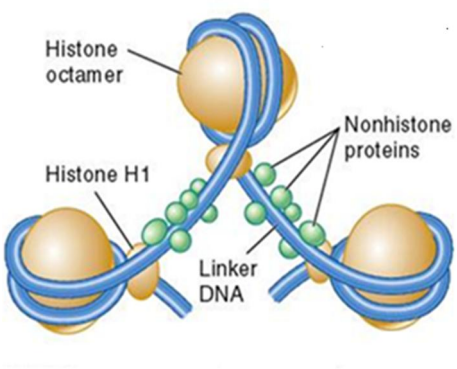
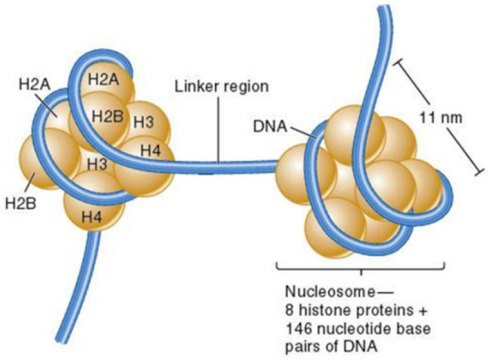
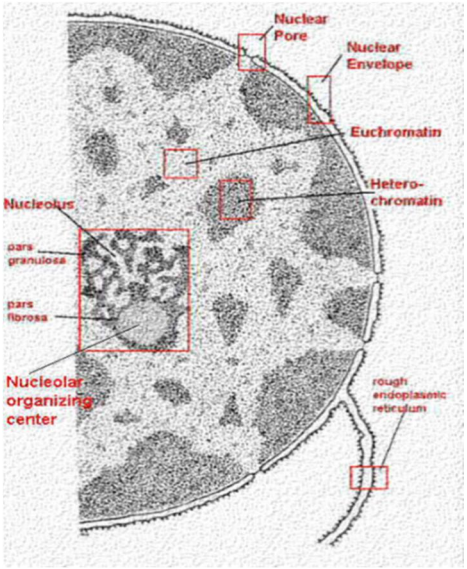
L.3 Human chromosomes

The chromosomes are made up of both DNA and protein about 50% protein including histones and non-histones. Non-histones called scaffold proteins, including 2 types: SC1 and SC2. The function of non-histone proteins are known to be regulators of gene activity such as replication, repair and transcription. Histone molecules are small, positively charged (basic) proteins rich in lysine and arginine amino acids , present in five types (H2A, H2B, H3, H4) form the core of histones ,two of each make up the octamer and H1the linker of histone .

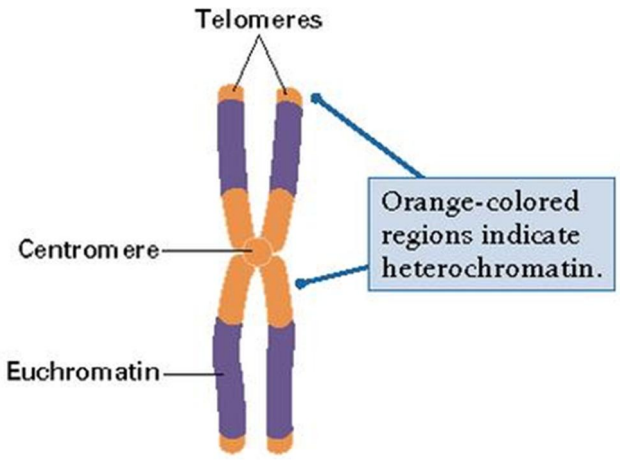




In interphase nucleus composed from darkly stained chromatin regions called heterochromatin while other regions do not stain as strongly and lightly stained chromatin called euchromatin .The Heterochromatin genetically inactive and euchromatin genetically active in protein synthesis. The distribution of both chromatins is shown in figure3.a. In metaphase, heterochromatin found near the centromeres or on the ends telomeres of the chromosome .

