2x sets of 23 chromosomes
 - 1 set from mum
 - 1 set from dad
 - Varies between species
 - Similar species have similar chromosome numbers
 - Eg: Chimps – 48 , **Humans – 46**
 - Chromosome number \neq sophistication

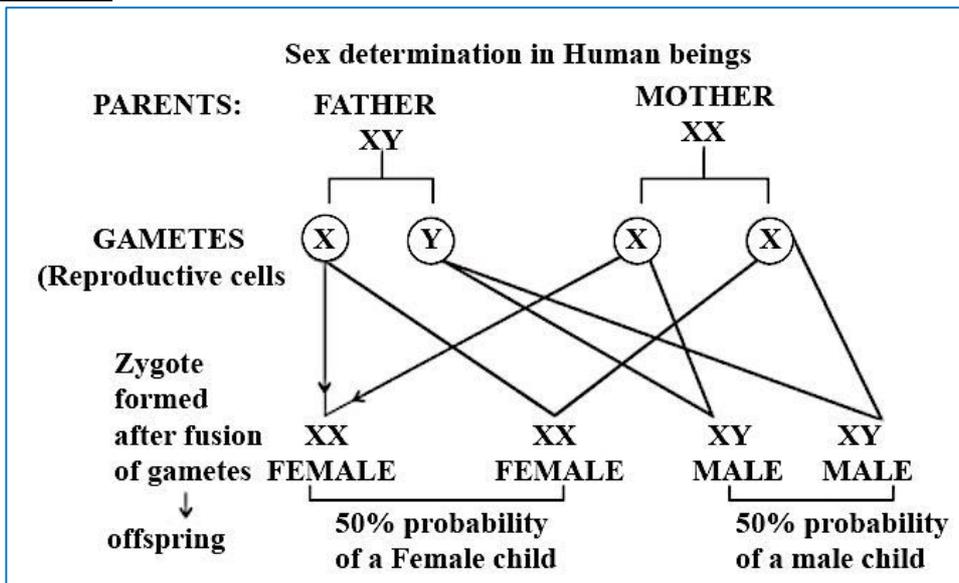
Autosomes Vs Sex Chromosomes:

- **2 Sex Chromosomes:**
 - X & Y - Determine whether you are born biologically Male or biologically Female
 - **XX = Female**
 - X from Dad
 - X from Mum
 - **XY = Male**
 - X from Mum
 - Y from Dad
- **44 Autosomes:**
 - All chromosomes that aren't X or Y
 - Not involved in sex determination



Public Domain: <https://www.genome.gov/genetics-glossary/Autosome>

Human Sex Determination:

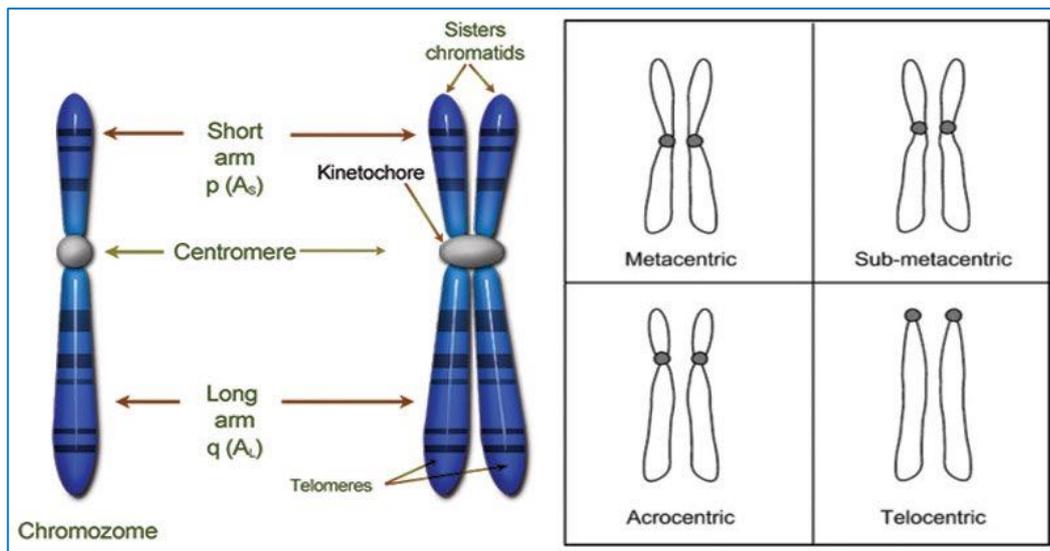


Chromosome Charting:

- **Arms**
 - Long = 'q'
 - Short = 'p'
- **Regions**
 - 2 regions/arm
 - Divided evenly
- **Bands**
 - Centromere = Band 10
 - Counts upward both ways toward the centromere
- **Centromere**
 - Where the 2 sister chromatids are anchored together
- **Telomere**
 - Repeated sequences of non-coding DNA at the Very ends of each chromosome arm

Chromosome Shapes:

1. **Metacentric:**
 - Arms of similar length
2. **Submetacentric:**
 - Centromere at approx 1/3
3. **Acrocentric:**
 - Centromere very close to telomere
4. **Telocentric:**
 - Centromere at the telomere



