CHAPTER 2: Introduction to the Human Genome (Part 1)

☒ Introduction

- **Genetics** is the science of heredity.
- **Heredity** is the study of the way that traits are passed from parent to offspring.
- **Traits** are the characteristics; **E.g.** hair color, eye color, or skin color.
- The traits which an organism inherits are determined during the life process of reproduction.
- More variation (differences) is found in sexual reproduction than asexual reproduction.
  - In sexual reproduction, the offspring resembles its parents but is also different from them.

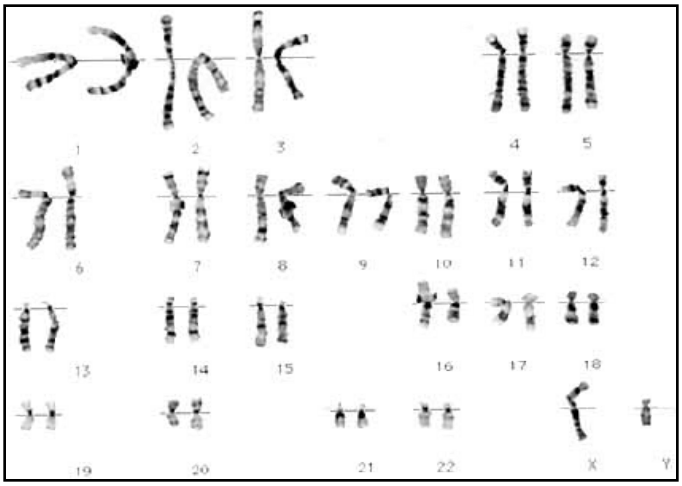
- The chromosome number is the same from generation to generation within an organism or species. But every species will have a different chromosome number.

  A. Dog = 48
  B. Cat = 38
  C. Crayfish (lobsters)= 100

The chromosome number in selected species

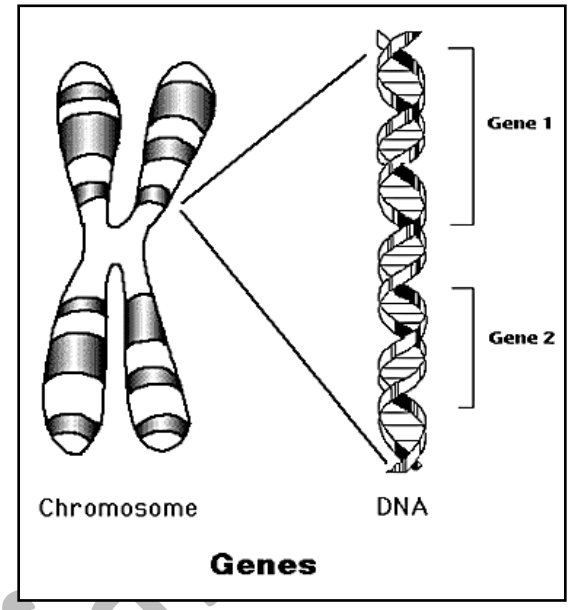
Species		Chromosome number (2n)	Species		Chromosome number (2n)
	human being	46		tobacco	48
	fruit fly	8		barley	14
	rat	42		water-melon	22
	fen duck	80		bean	22

- In a cell, chromosomes are arranged in pairs which are represented by a photograph called a **karyotype**.

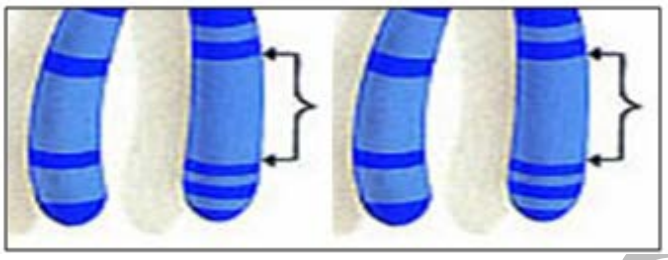


- Today's knowledge about genetics is a result of genetic studies started by Gregor Mendel **"Father of Genetics"** in the middle 1800's. Mendel did not know about genes, but thought that certain "factors" were responsible for traits passed from parents to offspring.

- **The Gene-Chromosome Theory;** states that chromosomes (found in the nucleus of the cell) are made of small units called genes.
  - **A.** Genes carry hereditary information and are found at specific locations along chromosomes. Each chromosome may contain several hundred genes.



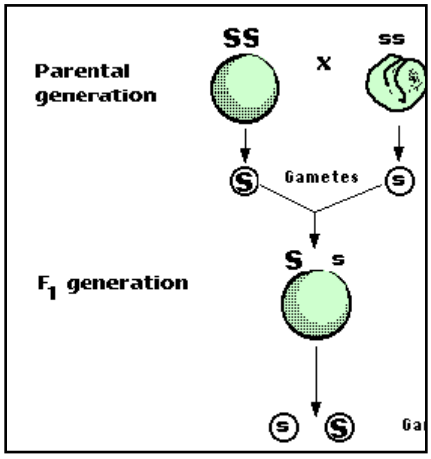
- **Alleles** are pairs of genes that carry the same traits and are found at the same locations on pairs of chromosomes.



- During fertilization, the male and female parents each contribute genetic information (traits) to the zygote (fertilized egg).
  - One half of its genetic traits from its male parent and the other half from its female parent.
  - Genetic traits are carried in chromosomes.

- **Mendel's Experiments**
  - Gregor Mendel conducted heredity experiments using common garden pea plants. But also crossed (mated) large numbers of plants.
  - Mendel **concluded** that; there were traits that always appeared (were expressed) when they were present in an organism.

    A. The purebred plants are called the parent **(P) generation**.
    B. The offspring of a cross between two parent (P) generation plants are called the **first filial (F_1) generation**.

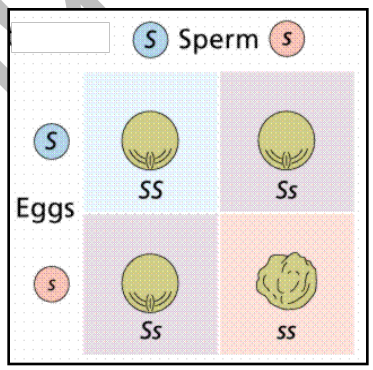


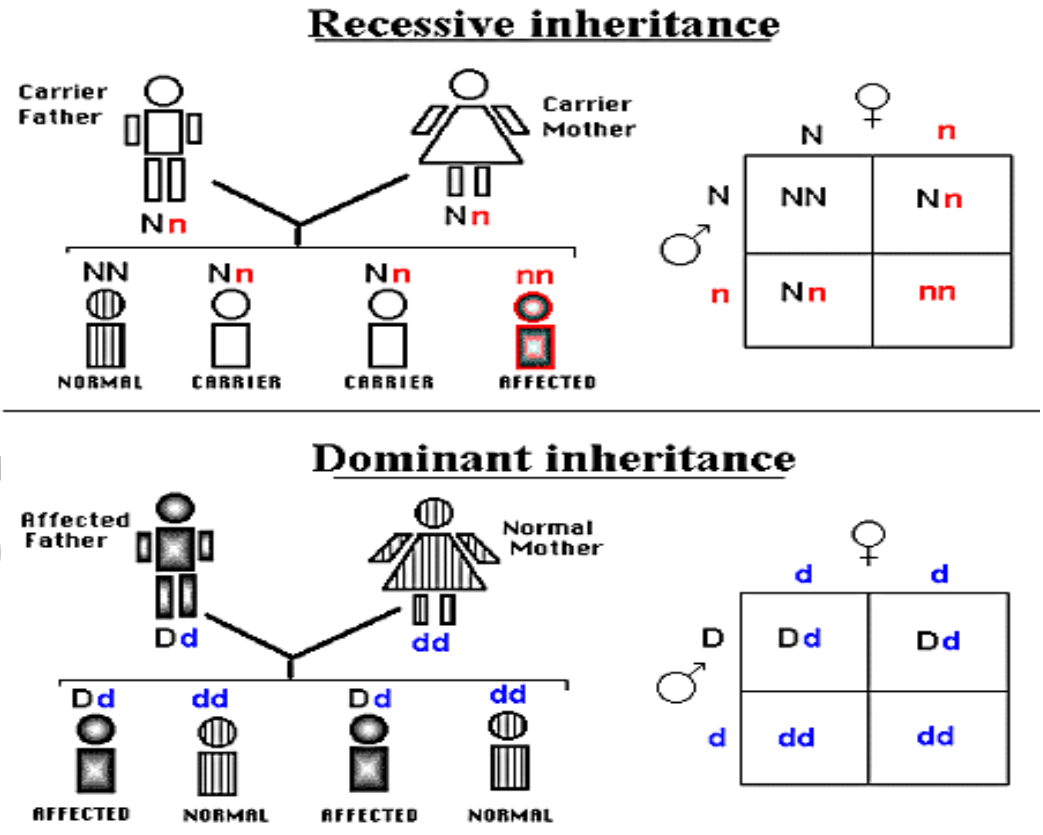
  - The trait that always appears when it is present is called the **Dominant Trait.**
  - The trait that is hidden by the dominant trait is called the **Recessive Trait.**

- **Genetic Terms**
  - **A. Homozygous Trait**; both genes for that trait are <u>the same</u>. **E.g.** A pea plant with two genes for tallness.
  - **B. Heterozygous Trait;** Both genes for that trait are <u>not the same</u>. **E.g.** A pea plant with one gene for tallness and one for shortness.
  - **C. Genotype;** The genetic makeup of an organism.
  - **D. Phenotype;** The external appearance of an organism.