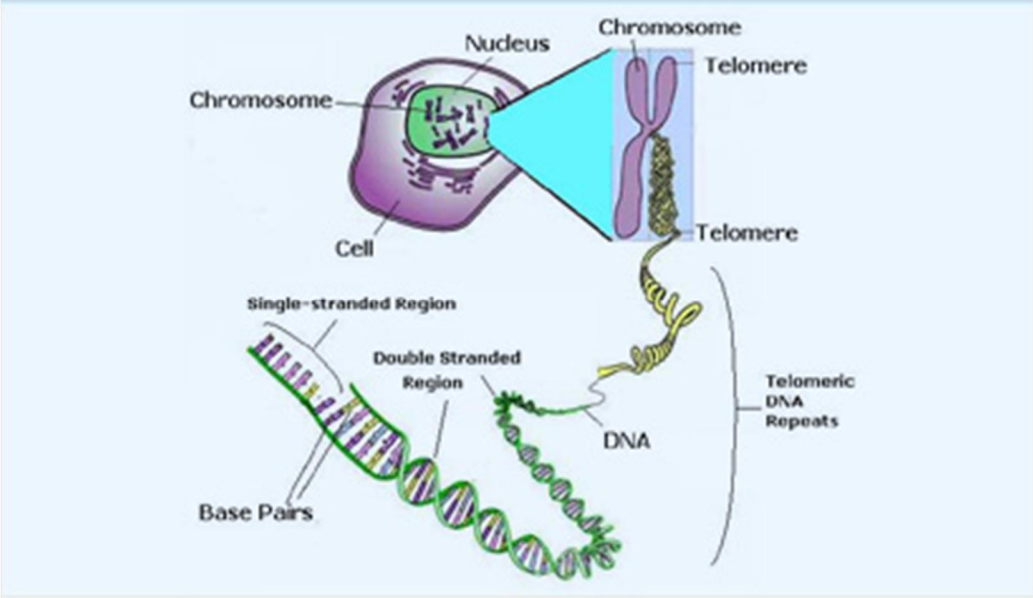


Interphase



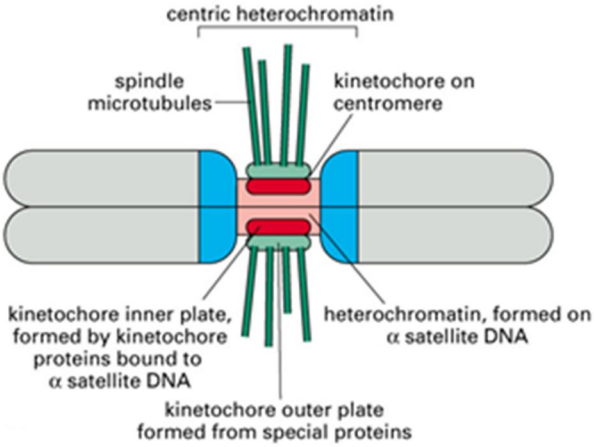
Metaphase

A human cell contains 46 chromosomes and the length of DNA in each is about 5 cm on the average. Therefore, a human cell contains at least 2 m of DNA, but DNA packed or bound into histones molecules to form string beads called nucleosomes. This string is coiled tightly to form loop at the first and then condense to give a highly compact form characteristic of metaphase chromosome .So, the metaphase chromosome consists of two chromatids attached to each other by centromere or kinetochore .



Chromosome structure

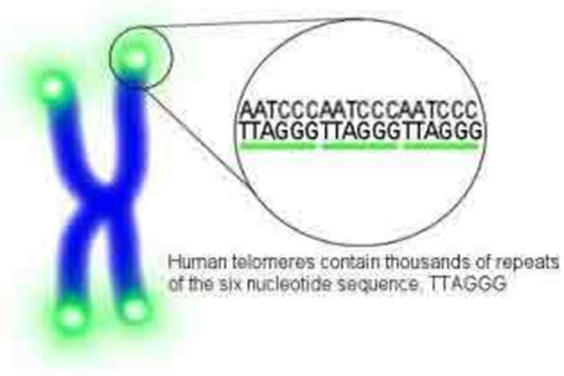
The terms centromere and kinetochore are frequently used interchangeably. The kinetochore is technically the interface between the visible constriction in the chromosome (the centromere) and the microtubules of the spindle. The kinetochore of higher organisms contains proteins and some RNA. Microscopically, it is trilaminar structure, attached to chromatin at the inner layer and to microtubules at the outer layer . The centromere divides the chromosome into a short arm called **p** and long end called **q**. Also the chromosome contains **origin of replication sites**, where replication forks began to form.



