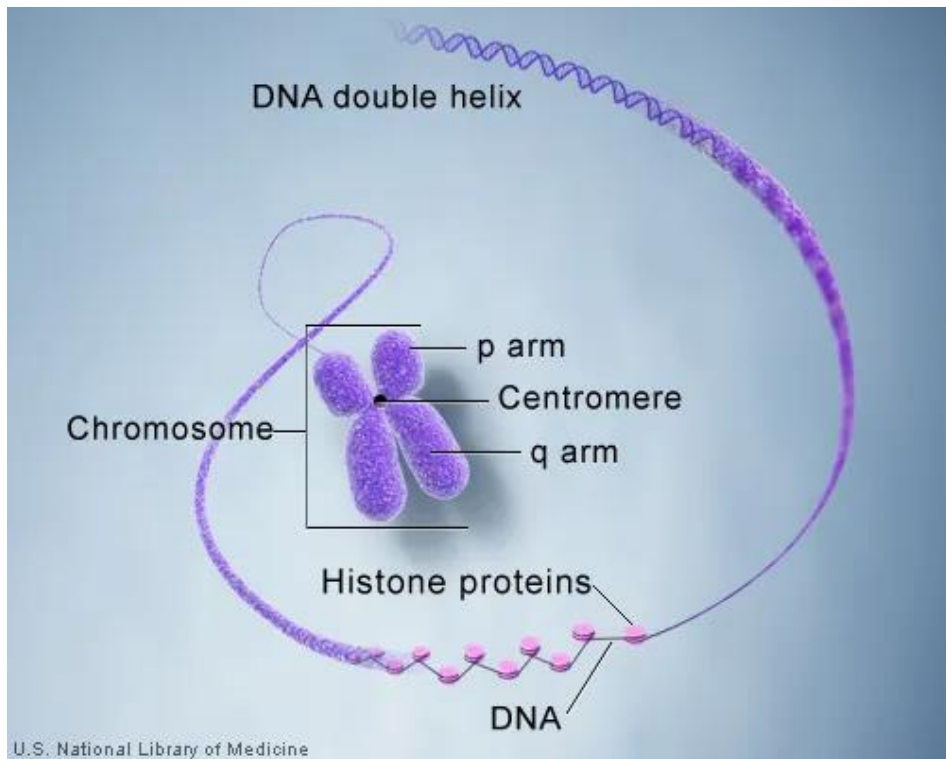


Introduction to Genetics



Presented by
Dr. Ayesha Fatima
Assistant Professor
Dept of Pharmacy Practice

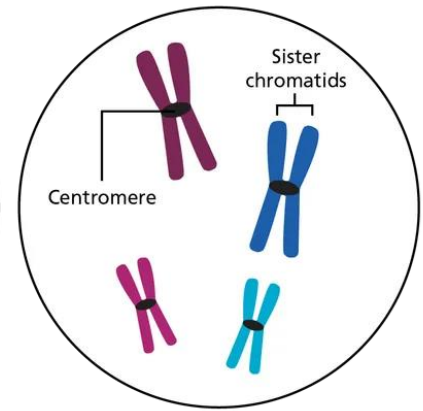
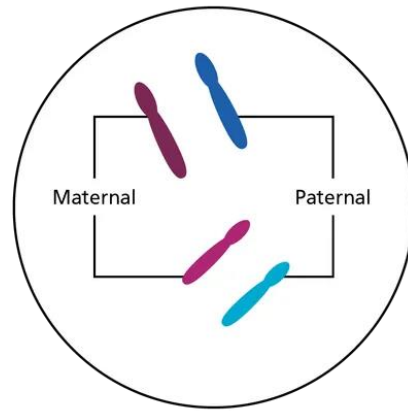
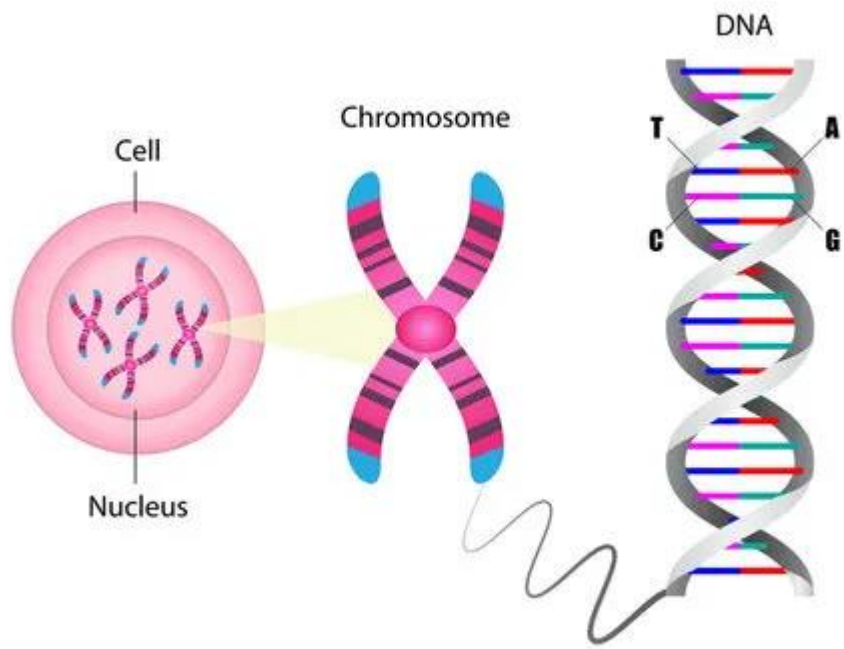


