# The Chromosomal Basis of Inheritance

Guide notes for year 2 (mbchb/Bpharm/BDS - 2018

By the end of the course, the learner should be able to:

1) Understand how genes and chromosomes relate to traits.

2) Appreciate how traits are passed on from parents to offspring.

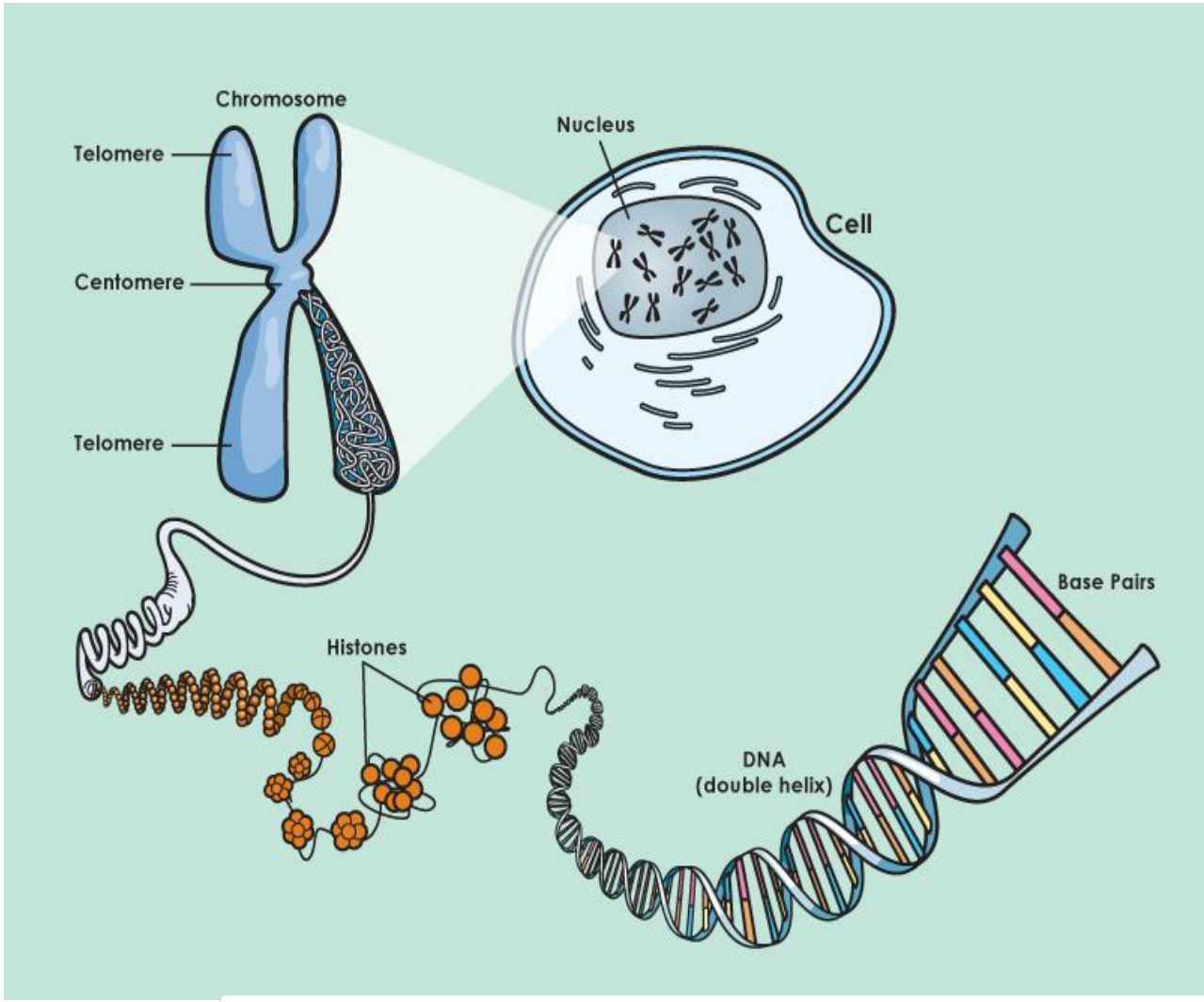
3) Explain the inheritance of genetic disorders and predict **genotypic**/**phenotypic** percentages/ratios.

4) Determine if a genetic disorder is sex-linked by analyzing a **pedigree**.

