HUMAN CHROMOSOMES

Objectives

- To understand the definition and terminology of human CHROMOSOMES
- To learn the morphological structure of human chromosomes.
- To explain how chromatin is formed and its level of organization.
- To understand the difference between euchromatin and heterochromatin.
- To describe the features of sex chromosomes.

The nucleus of a human cell contains all the genetic material necessary to direct all the functions in the body. The genetic material is arranged into chromosomes, which are structures that assist in the transmission of genetic information from one generation to the next. The instructions in each chromosome are contained within **genes**, which in turn are composed of **DNA**.

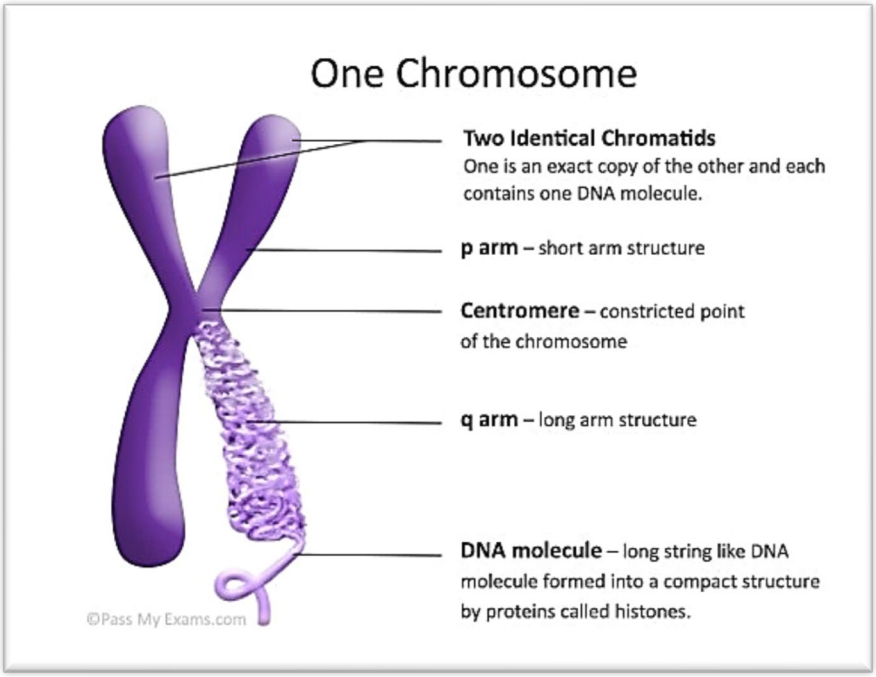
Introduction

- Humans have **46** chromosomes, which occur in **23 pairs**.
- Twenty-two of these chromosome pairs are called **autosomes,** which are found in both males and females.
- One pair of chromosomes is called the **sex chromosomes**, because this pair contains the genes that control gender. Males have the sex chromosomes **X** and **Y**, and females have two **X** chromosomes.
- **Chromosomes** (named from the Greek word **chroma,** "color," **some,** "body") were discovered in the nineteenth century, as threadlike structures in the nucleus of eukaryotic cells that become visible as the cells begin to divide.
- Each human cell contains about **2 meters** of DNA; yet the cell nucleus is only **5–8 µm** in diameter.
- In eukaryotic cells, very long double-stranded DNA molecules are packaged into chromosomes. *The complex task of packaging DNA is accomplished by specialized proteins that bind to and fold the DNA, generating a series of coils and loops that provide increasingly higher levels of organization and prevent the DNA from becoming a tangled, unmanageable mess. Amazingly,*