For example, an organism that looks tall can have a genotype that is pure tall or hybrid tall. This is because whenever the dominant trait is present, the organism expresses (shows) the dominant trait.

- **Punnett Squares**
  - **Step 1.** State the key by using the capital letter of the dominant trait to represent the dominant gene and the small letter of the dominant trait to represent the recessive gene.
  - **Step 2.** Write the cross and show the gametes.
  - **Step 3.** Draw the Punnett square and place the letters for the egg alleles on one side of the square and the letters for the sperm alleles on the other side of the square.
  - **Step 4.** Write the results next to the square.





- **A Dihybrid Cross**
  - In mice, black is dominant over tan and short tails are dominant over long. Now could you write the genotype for a heterozygous black, short- tailed mouse? **B b S s**
    - **B = black**
    - **b = tan**
    - **S = short tails**
    - **s = long tails**

BbSs x BbSs

	BS	Bs	bS	bs
BS				
Bs				
bS				
bs				

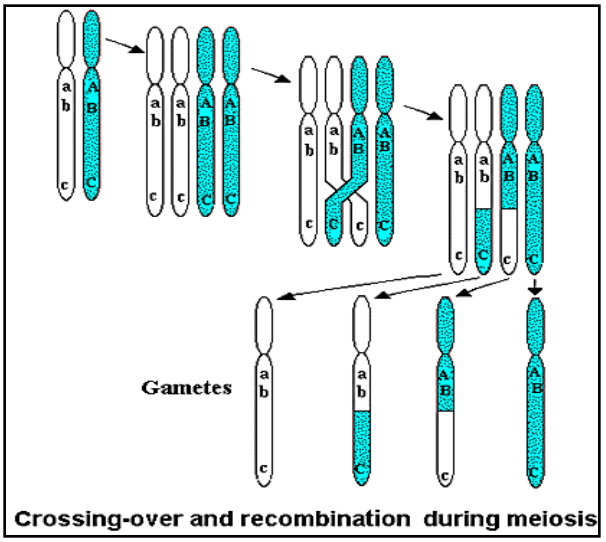
BbSs x BbSs

	BS	Bs	bS	bs
BS	BBSS	BBSs	BbSS	BbSs
Bs	BBSs	BBss	BbSs	Bbss
bS	BbSS	BbSs	bbSS	bbSs
bs	BbSs	Bbss	bbSs	bbss

What are the possible gametes for this mouse? Each gamete must have one "B" and one "S"

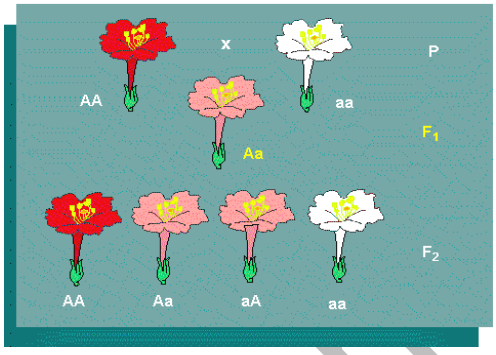
Describe the phenotype of the offspring.
- Black, Short-tail; 9
- Black, Long-tail; 3
- Tan, Short-tail; 3
- Tan, Long-tail; 1

- **Gene Linkage**
  - Today, we now know that traits are not all inherited independently of each other. Scientists have found that traits that are located on the same chromosome tend to be inherited together.
  - Traits located on the same chromosome are said to show **Linkage**. Although linked genes are generally inherited together, they can become separated by **Crossing-Over**, which may occur during a stage of meiosis.
  - During this stage, the four chromatids sometimes twist around each other. As they separate, the chromatids may break, exchange segments, and rejoin.



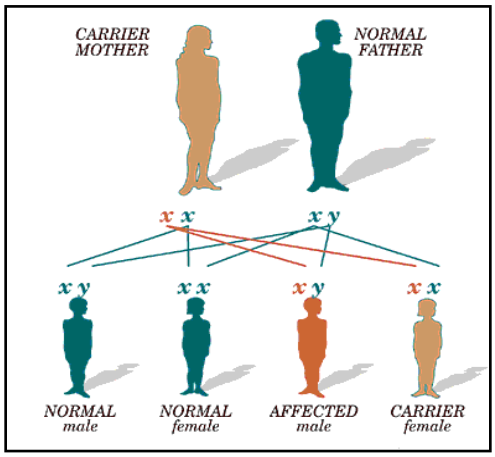
Crossing-over and recombination during meiosis

- **Incomplete Dominance;** or **blending inheritance** occurs when the offspring shows traits that are a blend or mix of the two parents.



- **Inheritance of Sex**
  - Your sex (male or female) was determined when your mother's egg was fertilized by your father's sperm.
  - Humans have one pair of chromosomes, called the **Sex Chromosomes**.
  - Sex chromosomes are represented as X and Y.
  - Egg cells have only X chromosomes while sperm carried either an X or a Y chromosome.
  - At fertilization, two X chromosomes produce a female (XX).
  - An X chromosome and a Y chromosome produce a Male (XY).
  - In most organisms, it is the sperm that determines the sex of the offspring.

- **Sex-Linked Inheritance**
  - The Y chromosome is smaller than the X chromosome.
  - Several of the genes found on the X chromosome are not found on the Y chromosome.
  - The genes on the X chromosome that have no matching genes on the Y chromosome are called **sex-Linked genes**. Sex-linked genes are usually recessive.
  - Two human diseases associated with sex-linked genes are hemophilia (blood does not clot properly) and color blindness.



  - Both of these disorders are more common in males than in females. This is because the sex-linked recessive gene on the male's X chromosome is the only gene the male has for the sex-linked trait. A female will not have hemophilia, color blindness or any other sex-lined condition, as long as she has one normal gene for the trait.

  - Females who have one recessive gene for a sex-linked trait are called "**Carriers**" for that trait.
    - That means they do not have the disorder, but they carry the recessive gene.
    - Children of carriers can inherit the sex-linked gene.

CHAPTER 2: Introduction to the Human Genome (Part 2)

☒ Genome

- All the genetic material in a cell or the DNA in all chromosomes of a cell.
- **DNA have :**
  1. Coding sequence (genes).
  2. Non coding sequence (repetitive sequence). **E.g.** Telomeres
- **Eukaryotes have 2-3 genomes types:**
  1. Nuclear genome.
  2. Mitochondrial genome.
  3. Plastid genome (in plant).
- **Human body have 2 type of cells:**
  1. Somatic cells, with 46 chromosomes (23 pair of chromosomes).
  2. Germ cells, with 23 chromosomes.
- **The somatic cells have 2 type of genome:**
  1. **Nuclear genome:** contain all the genetic material of a human. **E.g.**
     - Genes for hair color.
     - Genes for eye color.
     - Genes for tall.
  2. **Mitochondrial genome:**
     - Single copy of Circular DNA strand.
     - 16,500 base pair.
     - Inherited only from the mother.

Notes:

- Each one (nuclear and mitochondrial) has a specific DNA molecule, so we deal differently with each one.
- If not specified, "genome" usually refers to the nuclear genome. But if specified it is the entire DNA in an organelle.