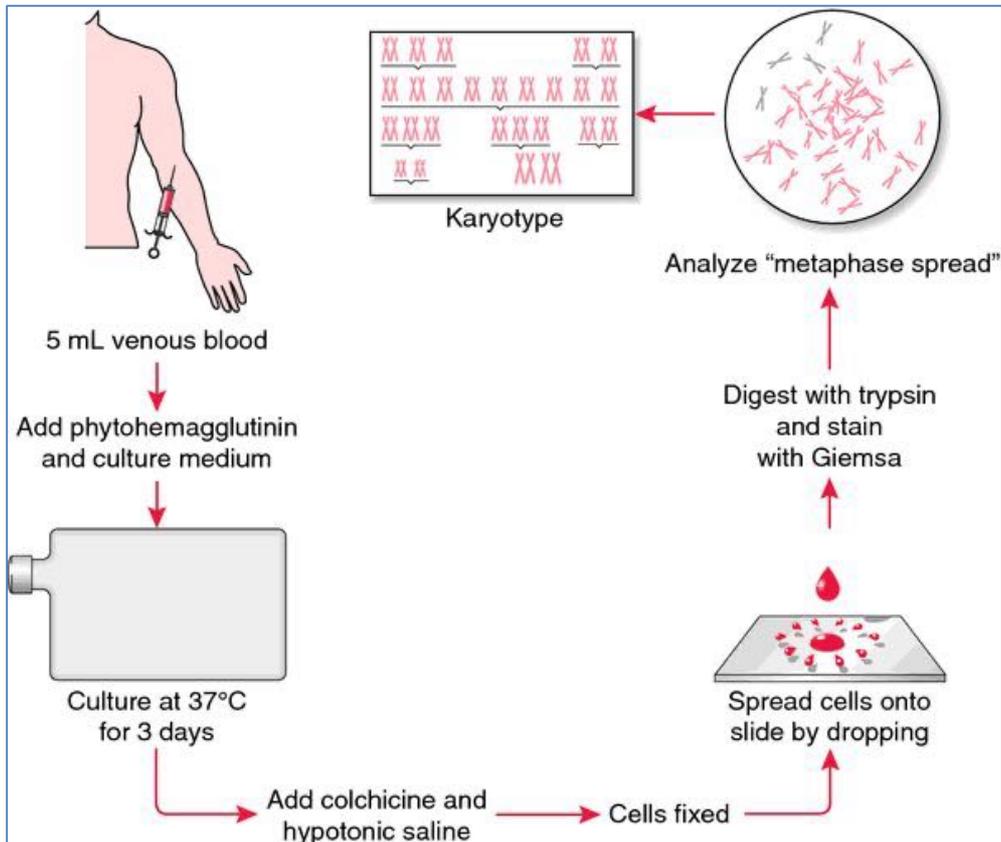
Credit: <https://microbenotes.com/chromosomes/>

Chromosomes Nomenclature:

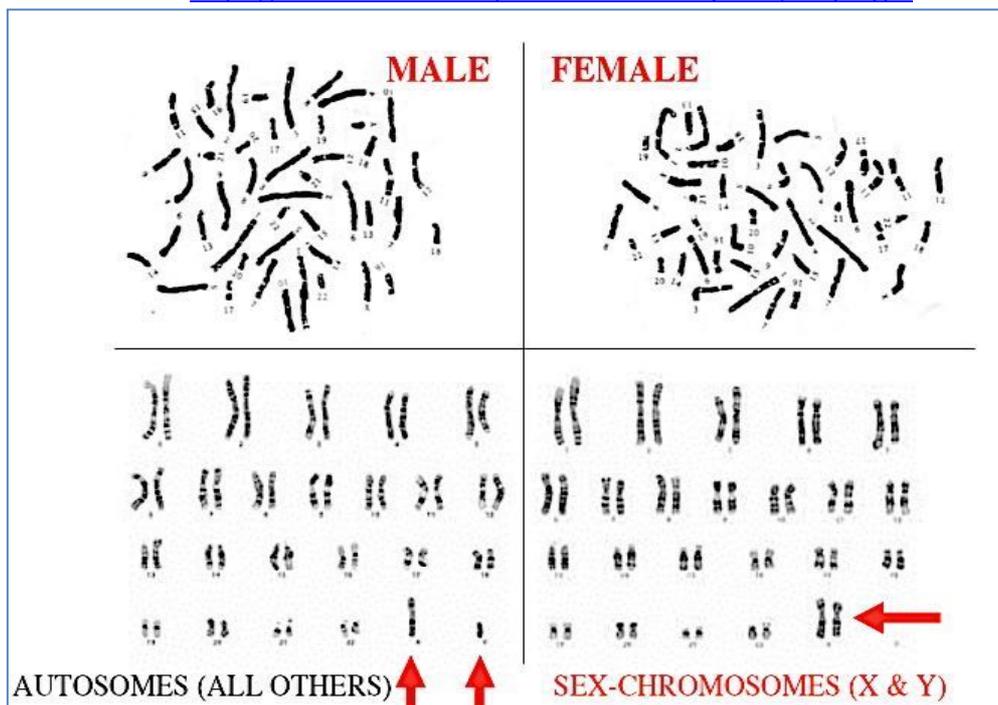
- 46, XX = normal Female
- 46, XY = normal Male
- 47, XX, +10 = abnormal Female - extra 10th chromosome
- 45, XY, -22 = abnormal Male – missing 22nd chromosome
- '+' = Gain / '-' = Loss
- 'cen' = Centromere
- 'del' = Deletion
- 'der' = Derivative chromosome
- 'dup' = Duplication
- 'ins' = Insertion
- 'inv' = Inversion
- 'mar' = marker chromosome
- 'mat' = Maternal / 'pat' = Paternal
- 'rob' = Robertsonian translocation

Karyotyping (Steps in Extracting Chromosomes):

- Extract cells
- Centrifuge - Collect cells
- Grow cells in culture – amplify numbers
- Treat with spindle-inhibitor → arrests cells in **metaphase**
- Treat with **Protease** and stain with **Giemsa**
- Drop cells onto slide – flattens cell → spreads chromosomes
- Analyse by computer – pair identical chromosomes
- Result: **Human Karyotype**