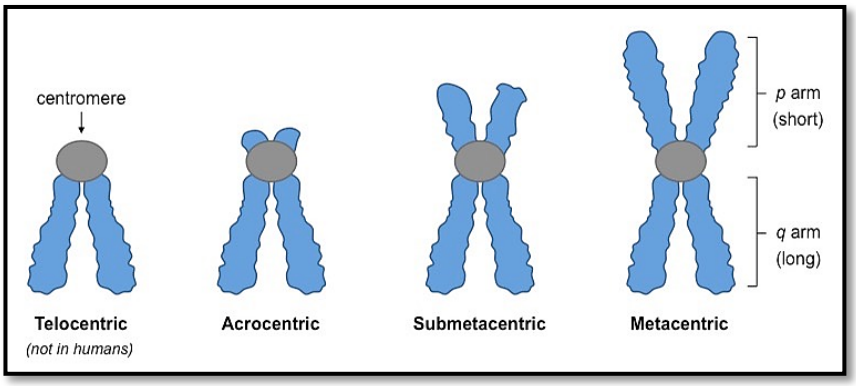
the DNA is compacted in a way that allows it to remain accessible to all of the enzymes and other proteins that replicate it, repair it, and control the expression of its genes.

Chromosomes Morphology

- At time of cell division each chromosome can be seen to consist of two identical strands known as **chromatids**, or **sister chromatids**, which are the result of DNA replication having taken place during the S phase of the cell cycle.
- These sister chromatids can be seen to be joined at a primary constriction known as the **centromere**.
- Centromeres consist of several hundred kilobases of repetitive DNA and are responsible for the movement of chromosomes at cell division.

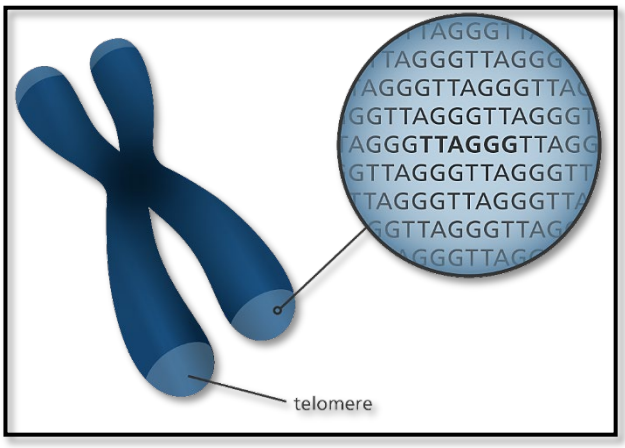


- The position of the centromere is variable, and thus chromosomes could be **acrocentric**, **submetacentric** or **metacentric** according to the position of centromere.



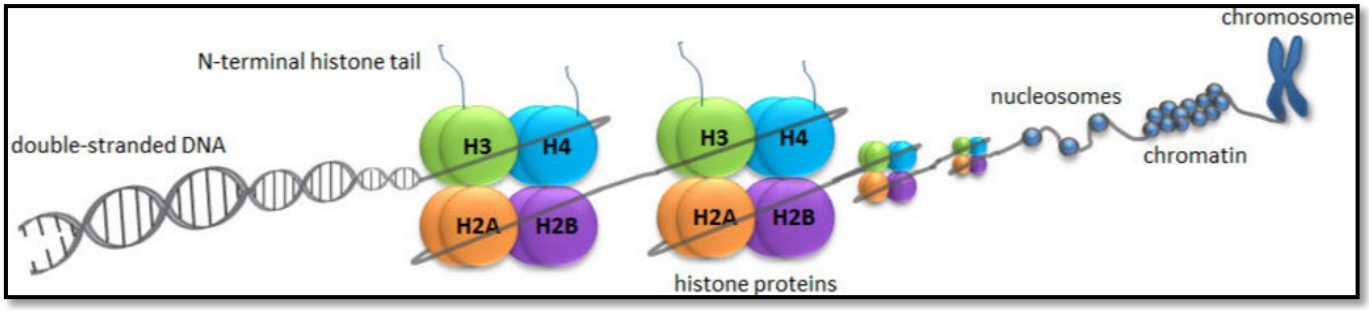
- Each centromere divides the chromosome into **short** and **long arms**, designated **p** (= petite) and **q** ('g' = grand), respectively.
- The tip of each chromosome arm is known as the **telomere**.

- Telomeres play a crucial role in sealing the ends of chromosomes and maintaining their structural integrity.
- Telomeres have been highly conserved throughout evolution and in humans they consist of many tandem repeats of a **TTAGGG** sequence.