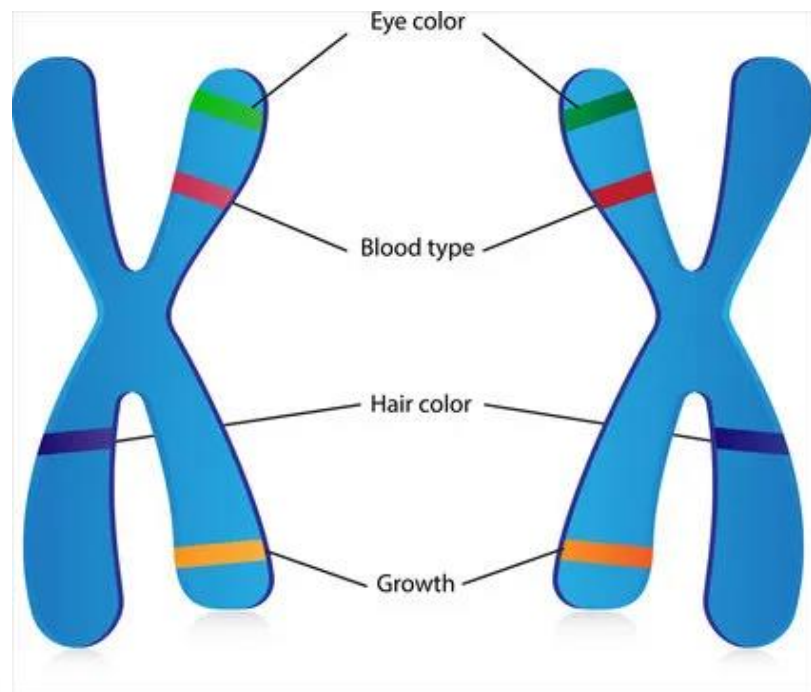
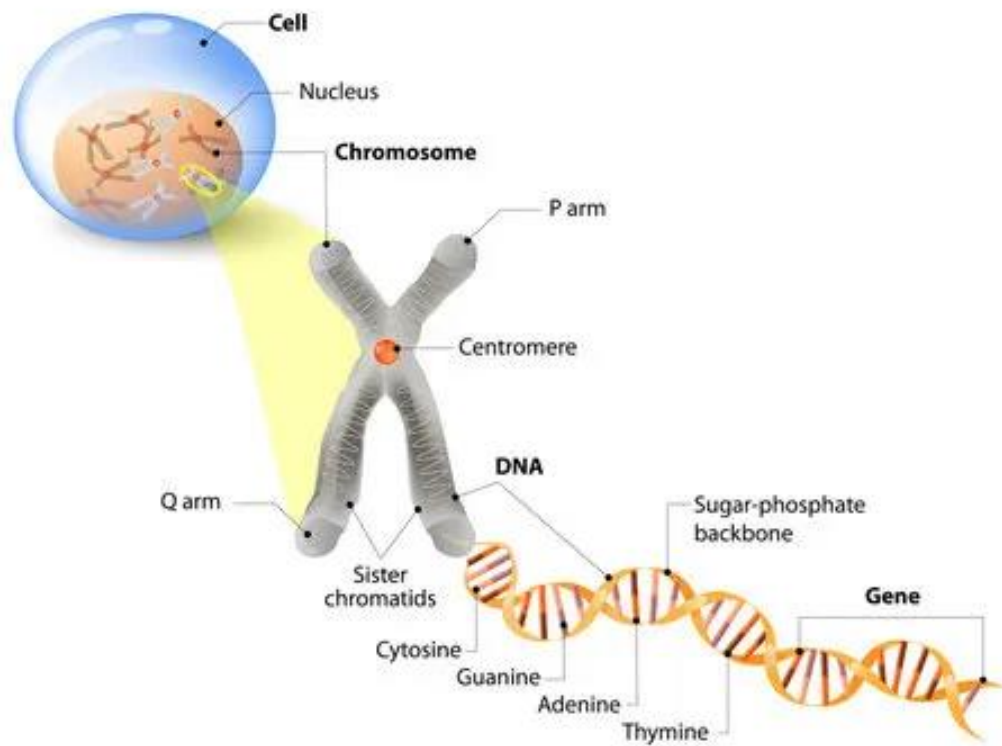
Chromosome