Source: <https://medical-dictionary.thefreedictionary.com/karyotype>

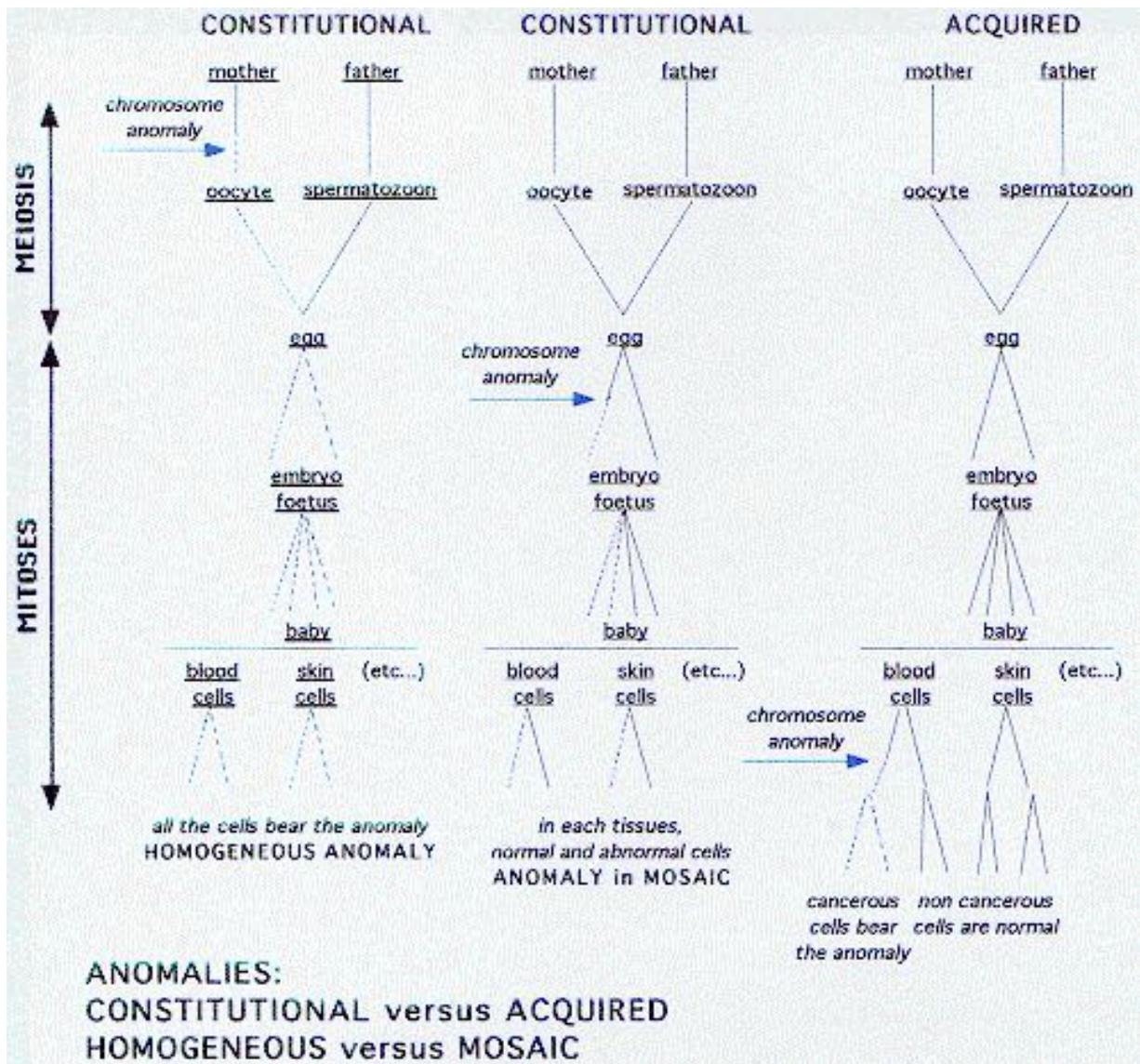


CHROMOSOMAL ERRORS

CHROMOSOMAL ERRORS

Abnormal Karyotypes (Chromosomal errors):

- **Result from Errors in Cell Division:**
 - During Meiosis or Mitosis
 - Gains/losses of parts of chromosomes
 - Rearrangements between chromosomes
 - Gains/losses of whole chromosomes
- **2 Classes:**
 - **Constitutional Chromosome Abnormalities**
 - Error happens During Gametogenesis (Prior to conception)
 - Found in every cell of the body
 - **Acquired Chromosome Abnormalities**
 - Error happens During Embryogenesis (After conception)
 - Found only in clusters of cells
 - Individuals are a 'mosaic' of normal & abnormal cells