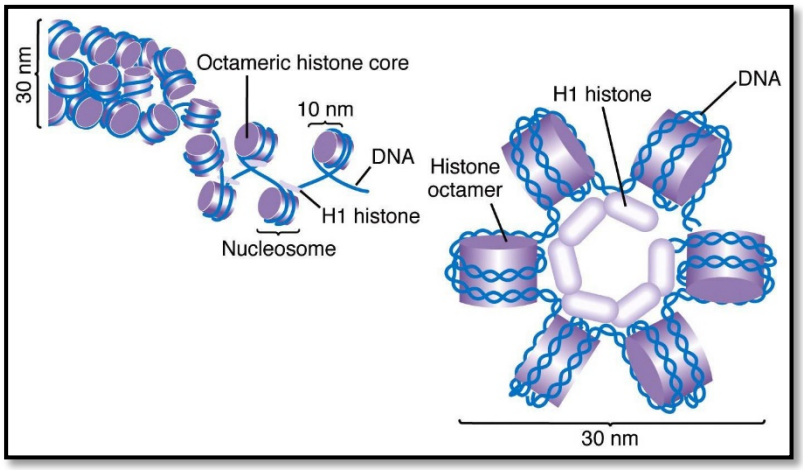
Organizational Levels of Chromosomes Structure

- The proteins that bind to DNA to form eukaryotic chromosomes are traditionally divided into two general classes: the **histones** and the **nonhistone** chromosomal proteins.
- The complex of histones and non-histone proteins with nuclear DNA is called **chromatin**.
- Histones are responsible for the first and most fundamental level of chromatin packing, the **nucleosome**.

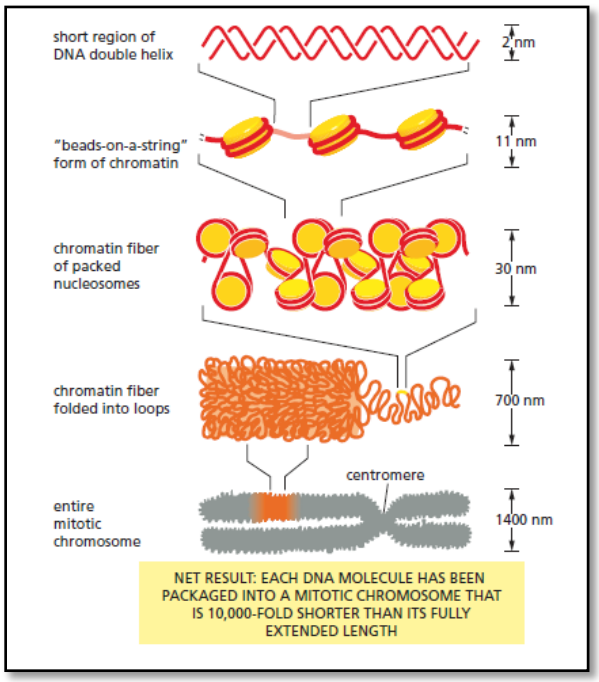


- Each nucleosome consists of DNA coiled around a core of eight histone proteins (octamer). These proteins are composed of two molecules of each of histones **H2A**, **H2B**, **H3**, and **H4**.
- A series of adjacent nucleosomes can be seen in the electron microscope as a series of **"beads on a string"**, with 50-80 bp of linker DNA separating each bead.

- The nucleosomes are further packed on top of one another to generate a more compact structure, known as the **chromatin fiber** (**30 nm** in diameter). This additional packing of nucleosomes into a chromatin fiber depends on a fifth histone called **histone H1**, which is thought to pull adjacent nucleosomes together into a regular repeating array.



- The chromatin fiber is folded into a series of loops, and that these loops are further condensed to produce the interphase **chromatin** (when the cell is not dividing)**.**
- Finally, this compact string of loops is thought to undergo at least one more level of packing to form the mitotic **chromosome** at time of cell division.