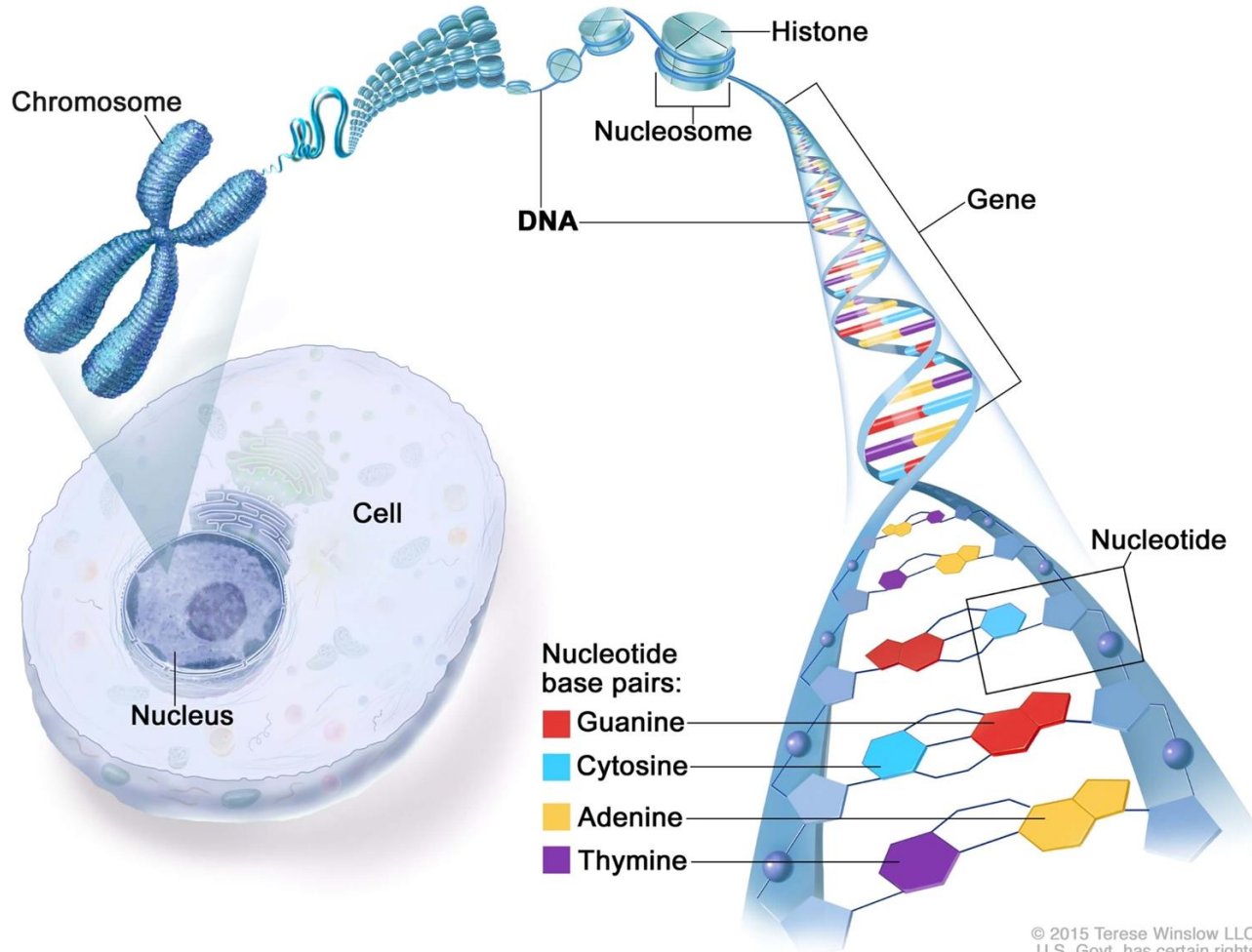
DNA







DNA Structure



GENE

- Gene is presently defined as 'the unit of inheritance composed of a segment of DNA situated at a specific locus that carries coded information and also has the ability to undergo mutation and crossing over.'

OR

- The basic unit of heredity passed from parent to child. Genes are made up of sequences of DNA and are arranged, one after another, at specific locations on chromosomes in the nucleus of cells. They contain information for making specific proteins that lead to the expression of a particular physical characteristic or trait, such as hair color or eye color, or to a particular function in a cell.
- Three nucleotides together codes for amino acid and a string of amino acids in a particular sequence forms a functional protein. These proteins may function as enzymes and control the metabolism.

- Every diploid organism has two copies of genes derived from each of its parents. They are expressed in a dominant or recessive manner.
- The complete set of all genes present in a cell is known as a genome. There are 30000 genes in human genome.
- The largest gene in the human genome is 2400 kbp long and the smallest gene in the human genome is 14 bp long.
- Genes normally exist in pairs, because each gene site (locus) is present at corresponding sites on both homologous chromosomes.

DNA (DeoxyriboNucleic Acid)

DNA is a polymer of deoxyribonucleotides (or simply deoxynucleotides).

It is composed of monomeric units namely deoxyadenylate (dAMP), deoxyguanylate (dGMP), deoxycytidylate (dCMP) and deoxythymidylate (dTMP).

Chargaff's rule of DNA composition

Erwin Chargaff in late 1940s quantitatively analysed the DNA hydrolysates from different species.

He observed that in all the species he studied, DNA had equal numbers of adenine and thymine residues ($A = T$) and equal numbers of guanine and cytosine residues ($G = C$).

This is known as Chargaff's rule of molar equivalence between the purines and pyrimidines in DNA structure.

Single-stranded DNA, and RNAs which are usually single-stranded, do not obey Chargaff's rule. However, double-stranded RNA which is the genetic material in certain viruses satisfies Chargaff's rule.

DNA DOUBLE HELIX

The double helical structure of DNA was proposed by James Watson and Francis Crick in 1953 (Nobel Prize, 1962).

The structure of DNA double helix is comparable to a twisted ladder.

The salient features of Watson-Crick model of DNA (now known as B-DNA) are described next

1. The DNA is a right handed double helix. It consists of two polydeoxyribonucleotide chains (strands) twisted around each other on a common axis.
2. The two strands are antiparallel, i.e., one strand runs in the 5c to 3c direction while the other in 3c to 5c direction.
3. The width (or diameter) of a double helix is $20 \text{ \AA}$ (2 nm).
4. Each turn (pitch) of the helix is $34 \text{ \AA}$ (3.4 nm) with 10 pairs of nucleotides, each pair placed at a distance of about $3.4 \text{ \AA}$.

5. Each strand of DNA has a hydrophilic deoxyribose phosphate backbone (3c-5c phosphodiester bonds) on the outside (periphery) of the molecule while the hydrophobic bases are stacked inside (core).
 6. The two polynucleotide chains are not identical but complementary to each other due to base pairing.
 7. The two strands are held together by hydrogen bonds formed by complementary base pairs. The A-T pair has 2 hydrogen bonds while G-C pair has 3 hydrogen bonds.
 8. The hydrogen bonds are formed between a purine and a pyrimidine only. If two purines face each other, they would not fit into the allowable space.
- And two pyrimidines would be too far to form hydrogen bonds. The only base arrangement possible in DNA structure, from spatial considerations is A-T, T-A, G-C and C-G.

9. The complementary base pairing in DNA helix proves Chargaff's rule.

The content of adenine equals to that of thymine ($A = T$) and guanine equals to that of cytosine ($G = C$).

10. The genetic information resides on one of the two strands known as template strand or sense strand. The opposite strand is antisense strand. The double helix has (wide) major grooves and (narrow) minor grooves along the phosphodiester backbone. Proteins interact with DNA at these grooves, without disrupting the base pairs and double helix

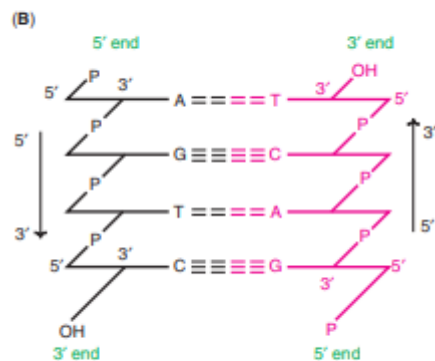
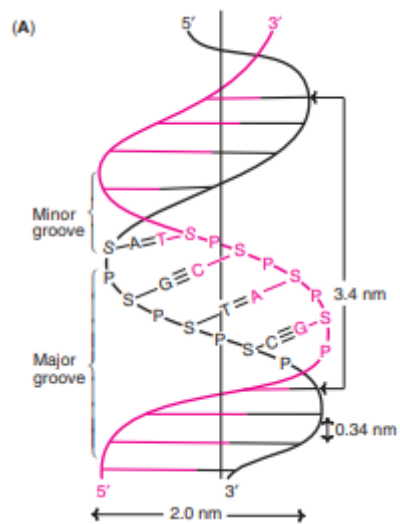


Fig. 5.9 : (A) Watson-Crick model of DNA helix
(B) Complementary base pairing in DNA helix.