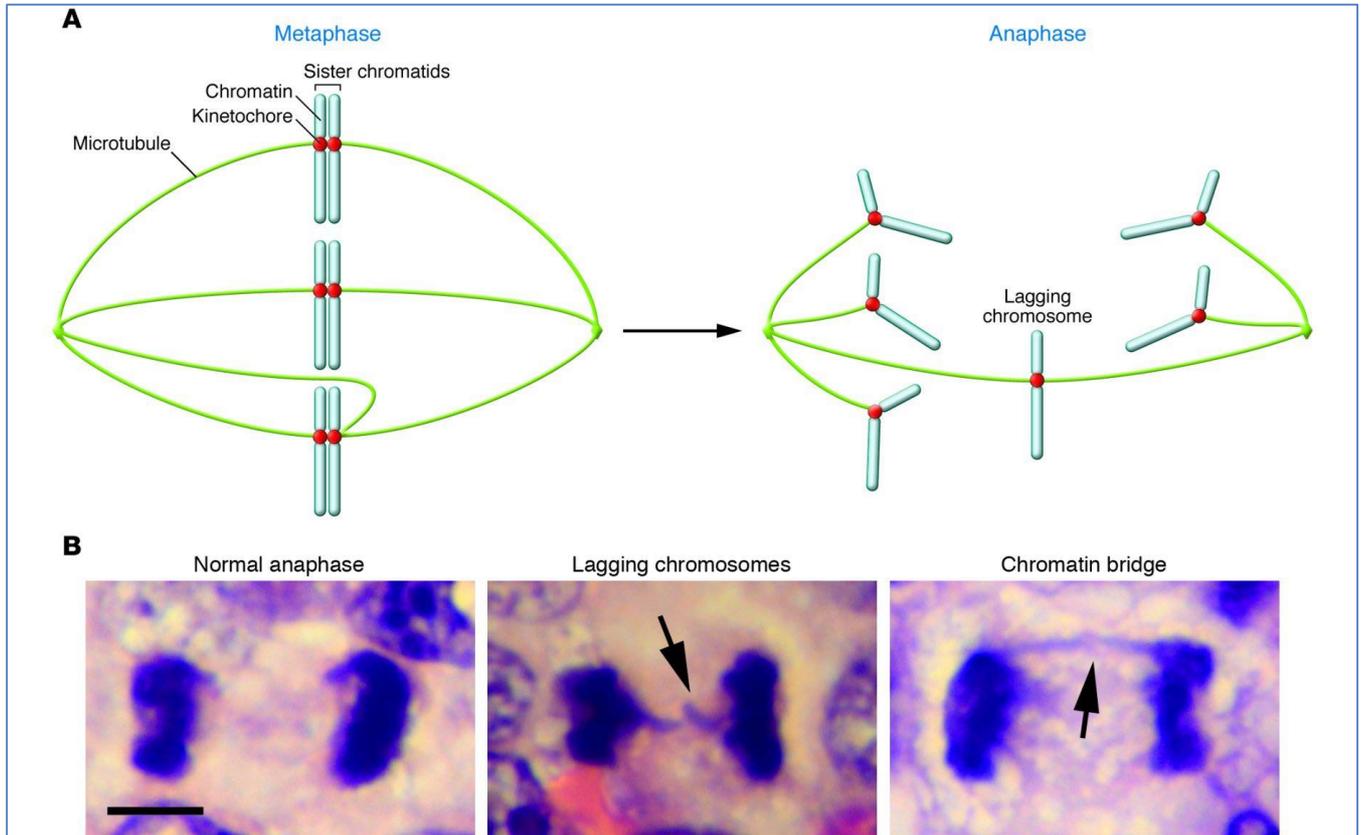


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Main Causes of Abnormal Karyotypes:

1. Anaphase Lag:

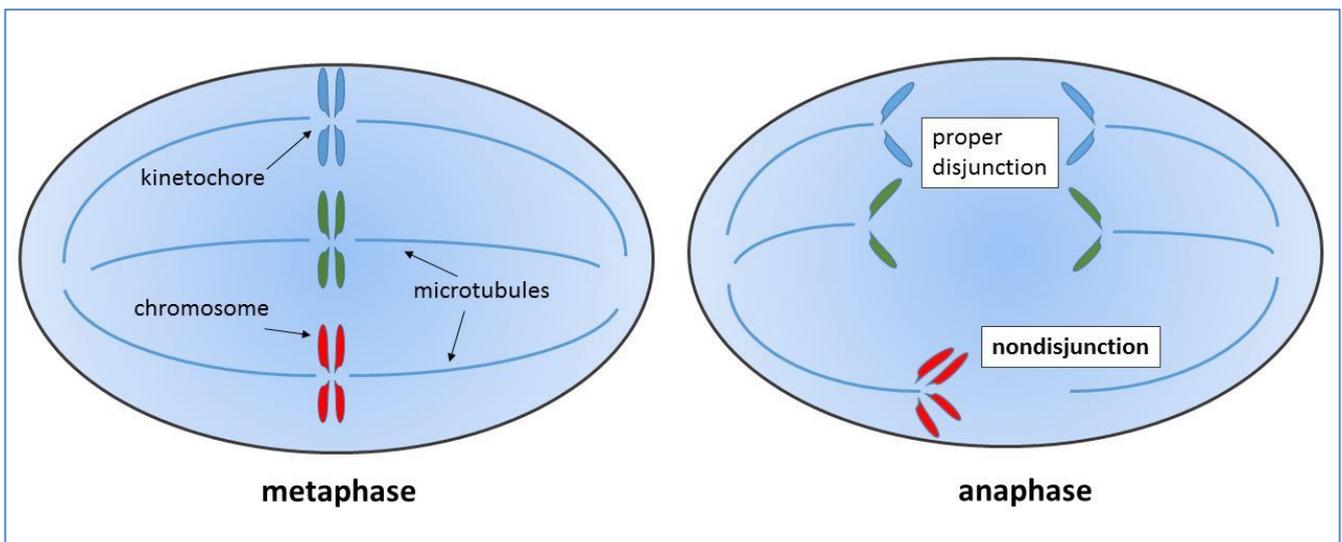
- Occurs During anaphase
- Is where one chromosome fails to migrate to the pole of the spindle
- That chromosome then fails to be enclosed by the new nuclear envelope
- Chromosome is lost and gets degraded
- Results in 1x normal cell + 1x cell with a missing/extra chromosome
- Leads to **monosomies & trisomies**