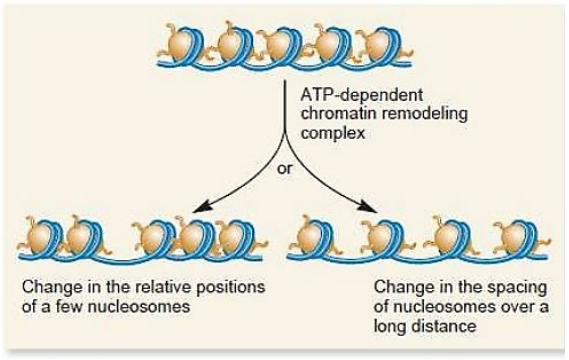


The Regulation of Chromosome Structure

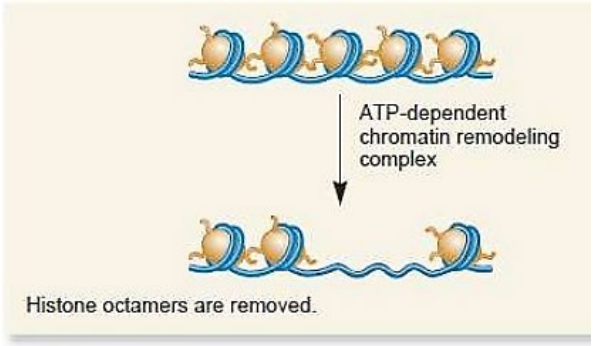
- The DNA in cells carries enormous amounts of coded information, and cells must be able to get to this information as needed.
- A cell can alter its chromatin structure to expose localized regions of DNA and allow access to specific proteins and protein complexes, particularly those involved in gene expression and in DNA replication and repair.
- The regulation and inheritance of chromatin structure play crucial parts in the development of eukaryotic organisms.
- Eukaryotic cells have several ways to adjust the local structure of their chromatin rapidly.
- One way takes advantage of **chromatin-remodelling complexes** (protein machines that use the energy of ATP hydrolysis to change the position of the DNA wrapped around nucleosomes). The

complexes, which attach to both the histone octamer and the DNA wrapped around it, can locally alter the arrangement of nucleosomes on the DNA, making the DNA either more accessible or less accessible to other proteins in the cell.

- Another way of altering chromatin structure relies on the reversible chemical modification of the histones, thereby loosening chromatin structure and allowing access to particular nuclear proteins.