☒ DNA structure ,A brief review :

- It's a polymer of nucleotides, so a nucleotide is the monomer (Building block).
- Nucleotide composed of 3 subunit molecule:
  1. Phosphate(s) group, give the (–) charge to the DNA.
  2. Deoxy-ribose sugar, i.e. carbon #2 on ribose sugar has (H) group not (OH) group.
  3. Nitrogenous bases.

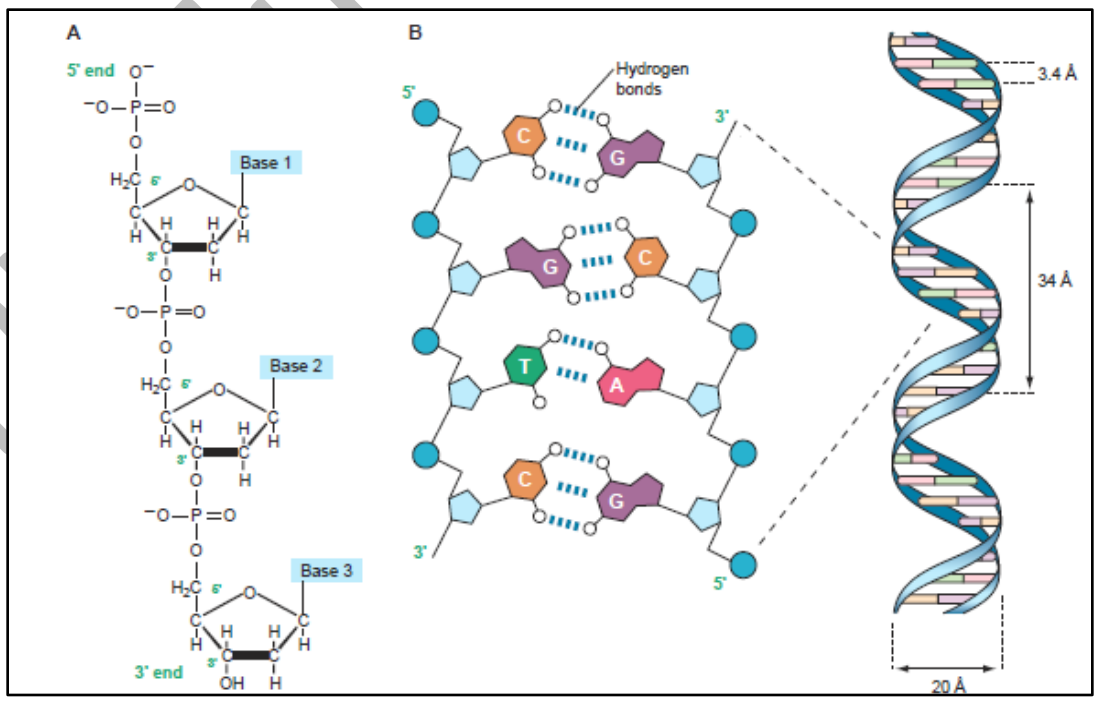
- **Purine**, it's a 2 ring structure.
  - **A.** Adenine
  - **B.** Guanine
  - **C.** Xanthine
  - **D.** Hypoxanthine

- **Pyrimidine**, it's a 1 ring structure.
  - **A.** Uracil
  - **B.** Cytosine
  - **C.** Thymine
  - **D.** Orotic acid

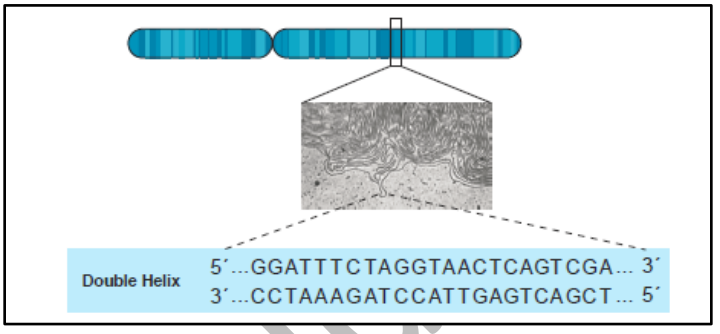
- **Fig A**, shows that:
  - DNA is polynucleotide chain.
  - **3' 5' phosphodiestere bond** that link adjacent nucleotide.
  - Backbone of the DNA is formed from **deoxy-ribose sugar** and **negative phosphate(s) group** which is to the outside.
- **Fig B,** shows that:
  - The DNA is a double helix strand.
  - The nitrogenous bases linked by hydrogen bonds.
  - **Two types of hydrogen bonds:**
    - **A.** 3-Hydrogen bonds type (C—G).
    - **B.** 2-Hydrogen bonds type (A—T).

Note; During DNA replication, a DNA rich in 3- hydrogen bonds need more energy to breakdown than 2- hydrogen bonds.

- **DISTANCE** between a paired base is 3.4 Angstrom or 3.4 A.
- Width if double helix is 20 A.
- These numbers are important in estimation the number of bases in a DNA molecule.

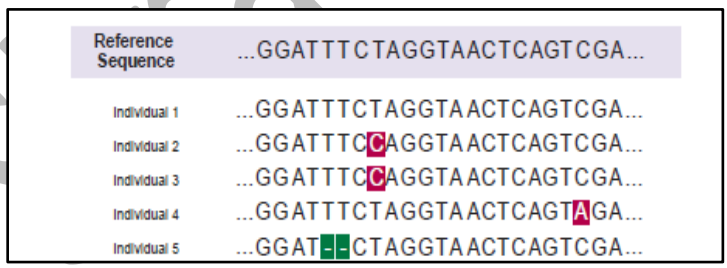


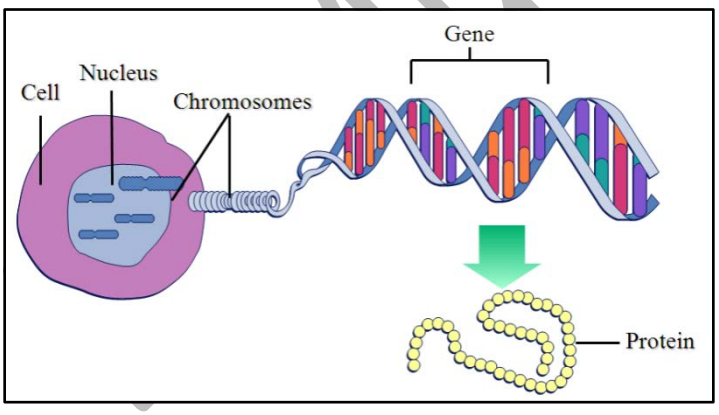
- **Chromosome composed of;** two identical or similar copies of chromatids.
- Each chromosome has multiple genes.
- **Gene** is a specific nucleotide sequence on a specific locus for specific function. E.g. eye color gene, hair color gene.
- DNA is a double strands molecule ,
  - Strands are antiparallel to each other **5'→3',, 3'→5'**.
  - The base pairing is **G → C ,, A → T** .

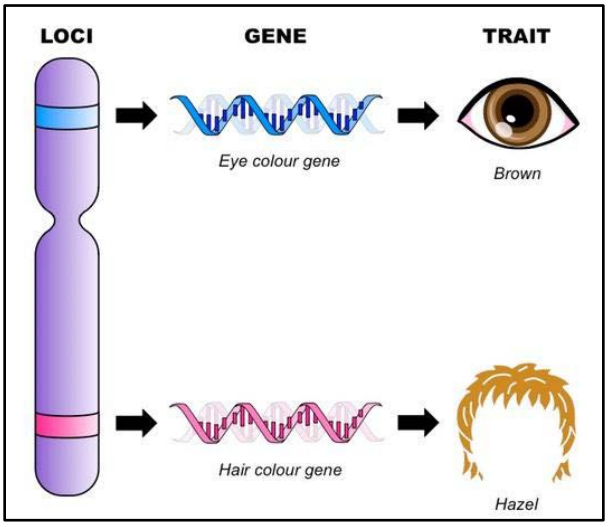


- If we take a reference sequence and compare it with certain number of individual, we will find out that each one of those individual has a **Finger Print** that make him with a special characteristic.

  The finger print is a result of **Single Nucleotide Polymorphism**.
  - ~ 99.9% of our genome is identical.
  - ~ 0.1% is what differentiate human from each other.







☒ Structural Difference between DNA and RNA.