Centromere structure

The ends of chromosome are called **telomeres**. Human telomeres contain thousands of repeats of six nucleotide sequence TTAGGG on the ends of eukaryotic chromosome produced by **telomerase**, telomerase contains an RNA region that is used as a template. At each mitosis , the telomeres lose 50-200 bases, gradually shortening the chromosome. After about 50 divisions a critical length of telomere DNA is lost, which signals mitosis to stop. The cell remains alive but not divides again, or may die. Telomeres not only mark the termination of the linear chromosome but also have several specific functions. Telomeres must prevent the chromosome end from acting in a "sticky" fashion, the way that broken chromosome ends act .It must also prevent the ends of chromosomes from being degraded by exonucleases and must allow chromosome ends to be properly replicated.

Not all cells have shortening telomeres. In eggs and sperm, stem cells, epidermal skin cells, follicular hair cells and in cancer cells, in a few types of these normal cells that must continually supply new cells ,an enzyme called telomerase keeps chromosome tips long .However most cells do not produce telomerase, and their chromosomes gradually shrink.



The chromosomes can be classified into four types according to location of centromere:

1-Metacentric:

The centromere is exactly in the middle.

2-Submetacentric:

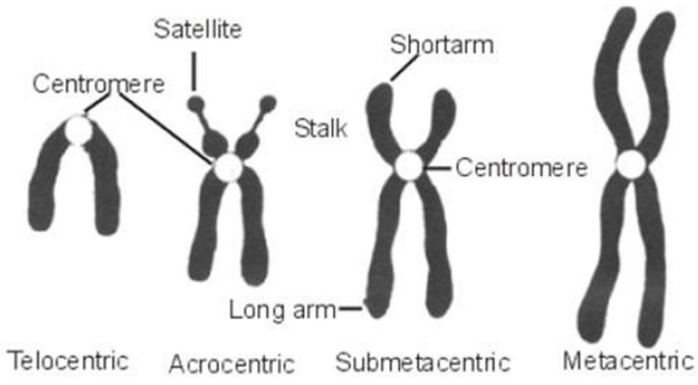
The centromere nearer one end of the chromosome

3-Acrocentric:

If the centromere is very near one end of the chromosome which have small short arms and may also have stalks and satellites (small masses of chromatin attached by narrow stalks to their short arm).

4- Telocentric:

It's exactly at the end of chromosome , there are no telocentric chromosomes normally in human.



Karyotype:

Is Image of an individual's complement of chromosomes arranged according to size, length, shape, and centromere location. The karyotype shows the chromosomes thick and doubled as they appear in metaphase of mitosis. The karyotype used for helpful in differentiating the chromosomes and detecting structural and numerical abnormalities.

The chromosomes have been prepared at metaphase by a method called G-banding (Giemsa stain) or some other banding methods are reviewed in from white blood cells:

1- Add blood sample to medium containing stimulator for mitosis incubate at 37 ^{o}C, add colchicine or colcemid to arrest mitosis at metaphase .

2- Add very dilute salt solution.
3- Add fixative
4- Gently suspend
5- Prepare and stain slide and observed slide through microscope .
6- Photograph and enlarged the metaphase chromosomes
7- Cut out chromosomes individually. Then the homologous chromosomes arranged according to size, shape, length of arms .

In Denver's system , the 46 chromosomes of single, diploid cell are arranged in 23 homologous pairs arranged from largest to smallest ,give numbered from 1 to 22 in the seven major groups A-G in autosomes and one pair of sex chromosome were not numbered in this system .