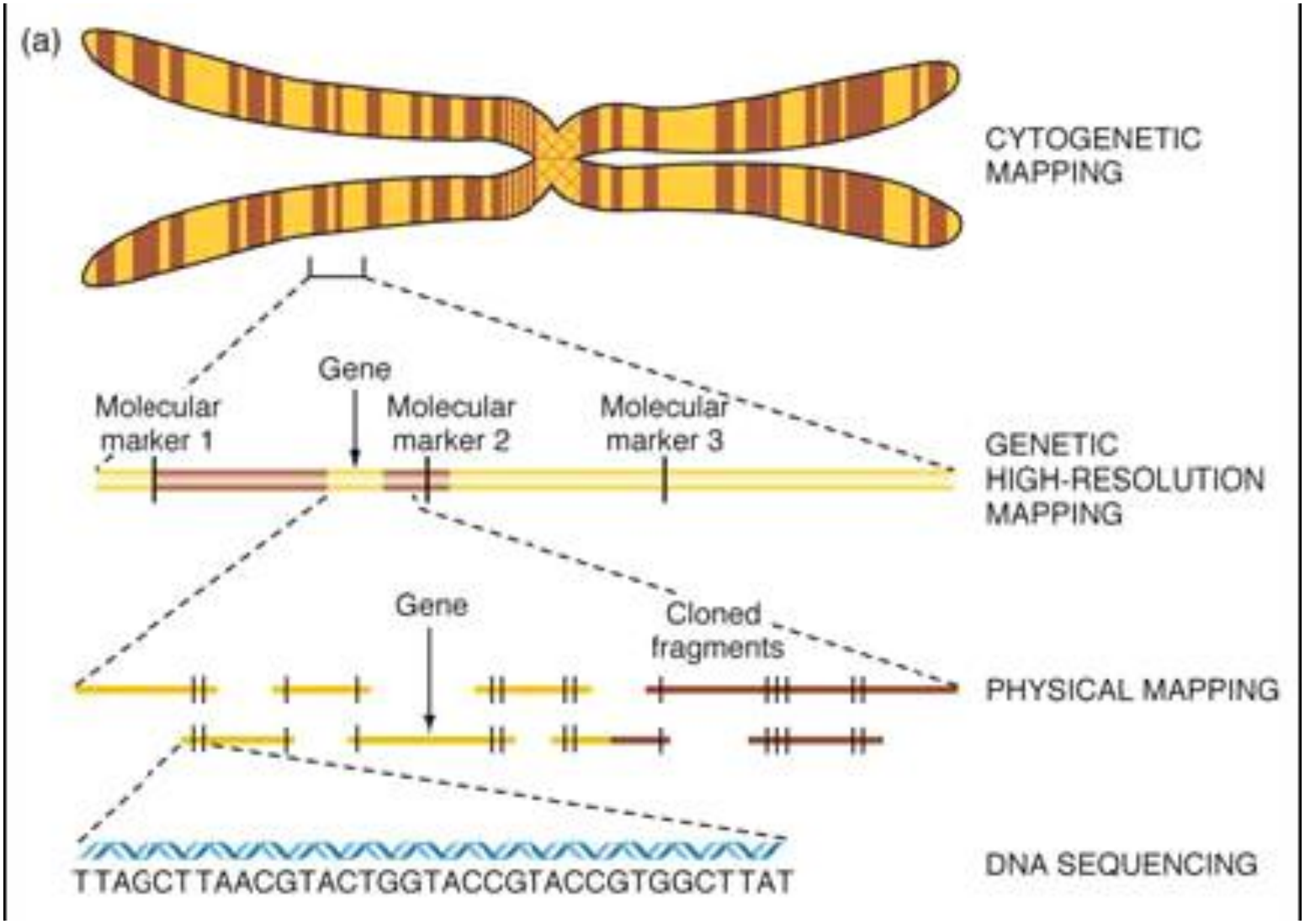
5) Distinguish between dominant versus recessive genetic disorders.

# DNA – genetic blueprint

- Deoxyribonucleic acid (**DNA**)
- Located in the **nucleus**
- rapped up in structures called **chromosomes**.
- **46** Chromosomes - **23** Pairs in every cell




- **One section of DNA is a gene**


(a)
CYTOGENETIC MAPPING
Gene
Molecular marker 1
Molecular marker 2
Molecular marker 3
GENETIC HIGH-RESOLUTION MAPPING
Gene
Cloned fragments
PHYSICAL MAPPING
TTAGCTTAACGTACTGGTACCGTACCGTGGCTTAT
DNA SEQUENCING