(a) Change in nucleosome position

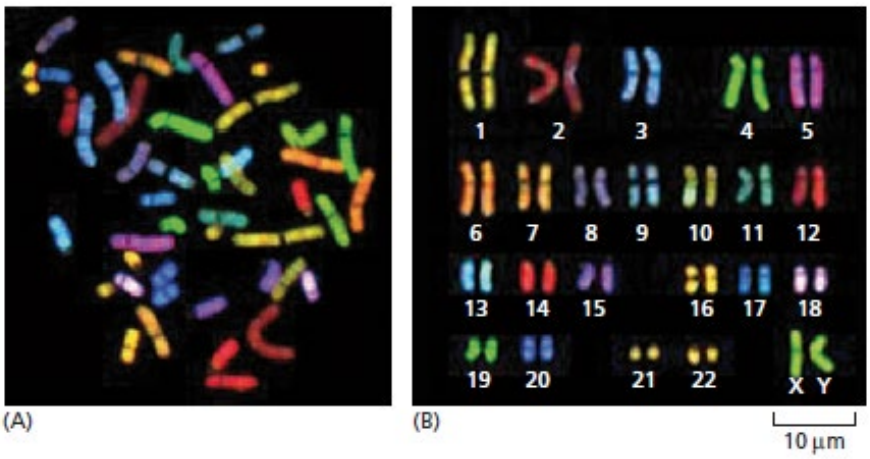


(b) Histone eviction

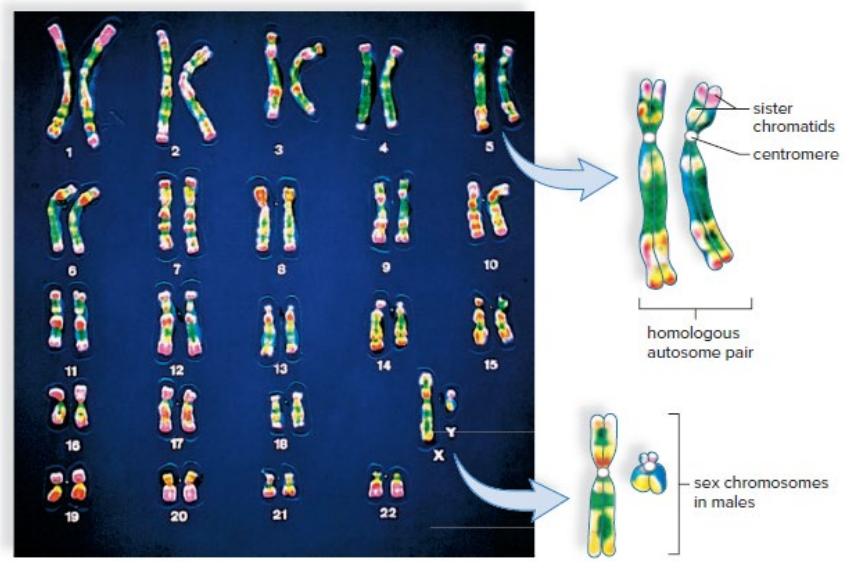
Methods of Chromosomal Study

In addition to being different sizes, the different human chromosomes can be distinguished from one another by a variety of techniques. Chromosomes are numbered from 1 to 22 according to their size; 1 being the largest and 22 the smallest.

- Microscopic analysis of chromosomes usually begins with cultured cells (usually White blood cells) arrested in mitotic metaphase by **colchicine** or other compounds that disrupt microtubules. After processing and staining the cells, the condensed chromosomes of one nucleus are photographed by light microscopy and rearranged digitally to produce a **karyotype** in which stained chromosomes can be analyzed.
- Each chromosome can be “painted” a different colour using sets of chromosome-specific DNA molecules coupled to different fluorescent dyes. This involves a technique called **DNA hybridization**. Then a computer is used to arrange chromosomes in pairs.



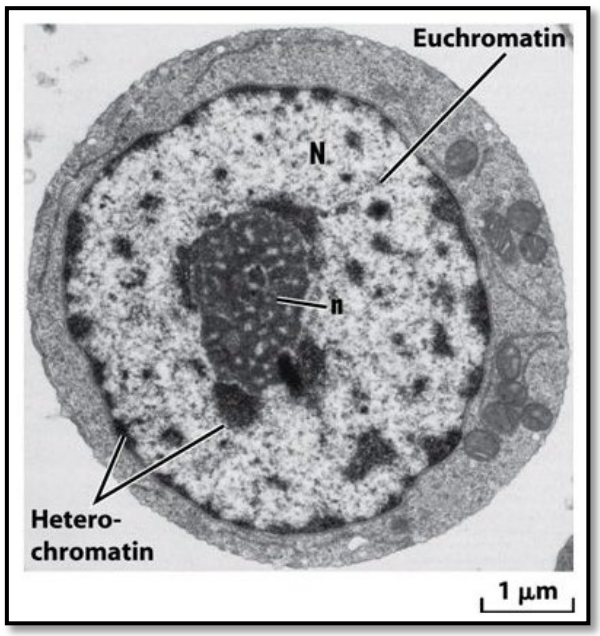
- A more traditional way of distinguishing one chromosome from another is to stain the chromosomes with dyes that bind to certain types of DNA sequences. Staining causes the chromosomes to have dark and light crossbands of varying widths, and these can be used—in addition to size and shape—to help pair up the chromosomes.
- A computer is used to arrange the chromosomes in pairs. The patterns that result allow each chromosome to be identified and numbered. An ordered display of the full set of human chromosomes is called the **human karyotype**.
- **Karyotyping** is the preparation and study of karyotypes in order to determine chromosomes number, size and shape and identify any abnormality and it is part of **cytogenetics**.