In this system ,a karyotype is described by (1) the number of chromosomes,(2)the sex chromosome status,(3)the presence or absent of individual chromosome ,and (4) the nature and extent of any structural abnormality .The symbols for structural alterations include **t** for translocation, **dup** for duplication, and **del** for deletion. The normal karyotype of man is written as 46, XY in male and 46,XX in female. If a male has a deletion in the short arm of chromosome 5, this would be represented as 46,XY, del(5p).

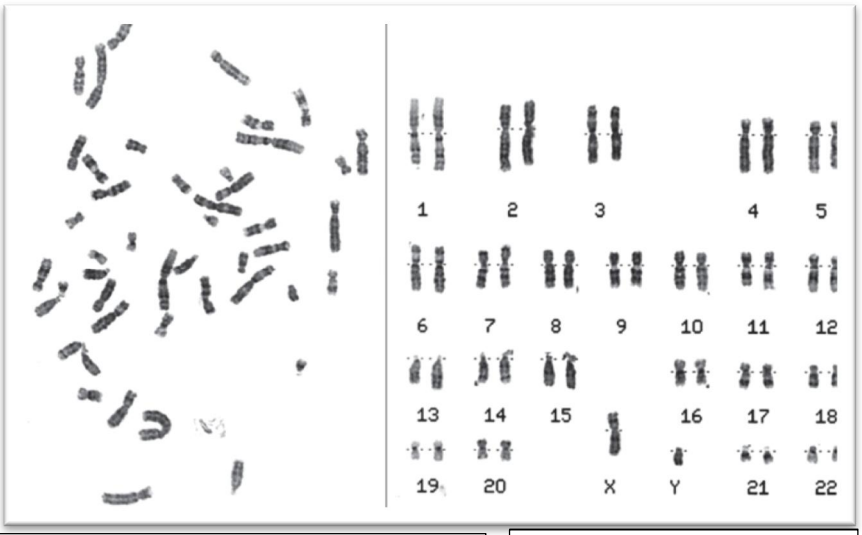
Arrengment of chromosomes according to Denever system

Group	Chromosomes	Description
A	1–3	Largest; 1 and 3 are metacentric but 2 is submetacentric
B	4,5	Large; submetacentric with two arms very different in size
C	6–12,X	Medium size; submetacentric
D	13–15	Medium size; acrocentric with satellites
E	16–18	Small; 16 is metacentric but 17 and 18 are submetacentric
F	19,20	Small; metacentric
G	21,22,Y	Small; acrocentric, with satellites on 21 and 22 but not on the Y
Autosomes are numbered from largest to smallest, except that chromosome 21 is smaller than chromosome 22.		

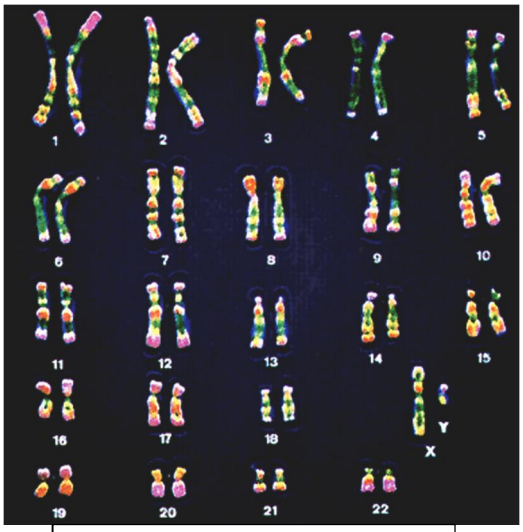
Recently there are other techniques used for karyotyping called **Fish techniques.**

Fish techniques (fluorescent in situe hybridization)

Fish uses DNA probes complementary to the specific DNA sequences, Fish probes are attached to molecules that fluoresce when illuminated, producing a flash of color precisely where the probe binds to a chromosome in the patient sample . Fish can paint entire karyotype; each chromosome is probed with several different fluorescent molecules. A computer in targets the images and create a unique false color for each chromosome, this method called spectral karyotyping (SKY)



Metaphase chromosome | **Male karyotype**



Color male karyotype