Conformations of DNA double helix

Variation in the conformation of the nucleotides of DNA is associated with conformational variants of DNA.

The double helical structure of DNA exists in at least 6 different forms-A to E and Z. Among these, B, A and Z forms are important .

The B-form of DNA double helix, described by Watson and Crick (discussed above), is the most predominant form under physiological conditions. Each turn of the B-form has 10 base pairs spanning a distance of 3.4 nm. The width of the double helix is 2 nm.

The A-form is also a right-handed helix. It contains 11 base pairs per turn. There is a tilting of the base pairs by 20° away from the central axis.

The Z-form (Z-DNA) is a left-handed helix and contains 12 base pairs per turn. The polynucleotide strands of DNA move in a somewhat 'zig zag' fashion, hence the name Z-DNA.

TABLE 5.2 Comparison of structural features of different conformations of DNA double helix

<i>Feature</i>	<i>B-DNA</i>	<i>A-DNA</i>	<i>Z-DNA</i>
Helix type	Right-handed	Right-handed	Left-handed
Helical diameter (nm)	2.37	2.55	1.84
Distance per each complete turn (nm)	3.4	3.2	4.5
Rise per base pair (nm)	0.34	0.29	0.37
Number of base pairs per complete turn	10	11	12
Base pair tilt	+19°	-1.2° (variable)	-9°
Helix axis rotation	Major groove	Through base pairs (variable)	Minor groove

Chromosomes

- Chromosome means 'coloured body', that refers to its staining ability by certain dyes.
- Chromosomes are thread-like structures present in the nucleus, which carries genetic information from one generation to another. They play a vital role in cell division, heredity, variation, mutation, repair and regeneration.
- In Eukaryotic cells, genetic material is present in the nucleus in chromosomes, which is made up of highly organized DNA molecules with histone proteins supporting its structure.
- **Karl Nägeli** in 1842, first observed the rod-like structure present in the nucleus of the plant cell.
- **W. Waldeyer** in 1888 coined the term 'chromosome'.
- **Walter Sutton and Theodor Boveri** in 1902 suggested that chromosomes are the physical carrier of genes in the eukaryotic cells.
- The number of chromosomes in any species is constant for all the cells.
- The number of chromosomes in gametes (e.g. sperms, egg) is half of the somatic cell and known as a haploid set of chromosomes, which is the result of meiosis during sexual reproduction.
- Chromosome number is preserved in the mitotic division of somatic cells, which is required for an organism to grow, repair and regenerate.

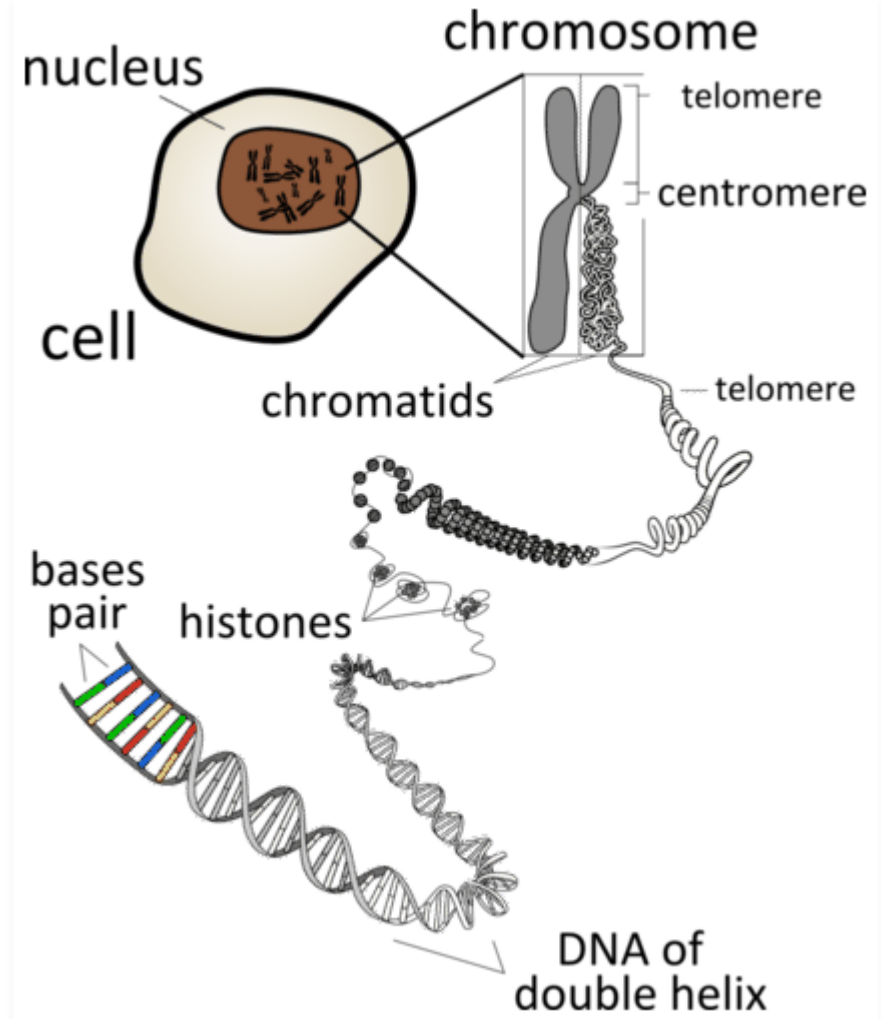
Chromosome number varies in different species.