If parts of a chromosome are lost, or switched between chromosomes, these changes can be detected. Cytogeneticists analyse karyotypes to detect chromosomal abnormalities that are associated with some inherited defects and with certain types of cancer.

Interphase Chromatin

- Interphase chromatin is not uniformly packed.
- Instead, regions of the chromatin that contain genes that are being expressed are generally more extended, while those that contain silent genes are more condensed.
- Thus, the detailed structure of an interphase chromatin can differ from one cell type to the next, helping to determine which genes are expressed. Most cell types express about 20 to 30 % of the genes they contain.

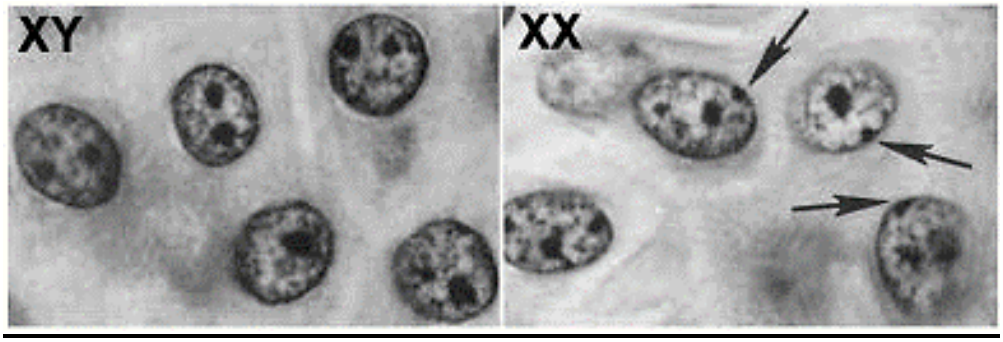


- Microscopically two categories of chromatin can be distinguished in nuclei of most nondividing cells (interphase chromatin).
- **Euchromatin** (from the Greek word **eu**, "true" or "normal,") is visible as finely dispersed granular material in the electron microscope and as lightly stained basophilic areas in the light microscope. It refers to chromatin that exists in a less condensed state than heterochromatin.
- **Heterochromatin** (from the Greek word **heteros**, "different or other,") appears as coarse, electron-dense material in the electron microscope and as intensely basophilic clumps in the light microscope. It represents the most highly condensed form of interphase chromatin and typically makes up about 10% of an interphase chromatin.

Relation of Female X-chromosome & Heterochromatin

- Perhaps the most striking example of the use of heterochromatin to keep genes shut down, or silenced, is found in the interphase X chromosomes of female mammals.
- In mammals, female cells contain two X chromosomes, whereas male cells contain one X and one Y.
- Because a double dose of X-chromosome products would be lethal, female mammals have evolved a mechanism for permanently inactivating one of the two X chromosomes in each cell.

- At random, one or other of the two X chromosomes in each cell becomes highly condensed into heterochromatin early in embryonic development.
- Thereafter, the condensed and inactive state of that X chromosome is inherited in all of the many descendants of those cells.
- The inactive X chromosomes can be seen in some cells (mostly neutrophils and buccal cells) under light microscope as darkly staining mass of heterochromatin called a **Barr body** (named after the person who discovered it).



the arrow refers to Barr Body

THE SEX CHROMOSOMES

- The X and Y chromosomes are known as the sex chromosomes because of their crucial role in sex determination.
- The X chromosome was originally labeled as such because of uncertainty as to its function when it was realized that in some insects this chromosome is present in some gametes but not in others.
- In human, the Y chromosome is much smaller than the X and carries only a few genes of functional importance, most notably the testis-determining factor, known as SRY.
- In the female each ovum carries an X chromosome, whereas in the male each sperm carries either an X or a Y chromosome. As there is a roughly equal chance of either an X-bearing sperm or a Y-bearing sperm fertilizing an ovum, the numbers of male and female conceptions are approximately equal. In fact, slightly more male babies are born than females, although during childhood and adult life, the sex ratio evens out at 1: 1.