DNA	RNA
• Double Strands • Deoxyribose • Thymine	• Single Strand • Ribose • Uracil

☒ Genome size comparison.

- o Complex organisms have more genes.
- o Human(homo sapiens)
  - 46 chromosomes
  - 28-35.000 genes
  - billion bases
- o Mouse; 40 chromosomes
- o Fruit fly; 8 chromosomes
- o Bacteria; 1 chromosome

Genome size comparison

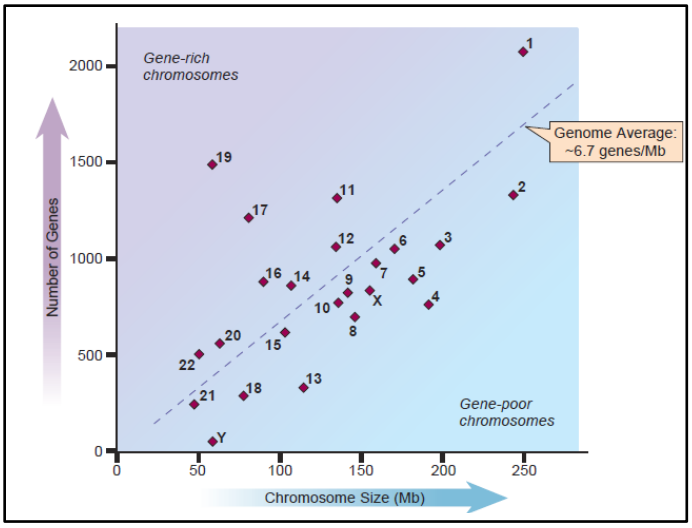
Species	Chromosomes	Genes	Base pairs
Human *(Homo sapiens)*	46 (23 pairs)	28-35,000	3.1 billion
Mouse *(Mus musculus)*	40	22.5-30,000	2.7 billion
Puffer fish *(Fugu rubripes)*	44	31,000	365 million
Malaria mosquito *(Anopheles gambiae)*	6	14,000	289 million
Fruit fly *(Drosophila melanogaster)*	8	14,000	137 million
Roundworm *(C. elegans)*	12	19,000	97 million
Bacterium * *(E. coli)*	1	5,000	4.1 million

*Bacterial chromosomes are chromonemes, not true chromosomes

JOHN BLANCHARD / *The Chronicle*

☒ Organization of the human genome.

- o Chromosomes are not just a random collection of different types of genes and other DNA sequences.
- o Regions of the genome with similar characteristics tend to be clustered together.
- o The functional organization of the genome reflects its structural organization and sequence.
- o Some chromosome regions or even whole chromosomes are high in gene content ("gene rich"), whereas others are low ("gene poor").
- o **Fig.**
  - Chromosomes that are relatively gene rich are above the diagonal line and tend to the upper left.
  - Chromosomes that are relatively poor are below the diagonal line and tend to the lower right.



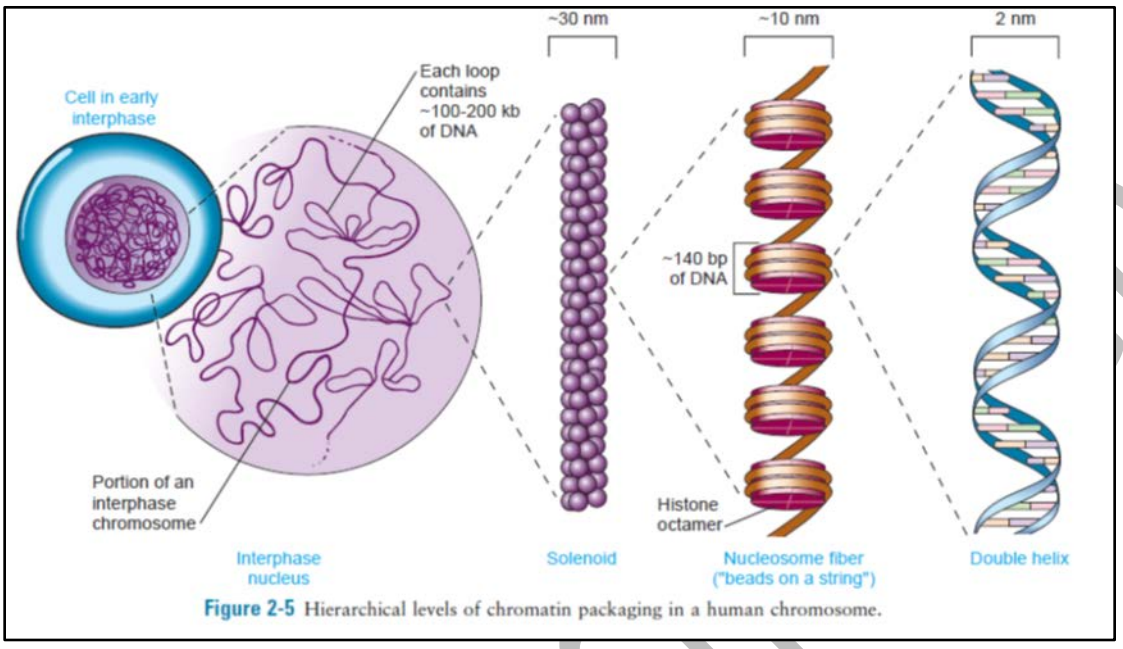
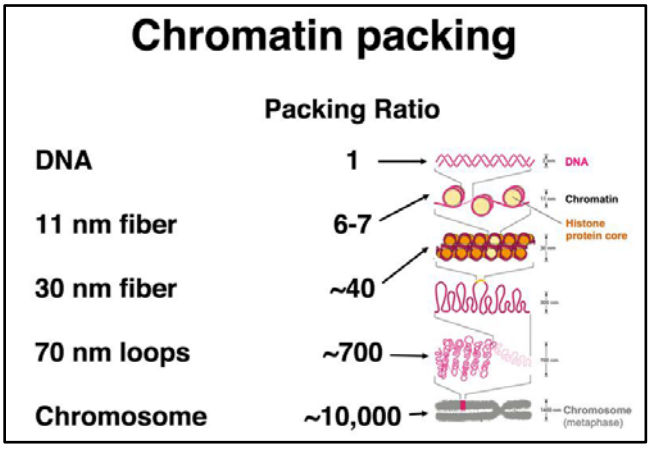


Figure 2-5 Hierarchical levels of chromatin packaging in a human chromosome.

- **Fig above** shows: A cell in early interphase (before the cell division).
  - An interphase nucleus with highly packed DNA to fit in the small nucleus.
  - If we take loop from the DNA, it contains ~100-200 kb of DNA.
  - If we take a section of the DNA and magnify it to -30nm, it appear as **solenoid** structure.
  - If we take a small section from the solenoid structure and magnify it to -10nm, it appear as nucleosome fiber (beads on string).
  - If we take a small section from the nucleosome fiber and magnify to 2mn, it appear as double helix stranded.

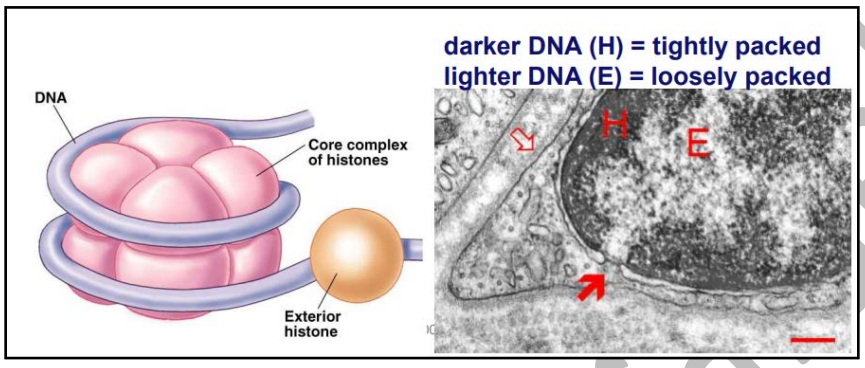
☒ Chromatin packing.

- Chromatin is a condensed DNA molecule; DNA + histone.
- **Fig**:
  - Packing ratio 1-2 →DNA double stranded.
  - Packing ratio 6-11 → beads on string.
  - Packing ratio 30-40 →solenoid.
  - Packing ratio 300-700 →zigzag shape.
  - Packing ratio 10.000- 14.000 →chromosome.