A nematode species contains only 2 chromosomes in a cell, whereas a protozoan species contains as much as 1600 chromosomes in the cell.

Most of the plant and animal species contain 8 to 50 number of chromosomes in its somatic cell.

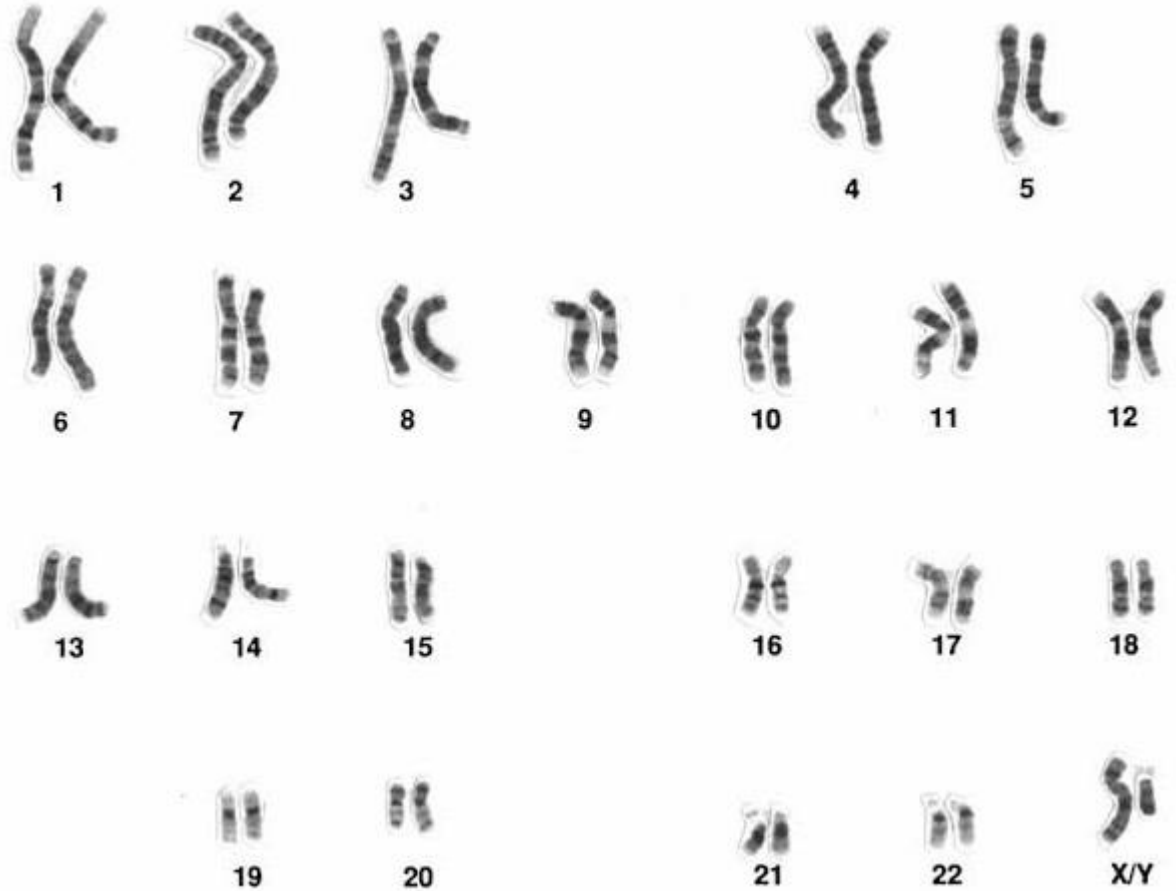
The number of chromosomes does not reflect the complexity of a species.

A human cell contains total 23 pair of chromosomes ($2n$, total $23 \times 2 = 46$), of which 22 are autosomes and 1 sex chromosome.



Karyotyping is a technique to study the structure of chromosomes present in a species.

Chromosomes are isolated, stained and photographed. This technique is useful in finding out any chromosomal abnormalities.



Chromosome Structure

The chemical composition of a chromosome is histone proteins and DNA.

Each cell has a pair of each kind of chromosome known as a homologous chromosome.

Chromosomes are made up of chromatin, which contains a single molecule of DNA and associated proteins.

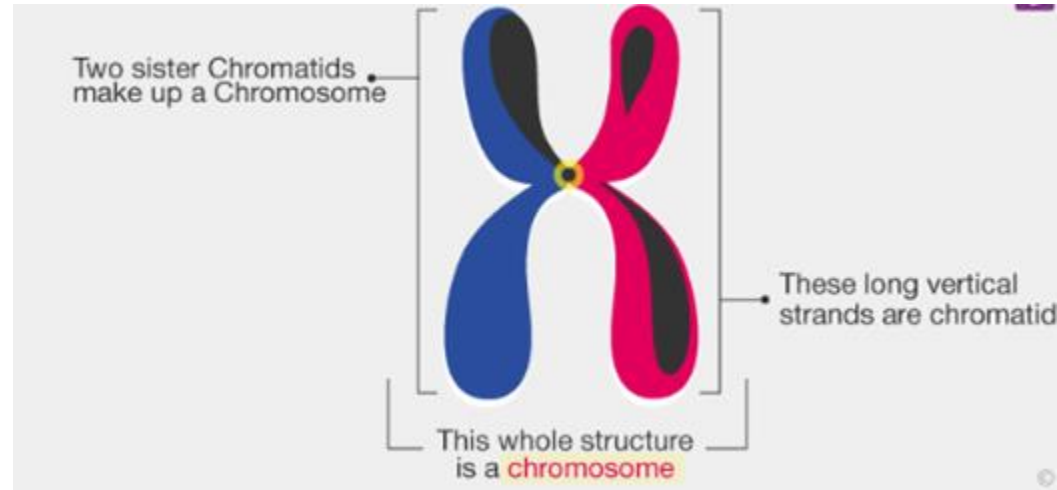
Each chromosome contains hundreds and thousands of genes that can precisely code for several proteins in the cell. Structure of a chromosome can be best seen during cell division.