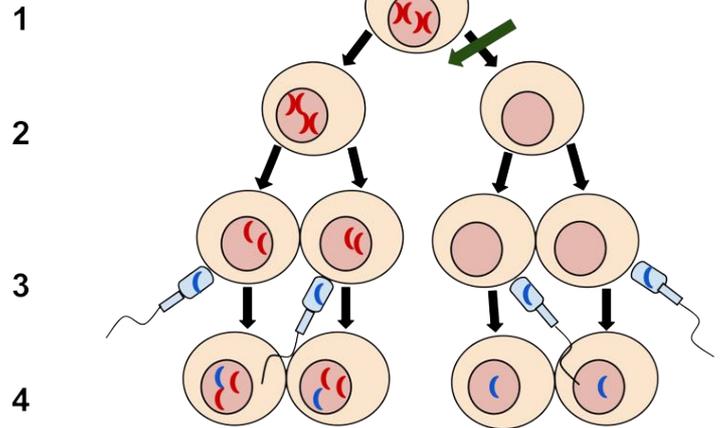
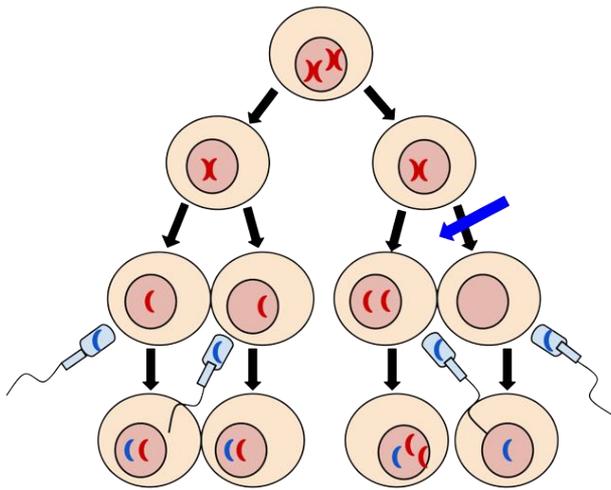
J Clin Invest. 2012;122(4):1138-1143. <https://doi.org/10.1172/JCI59954>

2. Chromosome Mis-Segregation (Nondisjunction)

- Error during meiosis
- Where chromosomes aren't divided equally among the gametes
- Results in either: gametes with extra or missing chromosomes
- If such gametes are fertilized → **monosomies & trisomies**



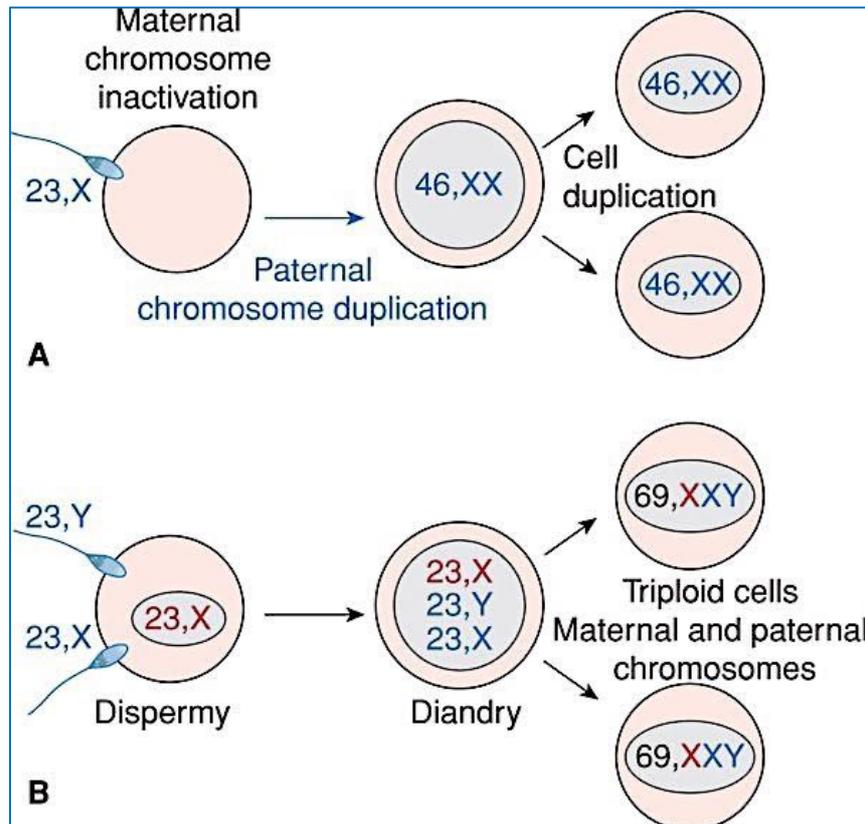
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3. Replication Failure (Meiotic/Mitotic)..and..Dispermy