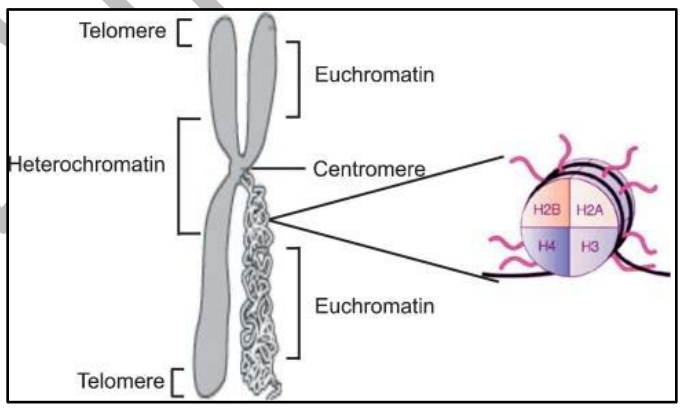
☒ Nucleosome

- 1st level of DNA packing "Beads on a string"
- 8 histone proteins molecules with many positively charged amino acids **E.g.** arginine & lysine will bind tightly to negatively charged DNA.
- Degree of packing of DNA regulates transcription. So tight packing → no transcription → genes turned off.



☒ Chromosome Structure.

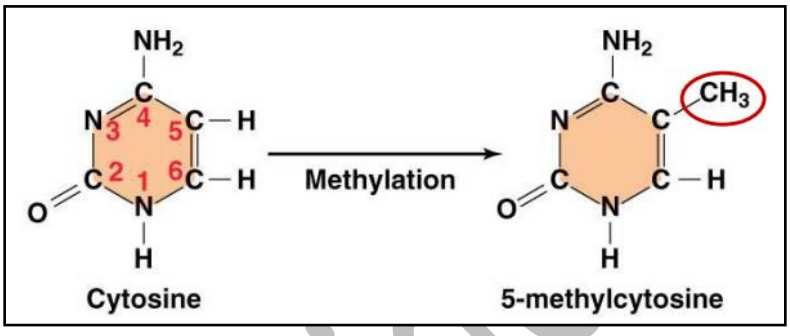
- Human genome composed of 46 chromosomes in 23 pairs.
- 22 pairs of chromosomes are autosomal chromosomes, # 23 pair are a sex chromosome either (XX, Female) or (XY, Male).
- All these chromosomes have the same structure, which composed of:
  1. Short arm (p)
  2. Long arm (q)
  3. Centromere
  4. Telomere
     - Capping both ends of the chromosome; prevent degradation.
     - Its Non-coding region.
     - In Dementia and Alzheimer's disease, there will be shortage in telomere (damage), so the coding sequences beyond the telomere are exposed to degradation.



Heterochromatin	Eu-Chromatin	Histone
▪ More condensed	▪ Less condensed (loosely packed).	▪ Octamer protein.
▪ Silenced gene (methylated).	▪ Gene expressed.	▪ 4 types of histones: H2A -- H2B -- H3 -- H4
▪ Gene poor (High AT content).	▪ Gene rich (High GC content).	
▪ Stain darker.	▪ Stain lighter.	▪ Histone helps in packing of DNA.

☒ DNA Modification

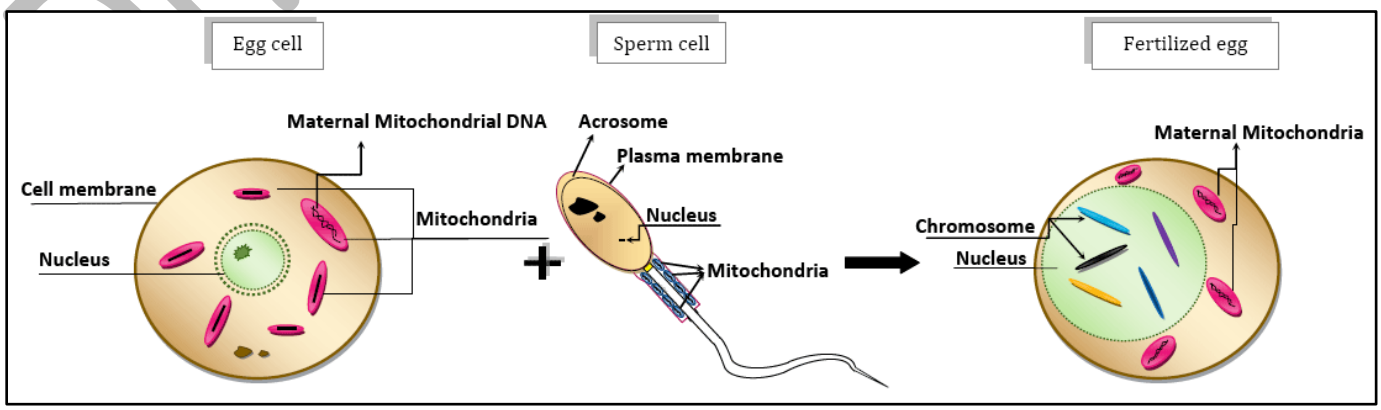
- **DNA Methylation**
  - Methylation of DNA will block the transcription factors "**No Transcription → Genes Turned Off**"
  - Done by attachment of methyl groups (–CH3) to cytosine amino acid.
  - Nearly permanent inactivation of genes.



- **Histone Acetylation**
  - Acetylation of histones will unwind DNA to become loosely packed and allow for the transcription process. Now transcription factors have easier access to genes.
  - Done by attachment of acetyl groups (–COCH3) to histones protein.

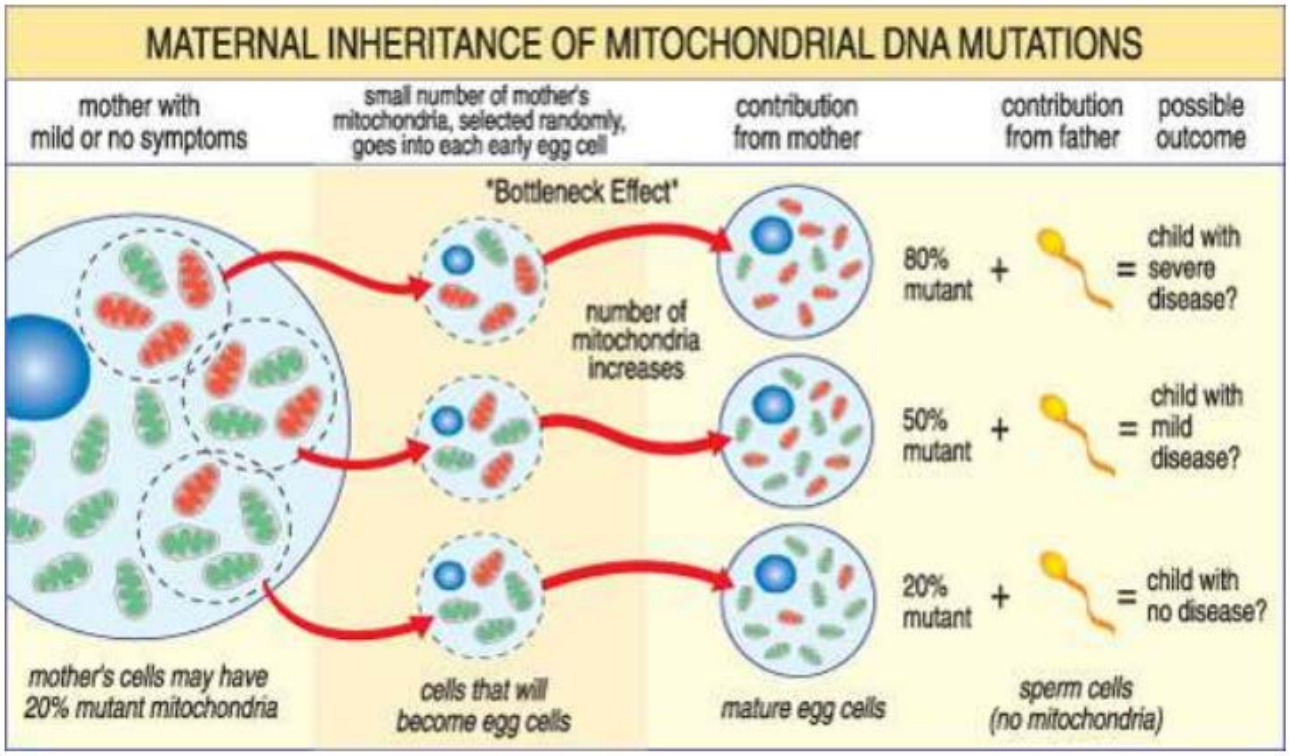
☒ The Mitochondrial Chromosome (mtDNA).