Main parts of chromosomes are:

- 1. Chromatid**
- 2. Centromere and kinetochore**
- 3. Secondary constriction and nucleolar organisers**
- 4. Telomere**
- 5. Satellite**
- 6. Chromatin**

- **Chromatid:** Each chromosome has two symmetrical structures called chromatids or sister chromatids which is visible in mitotic metaphase.
 - Each chromatid contains a single DNA molecule
 - At the anaphase of mitotic cell division, sister chromatids separate and migrate to opposite poles
- **Centromere and kinetochore:** Sister chromatids are joined by the centromere.
 - Spindle fibres during cell division are attached at the centromere
 - The number and position of the centromere differs in different chromosomes
 - The centromere is called **primary constriction**
 - Centromere divides the chromosome into two parts, the shorter arm is known as '**p**' arm and the longer arm is known as '**q**' arm.
 - The centromere contains a **disc-shaped kinetochore**, which has specific DNA sequence with special proteins bound to them
 - The kinetochore provides the centre for polymerisation of tubulin proteins and assembly of microtubules
- **Secondary constriction and nucleolar organisers:**
 - Secondary constrictions can be identified from centromere at anaphase because there is bending only at the centromere (primary constriction)
 - Secondary constrictions, which contain genes to form nucleoli are known as the **nucleolar organiser**

- **Telomere:** Terminal part of a chromosome is known as a telomere.
 - Telomeres are polar, which prevents the fusion of chromosomal segments
- **Satellite:** It is an elongated segment that is sometimes present on a chromosome at the secondary constriction.
 - The chromosomes with satellite are known as **sat-chromosome**

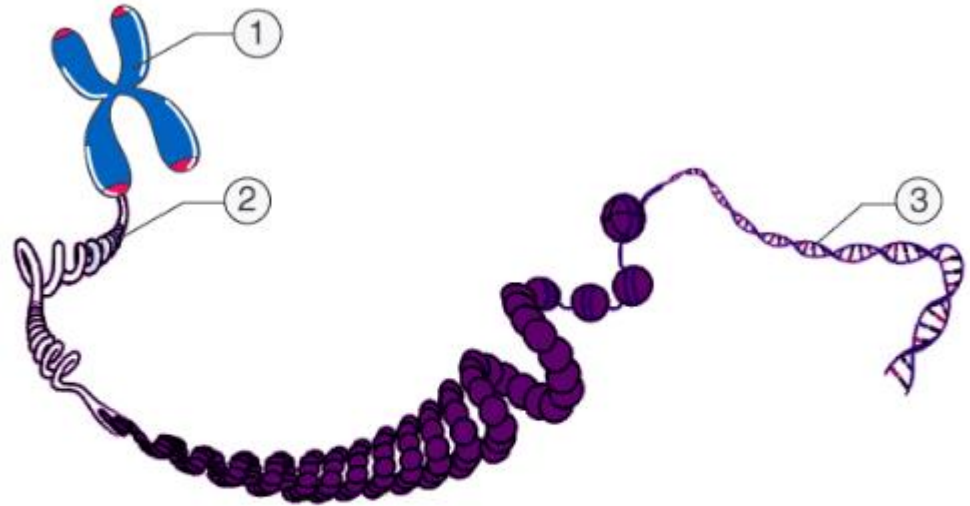


- **Chromatin:** Chromosome is made up of **chromatin**.
 - Chromatin is made up of DNA, RNA and proteins. At interphase, chromosomes are visible as thin chromatin fibres present in the nucleoplasm.
 - During cell division, the chromatin fibres condense and chromosomes are visible with distinct features.
 - The darkly stained, condensed region of chromatin is known as **heterochromatin**. It contains tightly packed DNA, which is genetically inactive
 - The light stained, diffused region of chromatin is known as **euchromatin**. It contains genetically active and loosely packed DNA
 - At prophase, the chromosomal material is visible as thin filaments known as **chromonemata**
 - At interphase, bead-like structures are visible, which are an accumulation of chromatin material called **chromomere**.
 - Chromatin with chromomere looks like a necklace with beads

Structural Organisation of Chromatin

- Chromatin consists of DNA and associated proteins. DNA is packaged in a highly organised manner in chromosomes
- 1. **Nucleosomes** are the basic unit of chromatin. It is 10 nm in the diameter
 - DNA packing is facilitated by proteins called **histones**.
 - DNA is wound around histone proteins to form a nucleosome
 - There are 5 types of histone proteins in the eukaryotic chromosomes, namely H1, H2A, H2B, H3 and H4
 - Histones are positively charged due to the presence of amino acids with basic side chains and it associates with negatively charged DNA due to the presence of phosphate groups
 - Histone proteins play an important role in gene regulation
 - A typical nucleosome contains 200 bp of DNA helix. The core particle of the nucleosome consists of approximately 146 base pairs (bp) of DNA coiled around a core of eight histone molecules (2 molecules of 4 histone proteins). That is linked by linker DNA of about 80 bp.
 - Nucleosomes prevent DNA from getting tangled

1. Linker DNA and the fifth histone (H1) pack adjacent nucleosomes to a 30 nm **compact chromatin fibre**
2. These fibres form a large coiled loop held together by non-histone proteins (actin, α and β tubulin, myosin) called **scaffolding proteins** to form **extended chromatin** which is 300 nm in diameter
3. Chromatin further condenses with the help of protein known as **condensin**, it binds to DNA and wraps it into coiled loops and we get the compacted chromosome



1 Chromosome | 2 Chromatin | 3 DNA Helix

Chromatin is a complex of DNA and protein found in eukaryotic cells and it helps in packaging the long DNA molecules inside the cell nucleus.