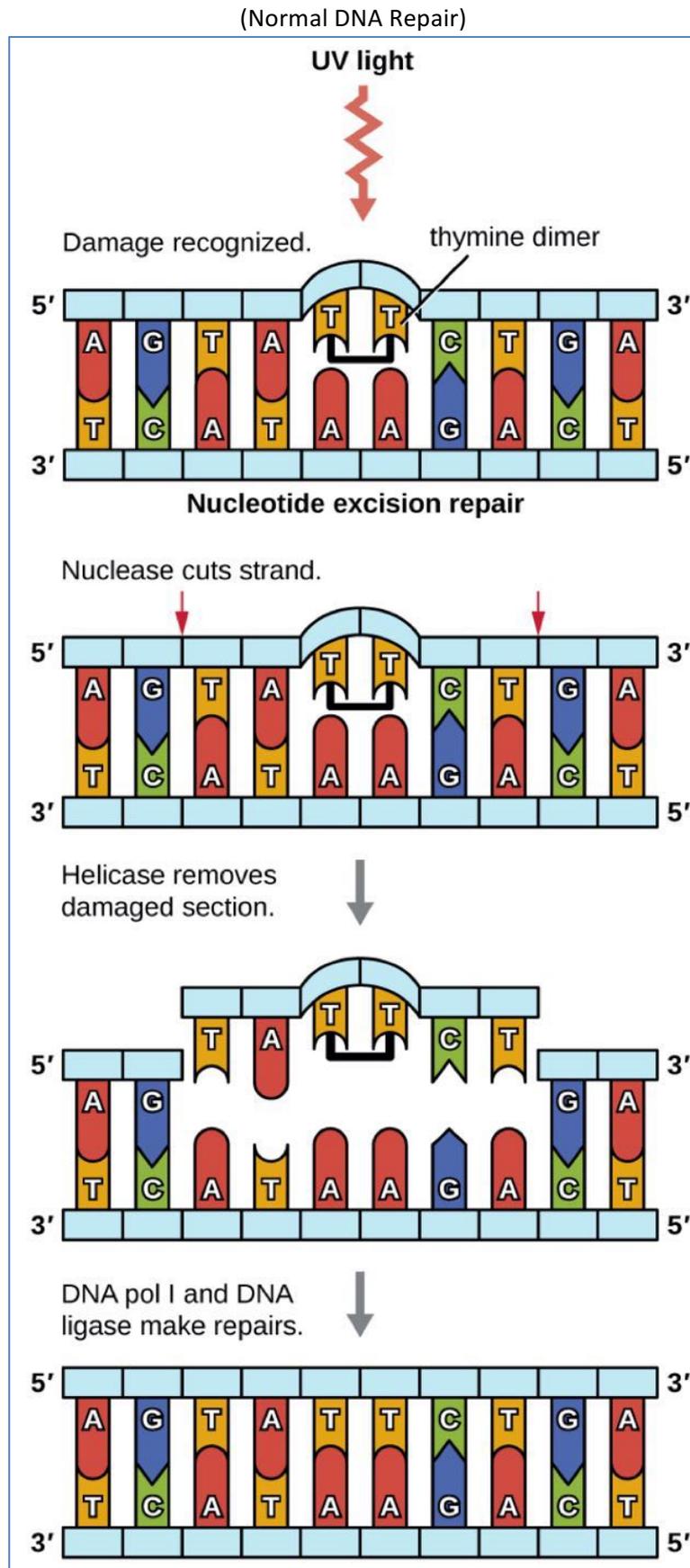
- a. Results in polyploidy
- b. How this can happen:
 - i. **Error in Gametogenesis**
 1. Chromosomes duplicate but the germ cell fails to divide → diploid gametes
 2. → Trisomy embryos
 - ii. **Error at Fertilisation**
 1. Eg: Dispermy → 2 sperm simultaneously fertilise egg → triploid embryo
 - iii. **Error in Embryogenesis**
 1. Errors during early mitotic cell divisions
 2. Chromosomes duplicate by the embryonic cell/s fail to divide → triploid mosaic embryo



Source: <https://obgynkey.com/gestational-trophoblastic-disease-8/>

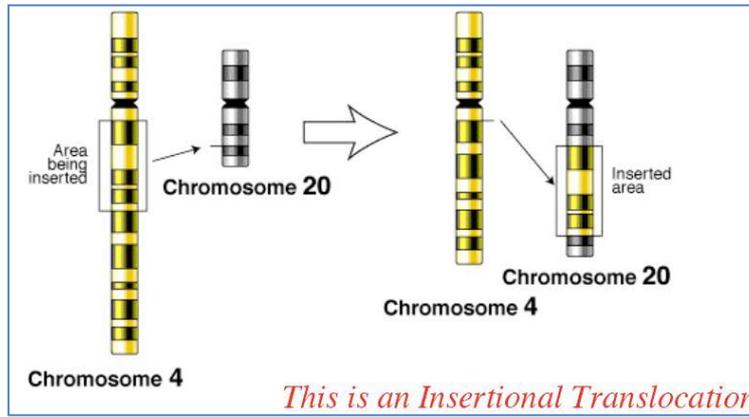
4. Incorrect DNA Repair:

- a. Cellular DNA damage happens regularly
- b. Usually DNA repair mechanisms work well
- c. Sometimes, DNA damage is incorrectly repaired



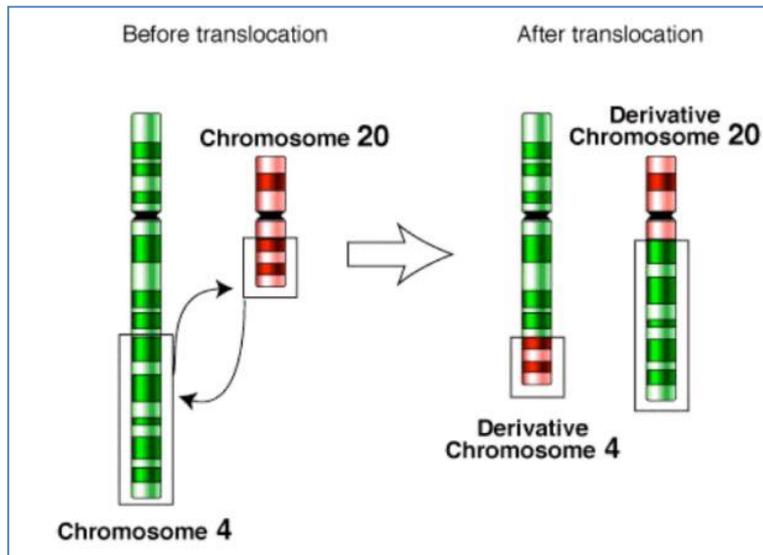
Mechanisms of Chromosomal Errors:

- **Insertional Translocations:**



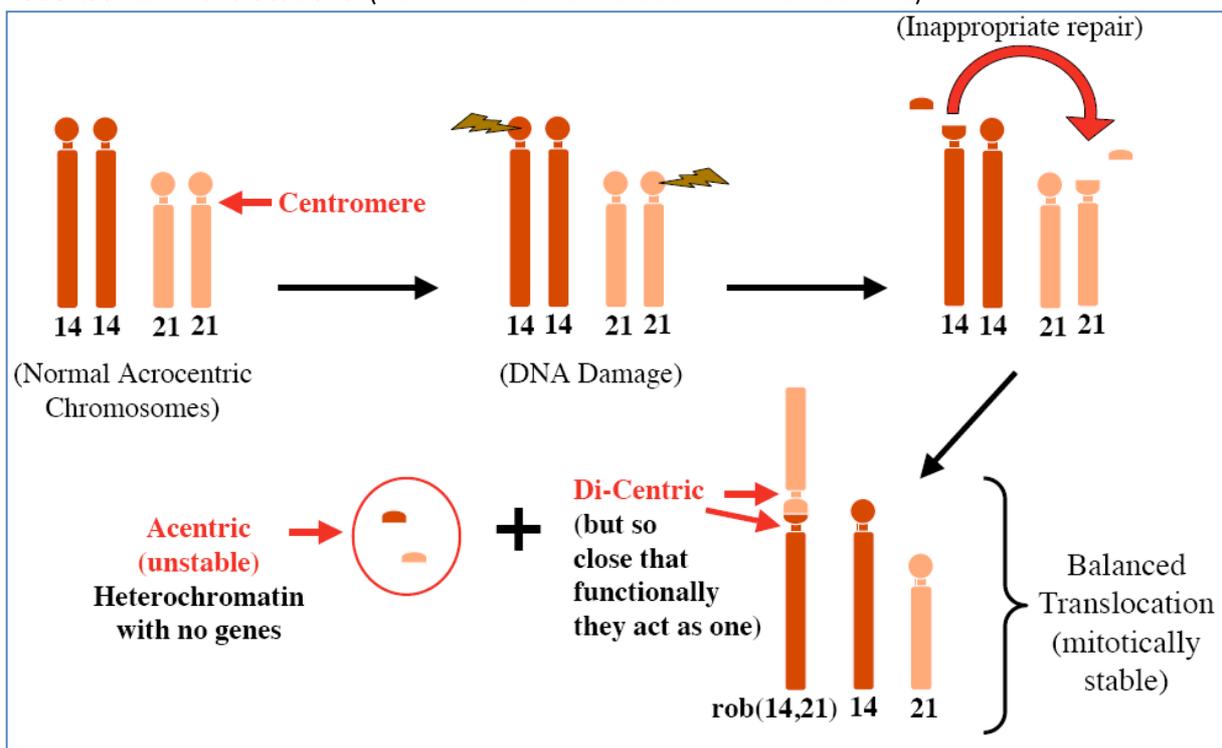
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- **Reciprocal Translocations:**



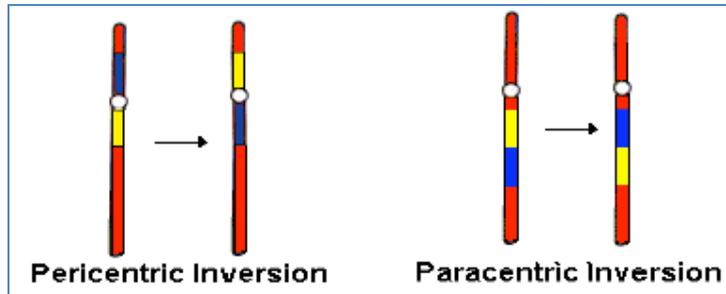
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- **Robertsonian Translocations: (Centric Fusions of Acrocentric Chromosomes)**



- **Inversions:**

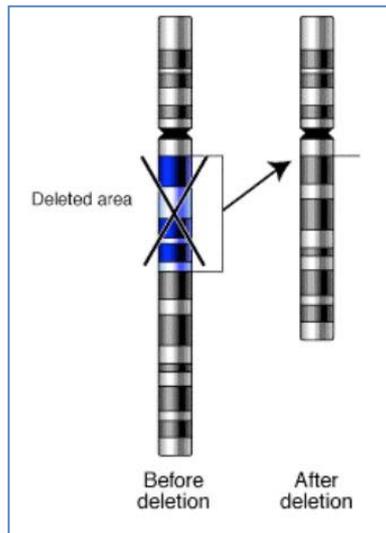
- A segment of the chromosome has been flipped
- No gain / loss of genetic material
- If breakpoints don't disrupt genes → no abnormality
- 2 Kinds:
 - Pericentric
 - Paracentric



<https://chromodisorder.org/introduction-to-chromosomes/>

- **Deletions:**

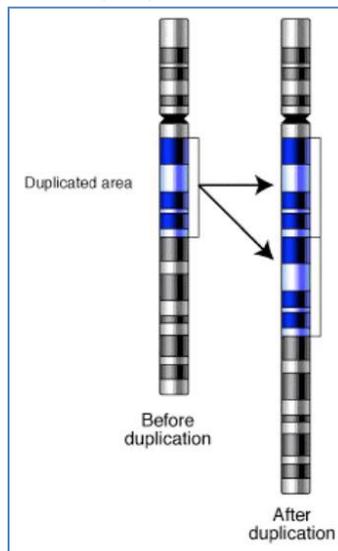
- A region of a chromosome is deleted
- Deletion size: proportional to: Severity of abnormality
- Eg: William's syndrome = DNA loss on Chromosome 7