- Single copy of 1 Circular strand chromosome.
- DNA spans about 16,500 base pairs "37 genes". Representing a small fraction of the total DNA in cells.
- Mitochondrial genes are essential for normal mitochondrial function.
- Thirteen of these genes coded for enzymes involved in oxidative phosphorylation (ATP synthesis).
  1. **Complex I** (NADH dehydrogenase)
  2. **Complex III** (cytochrome c reductase)
  3. **Complex IV** (cytochrome c oxidase)
  4. **Complex V** (ATP synthase)
- The remaining genes coded for molecules called (tRNA) and (rRNA), which are chemical cousins of DNA.
- **MATERNAL INHERETANCE;** Paternal mitochondrial DNA is found in the tail of a sperm which will detached from the head of a sperm during fertilization leaving the fertilized egg only with maternal mitochondrial DNA.



- **Conditions** associated with changes in the structure of mitochondrial DNA:
  - Cytochrome coxidase deficiency.
  - Kearns-Sayre syndrome, primarily affects the eyes.
  - Leber hereditary optic neuropathy.
  - Leigh syndrome, which is a progressive brain disorder.

o **Maternal inheritance of mitochondrial DNA mutations.**



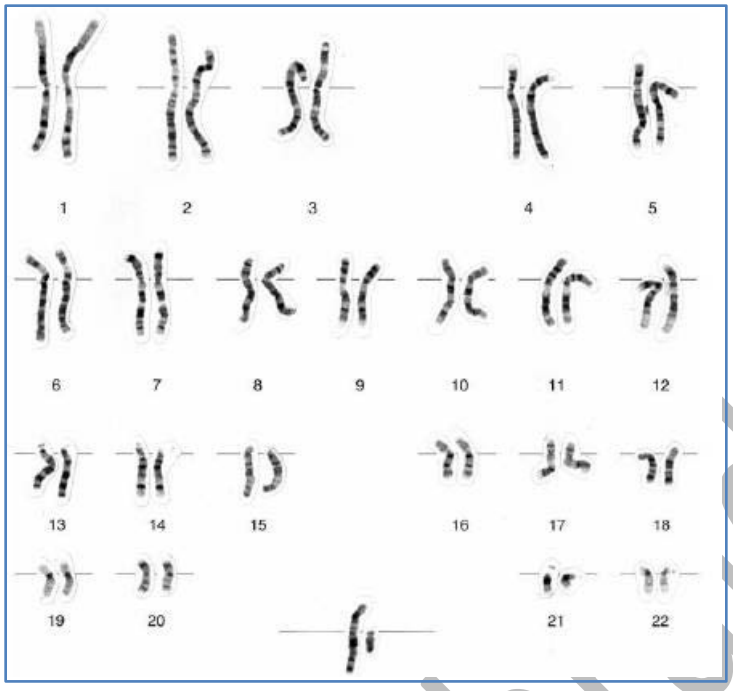
☒ Karyotyping.

o A test to identify and evaluate the size, shape, and number of chromosomes in a sample of body cells.

o **How it's done :**

1. Take a blood sample and put it on a slide.
2. Isolate WBCs from the sample.
3. Stop the cell division in **Metaphase Stage** of the cell cycle, using a certain type of drug. in this phase, chromosomes are highly condensed so it's easy to be visualized.
4. Stain the chromosomes by using a certain type of stain.
5. Finally, using a microscope to magnify, the chromosomes will be scattered.
6. Arrange the chromatids according to the pattern of the stain and length.

o The **Fig** next page is a **Karyotype**, which is the result of chromosomes arrangement.



- **Importance of Karyotyping:**
  1. To now the sex of the fetus, (XX, Female) or (XY, Male).
  2. To diagnose certain type of syndromes (Genetic Diseases)
     - **Polyploid**: Chromosome numbers are greater than diploid **(3n, triploid).**
     - **Aneuploid**: Chromosome numbers are not exact multiples of the haploid set, **(2n+1 trisomy; 2n-1 monosomy).** For Examples:
       - ✓ Down syndrome (trisomy 21).
       - ✓ Turner syndrome 45XO.
  3. To identify if there is any type of gene mutation.
     - Deletion.
     - Duplication.
     - Inversion.
     - Insertion.
     - Substitution.

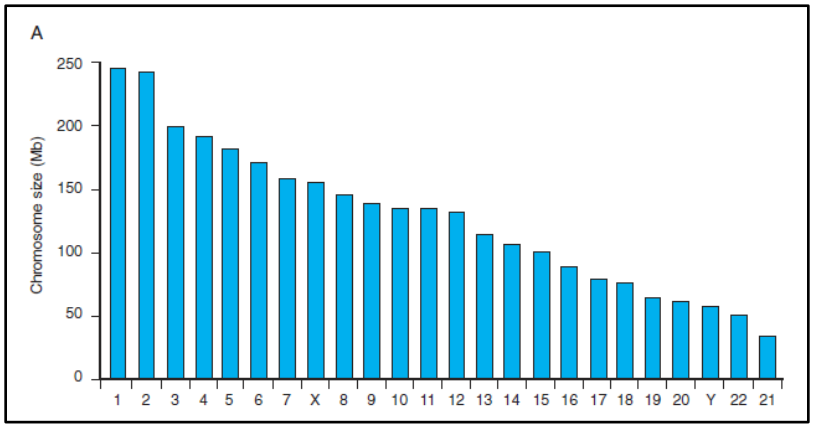
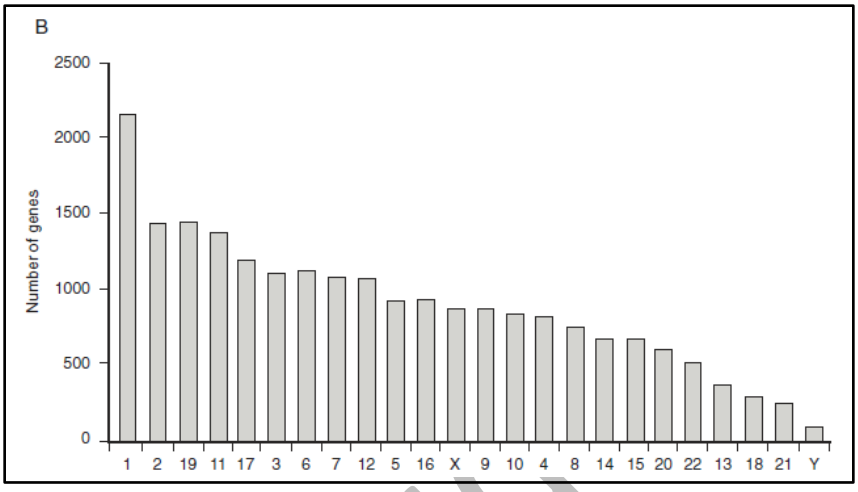


Fig. It shows the size of each chromosome in a male (46, XY), as we see chromosome #1 is the largest.

Fig. It shows the number of the genes in each chromosome.



- **Note:** the number of the genes dose not related proportionally to the size of the chromosome. For example chromosome #13 is large but contain small amount of genes.

- Chromosome #13 has **coding sequences** and **non-coding sequences** which are larger than the coding one, thus making the chromosome big but with few numbers of genes.