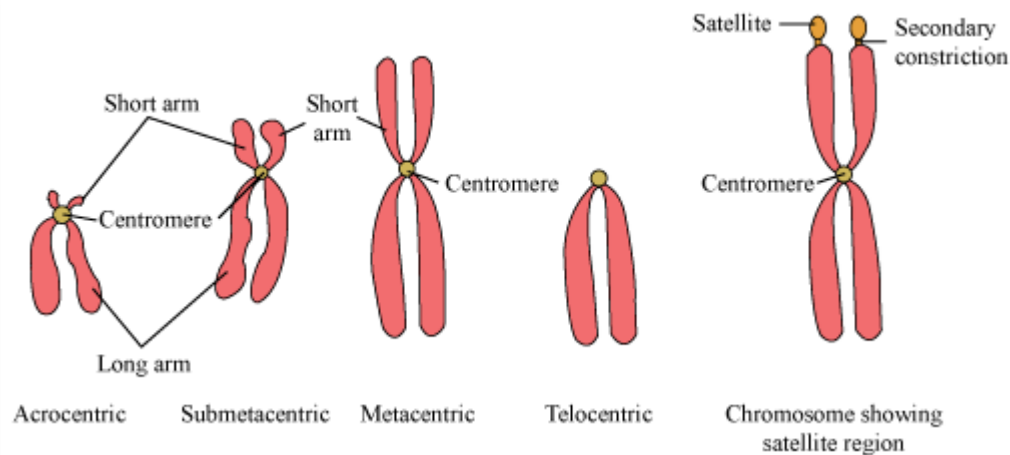
Types of Chromosome

Based on the number of centromeres present

- i. **Monocentric:** having only one centromere
- ii. **Holocentric:** having diffused centromere and microtubules are attached along the length of a chromosome
- iii. **Acentric:** chromosome may break and fuse together to form a chromosome without a centromere. It cannot attach to the mitotic spindle
- iv. **Dicentric:** chromosomal aberration where chromosomes break and fuse together with two centromeres. They are also unstable as two centromeres tend to migrate to opposite poles resulting in fragmentation

Based on the position of the centromere

- i. **Telocentric:** rod-like chromosome with centromere present on the proximal end. No 'p' arm or short arm of chromosome, is present. Telomeric chromosomes are not found in humans
- ii. **Acrocentric:** rod-like, centromere present at one end giving rise to one very short arm and an exceptionally long arm
- iii. **Submetacentric:** L-shaped or J-shaped, with centromere near the centre of the chromosome giving rise to two unequal arms
- iv. **Metacentric:** V-shaped chromosomes with centromere in the middle giving rise to two equal arms.



Functions of Chromosomes

- The main function of chromosomes is to carry the genetic material from one generation to another
- Chromosomes play an important role and act as a guiding force in the growth, reproduction, repair and regeneration process, which is important for their survival
- Chromosomes protect the DNA from getting tangled and damaged
- Histone and non-histone proteins help in the regulation of gene expression
- Spindle fibres attached to the centromere help in the movement of the chromosome during cell division
- Each chromosome contains thousands of genes that precisely code for multiple proteins present in the body

GENETIC DISEASES IN HUMANS

A genetic disorder caused by one or more abnormalities in the genome, especially a condition that is present from birth (congenital).

Most genetic disorders are quite rare and affect one person in every several thousands or millions.

Genetic disorders may or may not be heritable, i.e., passed down from the parents' genes.

In non-heritable genetic disorders, defects may be caused by new mutations or changes to the DNA. The defect will only be heritable if genetic disorder occurs in the germ line.

Classification:

- Single gene disorder
- Chromosomal genetic disorder
- Multifactorial genetic disorder

Single gene disorder

These disorders involve mutations in the DNA sequences of single genes.

As a result, the protein the gene codes for is either altered or missing.

Over 4000 human diseases caused by single gene defects.

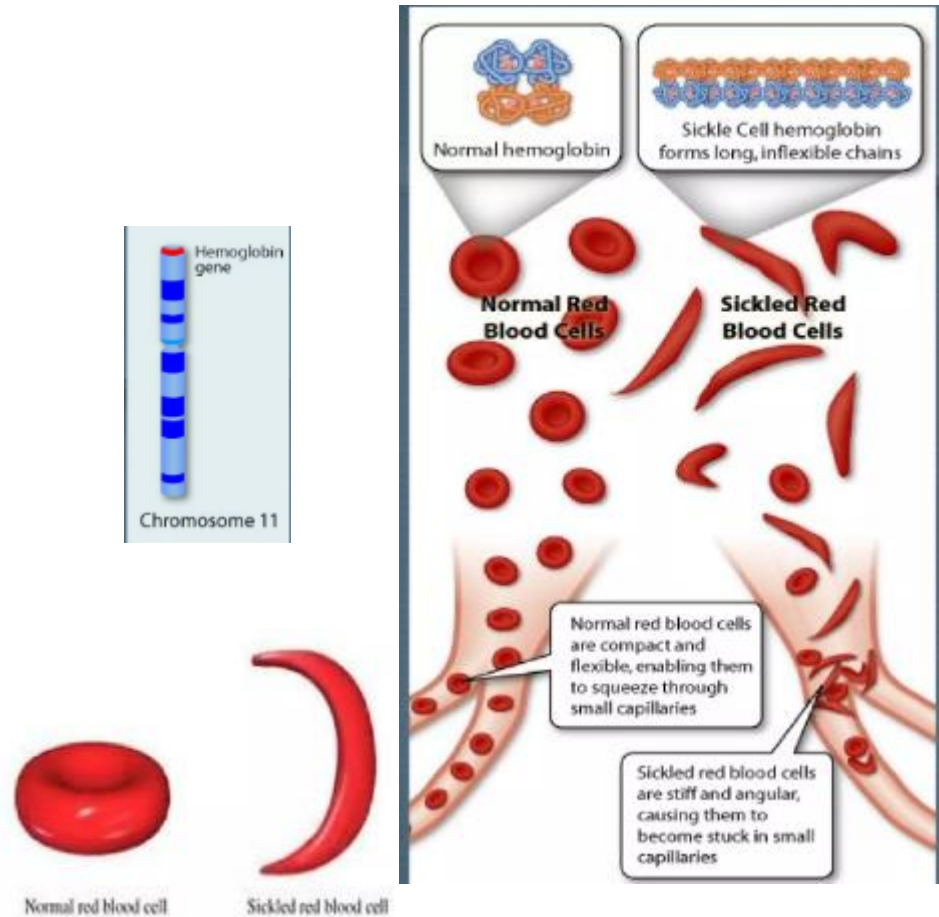
Some Example : Adenosine deaminase deficiency, Alpha-1 Antitrypsine deficiency, Cystic fibrosis, Galatosemia, Huntington's disease, Maple syrup urine disease, Phenylketonurimea c, Severe combined immunodeficiency, Sickle cell disease, Smith-Lemil-Optiz Syndrome