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- **Duplications:**

- A region of a chromosome is doubled
- If duplication occurs outside a coding region & doesn't result in a frameshift → no abnormalities



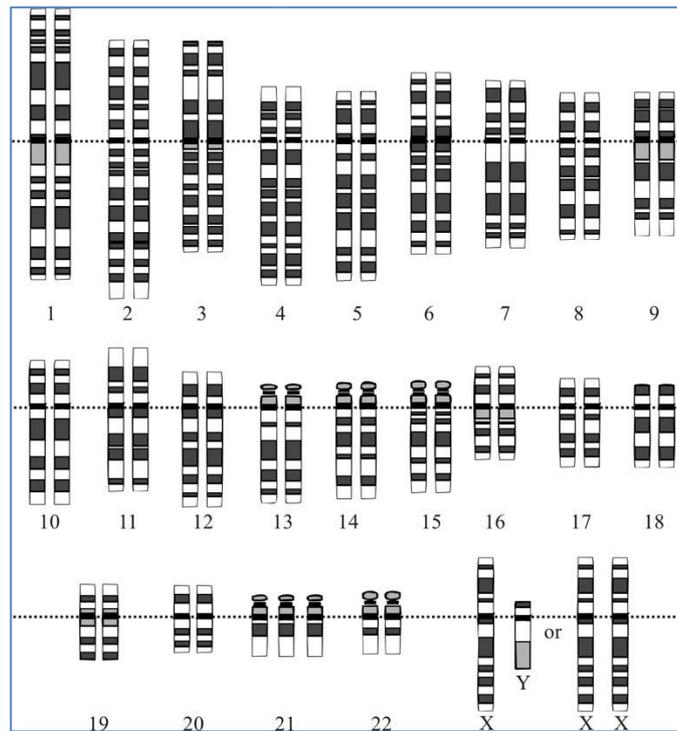
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Aneuploidy Vs Polyploidy

- **Aneuploidy:**

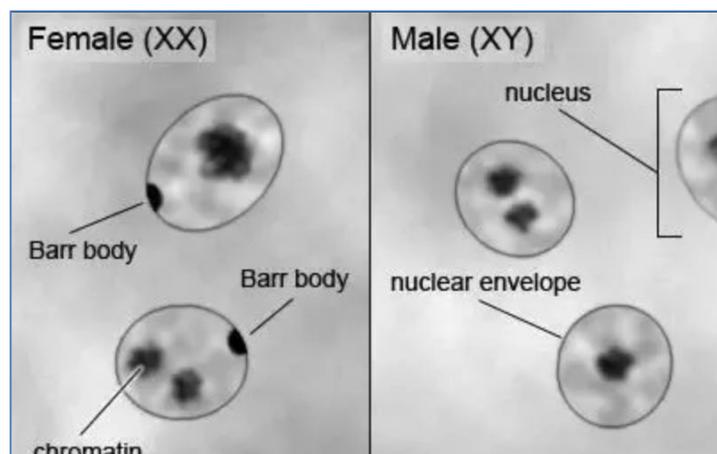
- The addition/loss of a chromosome from the **normal (euploid) 23 pairs**
- **Common cause: Nondisjunction** – failure of chromosomes to separate properly during meiosis
- **Generally manifests as a trisomy - 3 sets of a chromosome**
 - Most trisomies are lethal except on the small chromosomes
 - Eg: Chromosome 21 – Down's Syndrome;
 - Chromosome 18 – Edward's Syndrome
- **Rarely manifests as a monosomy – loss of a chromosome**
 - All embryonically lethal – except on sex chromosomes

(Eg: Trisomy 21)



Courtesy: National Human Genome Research Institute, Public domain, via Wikimedia Commons

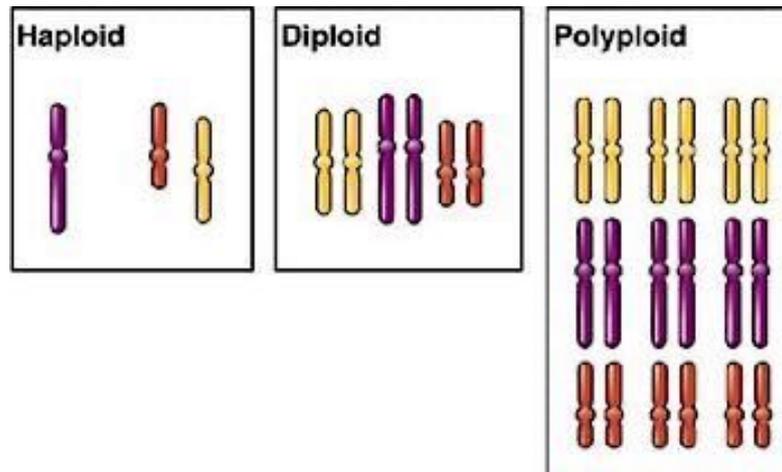
- **Aneuploidy of Sex Chromosomes:**
 - **Males** must cope with a single X-chromosome
 - Evolution developed a mechanism: **dosage compensation**
 - **Females** only use one of their X-chromosomes
 - One X-chromosome in each cell is randomly **hypercondensed** (inactivated) → **Barr Bodies**
 - **Barr Bodies:** areas of heterochromatin
 - Therefore all females are **mosaics** (Eg: Dermal dysplasia)



Source: <https://qph.fs.quoracdn.net/main-qimg-b2f86c419d65729fd7d8d70081cd24b7.webp>

- **Ployploidy:**

- Addition of whole *sets* of chromosomes
- Eg: 3 copies of every chromosome (or 4, or 5, etc)
- Almost always embryonically lethal & results in spontaneous miscarriage



Source: <https://uvmgg.fandom.com/wiki/Diploid>

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