☒ Comparison between coding and non-coding sequences:

	Single-copy DNA Sequences	Repetitive DNA Sequences
▪ **Proportion**	▪ Small (~1.5%) Of the genome	▪ High (5 -45%) of the genome
▪ **Rate of Mutation**	▪ Low	▪ Higher
▪ **Occurrence**	▪ Once in the genome	▪ Occurs many times
▪ **Function**	▪ Makes protein (coding function)	▪ Not translated (do not have coding function)
▪ **Length**	▪ Long –unique sequence	▪ Short-repeating sequence
▪ **Similarity**	▪ Very similar between individuals	▪ Varies greatly between individuals
▪ **DNA profiling**	▪ Not used for DNA profiling	▪ Used for DNA profiling
▪ **Example**	▪ Exons	▪ Telomere, introns

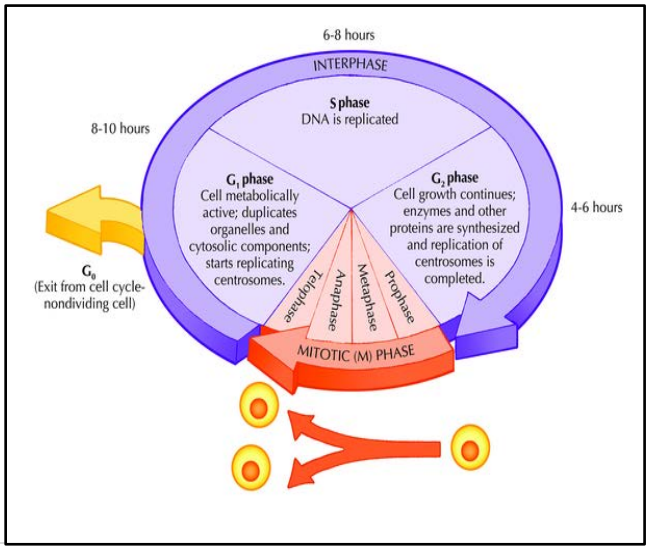
☒ Cell Cycle.

- **Two types of human cells:**
  1. **Somatic cells** are diploid (2n_46) and divide by mitosis (growth) to produces two identical diploid (2n) daughter cells.

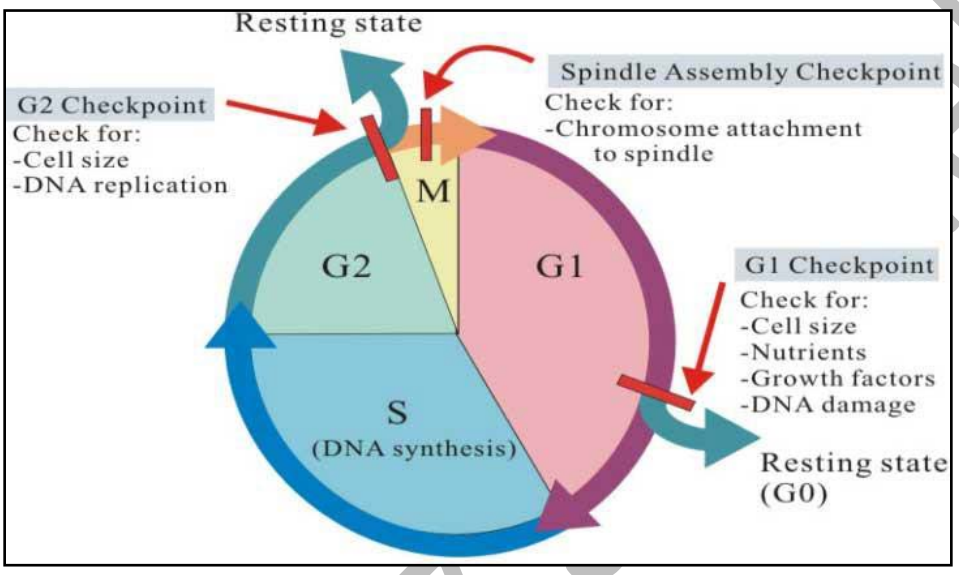
- **The cell cycle of Somatic cells consists of:**
  - **A. Long** interphase. The stages are:
    - G1 gap phase.
    - S phase.
    - G2 gap phase.
  - **B. Short** mitotic (M) phase during which mitosis occurs. The stages are:
    - Prophase.
    - Prometaphase.
    - Metaphase.
    - Anaphase.
    - Telophase.

2. **Germ cells** are diploid (2n_46) divide by meiosis (reproduction) to produce haploid gametes (n_23).
   - **Two types Germ cells:** Oocytes, Spermatocytes.
   - The cell cycle using **Meiosis** proceeded by a single round of DNA synthesis (**S phase**) and followed by two cell divisions to produce the **haploid gametes (n)**.
     - **Meiosis I**: The **first** cell division involves the pairing and separation of maternal and paternal chromosome homolog's during which exchange of chromosomal material takes place. This process of recombination separates groups of genes that were originally located on the same chromosome and gives rise to individual genetic variation.
     - **Meiosis II**: The **second** cell division is the same as in mitosis, but there are only 23 chromosomes at the start of division.
   - During **spermatogenesis**, each spermatocyte produces four spermatozoa.
   - During **Oogenesis** there is unequal division of the cytoplasm, giving rise to the first and second polar bodies with the production of only of one large mature egg cell.

- **Interphase Stages:**
  - **G1 phase : (8-10 hrs)**
    - Cell metabolically active.
    - Duplicates organelles and cytosolic components.
    - Starts replicating centrosomes.
  - **S phase : (6-8hrs)**
    - DNA is replicated (synthesis).
  - **G2 phase : (4-6hrs)**
    - Cell growth continues.
    - Enzymes and other proteins are synthesized and replication centrosome is completed.

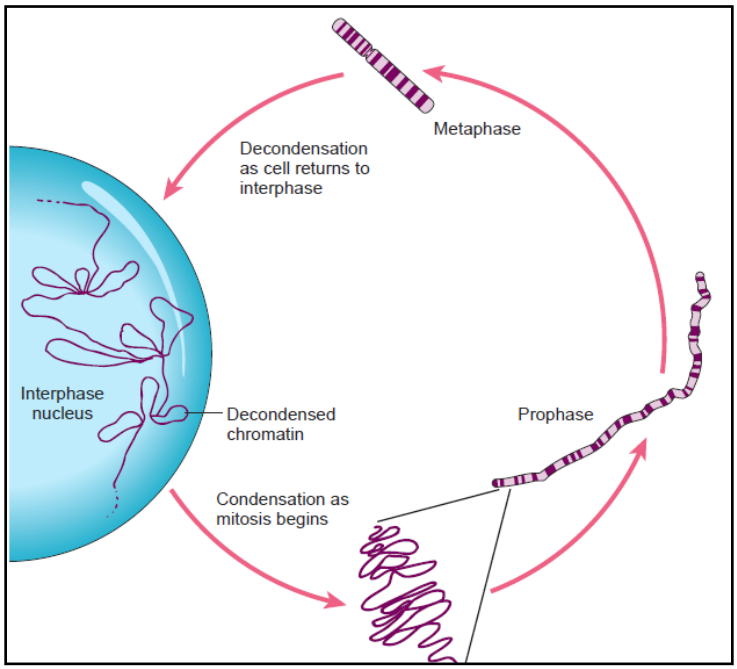


- **Cell cycle checkpoint**
  - Some cells pass through G1 stage in hours; others spend long time, days or years, in G1.
  - In fact, some cells do not divide at all once they are fully differentiated; rather they are permanently arrested in G0 (nerve cell). Other cells, such as liver cells, may enter G0 but after organ damage return to G1 and continue through the cell cycle.
  - The cell cycle is governed by a series of **checkpoints** that determine the timing of each step in mitosis.