Cystic Fibrosis:

- Cystic fibrosis is a genetic disorder that affects the respiratory and digestive systems.
- People with cystic fibrosis inherit a defective gene on chromosome 7 called CFTR (cystic fibrosis transmembrane conductance regulator).
- The protein produced by this gene normally helps salt (sodium chloride) move in and out of cells.
- If the protein doesn't work correctly, that movement is blocked and an abnormally thick sticky mucus is produced on the outside of the cell.
- The cells most seriously affected by this are the lung cells. This mucus clogs the airways in the lungs, and increases the risk of infection by bacteria.
- The thick mucus also blocks ducts in the pancreas, so digestive enzymes can't get into the intestines

Sickle Cell Disease

- Sickle cell disease is a disorder that affects the red blood cells, which use a protein called hemoglobin to transport oxygen from the lungs to the rest of the body.
- Normally, red blood cells are round and flexible so they can travel freely through the narrow blood vessels.
- The hemoglobin molecule has two parts: an alpha and a beta.
- Patients with sickle cell disease have a mutation in a gene on chromosome 11 that codes for the beta subunit of the hemoglobin protein.
- As a result, hemoglobin molecules don't form properly, causing red blood cells to be rigid and have a concave shape.



Chromosomal Genetic Disorder

- In these disorders, entire chromosomes, or large segments of them, are missing, duplicated, or otherwise altered.
- Chromosomal genetics disorder organized into two basic groups:
 - 1) Numerical Abnormalities: When an individual is missing either a chromosome from a pair (monosomy) or has more than two chromosomes of a pair (trisomy)
 - 2) Structural Abnormalities: When the chromosome's structure is altered.

Some Examples: Cri-Du-Chat Syndrome, Down Syndrome, 47 XXY Klinefelter Syndrome, Turner Syndrome (Monosomy), William Syndrome

Cri-du-cat Syndrome

- The name of this syndrome is French for "cry of the cat," referring to the distinctive cry of children with this disorder.
- The cry is caused by abnormal larynx development, one of the many symptoms associated with this disorder.
- Cri-du-chat is caused by a deletion (the length of which may vary) on the short arm of chromosome 5.
- Multiple genes are missing as a result of this deletion, and each may contribute to the symptoms of the disorder.
- **Babies with** cri-du- chat are usually small at birth, and may have respiratory problems.
- Often, the larynx doesn't develop correctly, which causes the signature cat-like cry.

Down Syndrome

- Down syndrome is a developmental disorder caused by an extra copy of chromosome 21 (which is why the disorder is also called "trisomy 21").
- Having an extra copy of this chromosome means that individuals have three copies of each of its genes instead of two, making it difficult for cells to properly control how much protein is made.
- Producing too much or too little protein can have serious consequences.
- Down syndrome have very distinct facial features: a flat face, a small broad nose, abnormally shaped ears, a large tongue, and upward slanting eyes with small folds of skin in the corners.
- Down syndrome have an increased risk of developing a number of medical problems: respiratory infections, gastrointestinal tract obstruction, leukemia, heart defects, hearing loss, hypothyroidism, and various eye abnormalities.
- **No cure** exists for Down syndrome.
- But physical therapy and/or speech therapy can help people with the disorder develop more normally.

XXY (Klinefelter syndrome)

- Males (46, XY) and females (46, XX). 47, XXY (or XXY) is a genetic condition caused when someone has two X chromosomes and one Y chromosome.
- **XXY** is usually caused by what is called nondisjunction.
- Nondisjunction happens when a pair of sex chromosomes fails to separate during egg (or sperm) formation.
- The XXY chromosome arrangement affects primarily sexual development.
- Because of an XXY chromosome arrangement have a Y chromosome, they are considered genetic males.
- Most XXY individuals develop as males, often not knowing they have an extra chromosome.
- Typically, testes don't fully develop, and the levels of the hormone testosterone (important for male sexual development) are lower than average.
- **As adults**, nearly all XXY males are unable to make sperm and so cannot have biological children.
- Many men discover their condition only after they seek medical help for infertility.
- Changes that appear at puberty can include low growth of facial and body hair, development of breast tissue, and small testes.

Turner Syndrome

- Turner syndrome is caused by a missing or incomplete X chromosome.
- People who have Turner syndrome develop as females.
- The genes affected are involved in growth and sexual development, which is why girls with the disorder are shorter than normal and have abnormal sexual characteristics.

Williams Syndrome

- Williams syndrome is a rare genetic disorder that affects a child's growth, physical appearance, and cognitive development.
- People who have Williams syndrome are missing genetic material from chromosome 7, including the gene elastin.

Color Blindness:

- Mutated genes are located on the X- chromosome (for red/green color blindness) or both the X and Y chromosomes (for total color blindness).

Multifactorial Disorder

These disorders involve variations in multiple genes, often coupled with environmental causes.

Some example: Alzheimer's Disease, Breast/Ovarian Cancer, Colon Cancer, Hypothyroidism. Asthma, cancers, cleft palate, diabetes, heart disease, hypertension, inflammatory bowel disease, mood disorder, obesity, refractive error, infertility.

Alzheimer's Disease

- Alzheimer's is a disease that causes dementia, or loss of brain function. It affects the parts of the brain that deal with memory, thought, and language.
- The brain of a person with Alzheimer's contains abnormal clumps of cellular debris and protein(plaques) and collapsed microtubules (support structures of the cell).
- Microtubule disintegration is caused by a malfunctioning protein called tau, which normally stabilizes the microtubules.
- In Alzheimer's patients, tau proteins instead cluster together to form disabling tangles.
- These plaques and tangles damage the healthy cells around them.
- Because Alzheimer's destroys brain cells, people who have the disorder slowly lose their ability to think clearly.
- At first, they may forget words or names, or have trouble finding things.
- As the disorder worsens, they may forget how to do simple tasks.