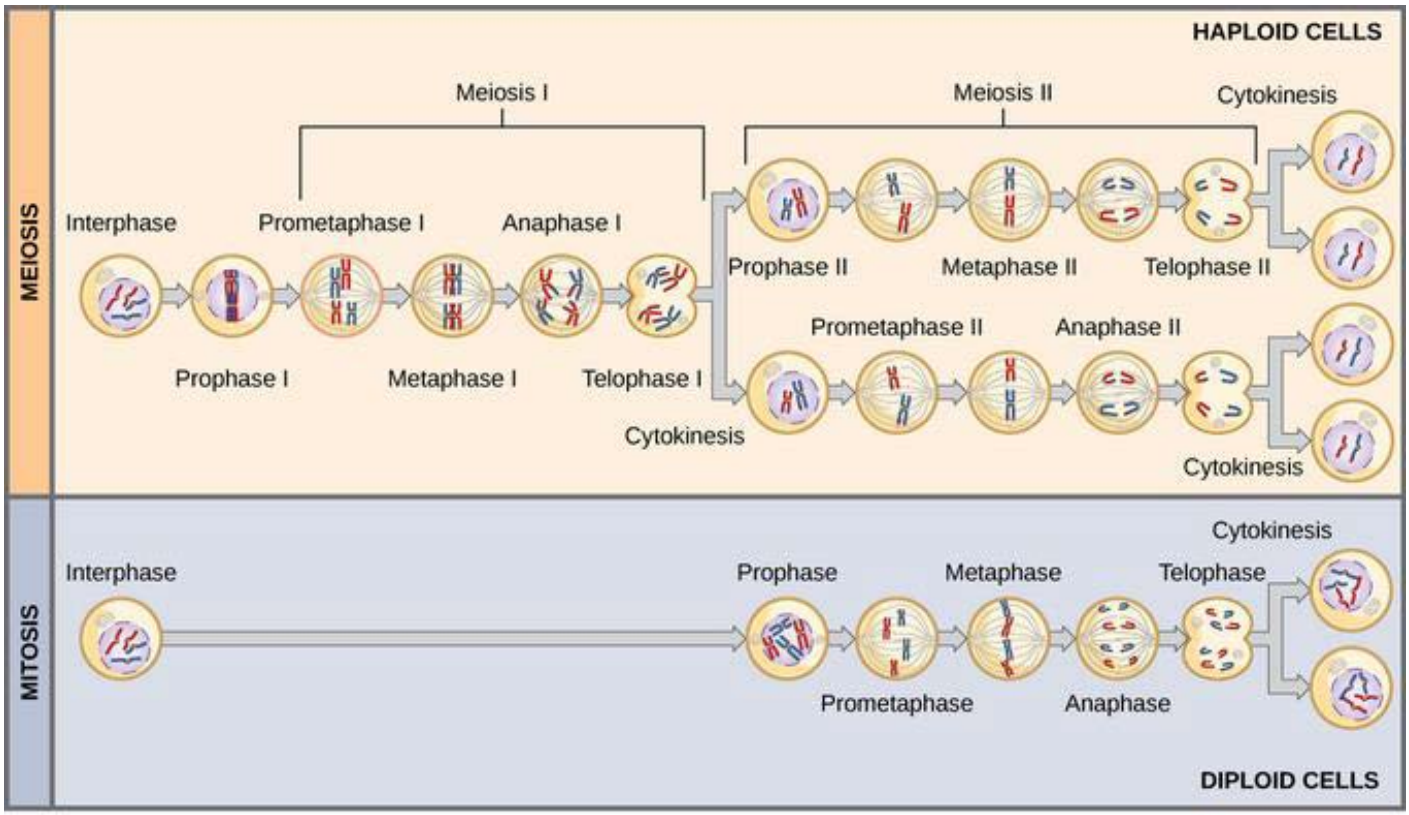


  - During the cell cycle if the cell size is 100% ok .the cell will pass the checkpoint to the S phase but if there is a defect in the dividing cell, it will enter **G0**.
  - Certain type of proteins work in these checkpoints. If there is any mutation in the genes coded for these proteins. The checkpoint will not function well and uncontrolled cell division may occur which may lead to **cancer**.

Fig:



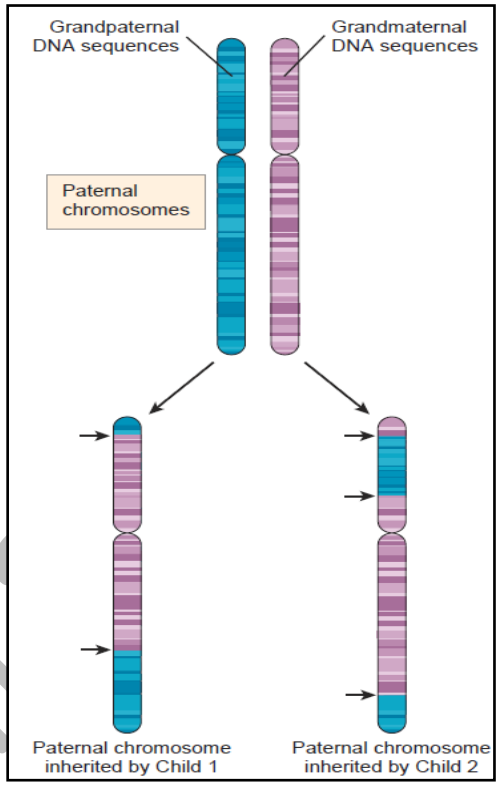
  - During the cell cycle a condensation occurs as mitosis begins and chromosomes become highly condensed and may visualize under the microscope in **Metaphase stage**.
  - **De**condensation occurs as the cell returns to interphase.

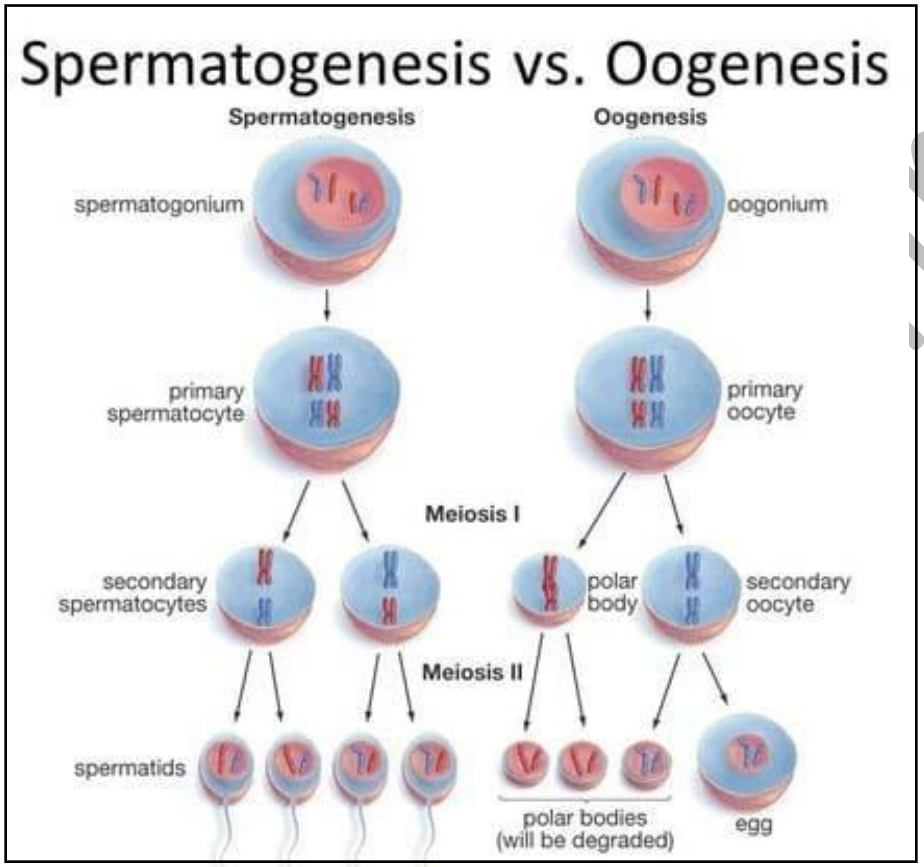


The above **table** is important, **memorize** it.

						OUTCOME
PROCESS	DNA synthesis	Synapsis of homologous chromosomes	Crossover	Homologous chromosomes line up at metaphase plate	Sister chromatids line up at metaphase plate	Number and genetic composition of daughter cells
MEIOSIS	Occurs in S phase of interphase	During prophase I	During prophase I	During metaphase I	During metaphase II	Four haploid cells at the end of meiosis II
MITOSIS	Occurs in S phase of interphase	Does not occur in mitosis	Does not occur in mitosis	Does not occur in mitosis	During metaphase	Two diploid cells at the end of mitosis

Figure 2-15 The effect of homologous recombination in meiosis. In this example, representing the inheritance of sequences on a typical large chromosome, an individual has distinctive homologues, one containing sequences inherited from his father (*blue*) and one containing homologous sequences from his mother (*purple*). After meiosis in spermatogenesis, he transmits a single complete copy of that chromosome to his two offspring. However, as a result of crossing over (*arrows*), the copy he transmits to each child consists of alternating segments of the two grandparental sequences. Child 1 inherits a copy after two crossovers, whereas child 2 inherits a copy with three crossovers.





- Oogonium (2n, 46 XX).
- Spermatogonium (2n, 46 XY).
- **After meiosis I**
  - 2 secondary Spermatocytes (n, 23), One (X) and the other is (y).
  - 1 secondary Oocytes (n, 23, X) and a polar body.
- **After Meiosis II**
  - 4 spermatides (n,23) , 2 (X) and 2 (Y)
  - One mature egg and 3 polar bodies (will be degraded).