# Genetics terms :

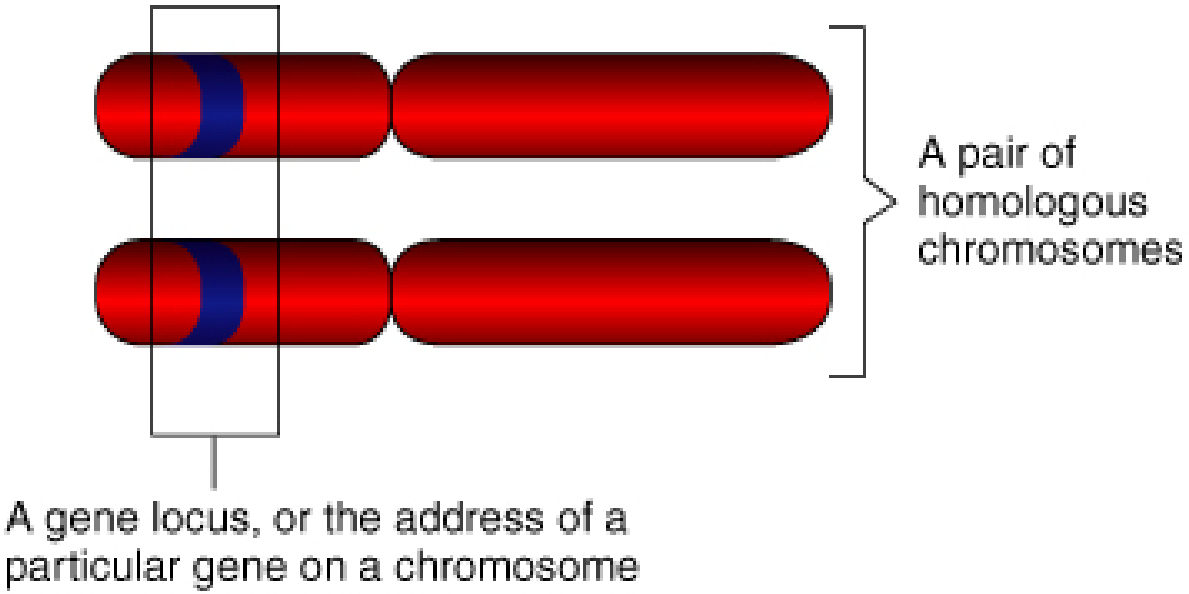
- **Gene** – a unit of heredity; a section of DNA sequence encoding a single protein

- **Genome** – is an organism's complete set of genetic material, including all of its genes.

- **Locus** – a fixed location on a strand of **DNA** where a gene or one of its alleles is **located**.

- **Alleles** – two genes that occupy the same position (**Locus**) on **homologous chromosomes** and that cover the same trait (like **color**).

# Gene are located on chromosomes

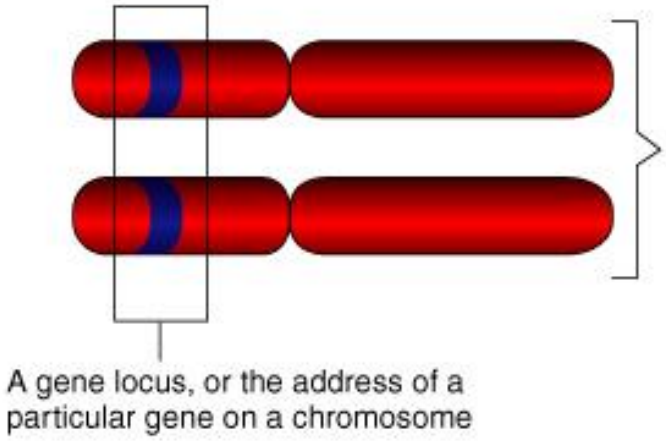



**Homologous chromosomes:**

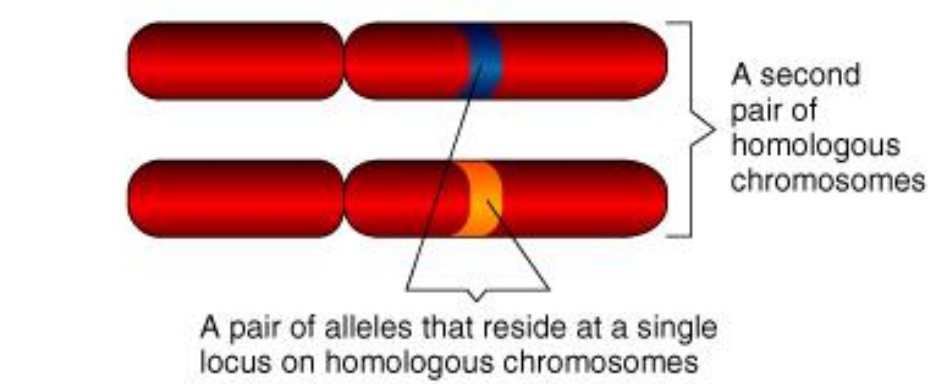
Chromosomes that pair at meiosis and having the same structural features and pattern of genes.

**The two members of an homologous pair carry alleles for the same genes and, therefore, affect the same traits.**

# Genetic polymorphisms
# (The source of genetic variation)




**ONE locus (monogenic),**
**TWO different alleles**
**THREE combinations possible**






**Detection of Polymorphism:**

- Restriction Fragment Length Polymorphism (**RFLPs**)
- Amplified fragment length polymorphism (**AFLPs**))

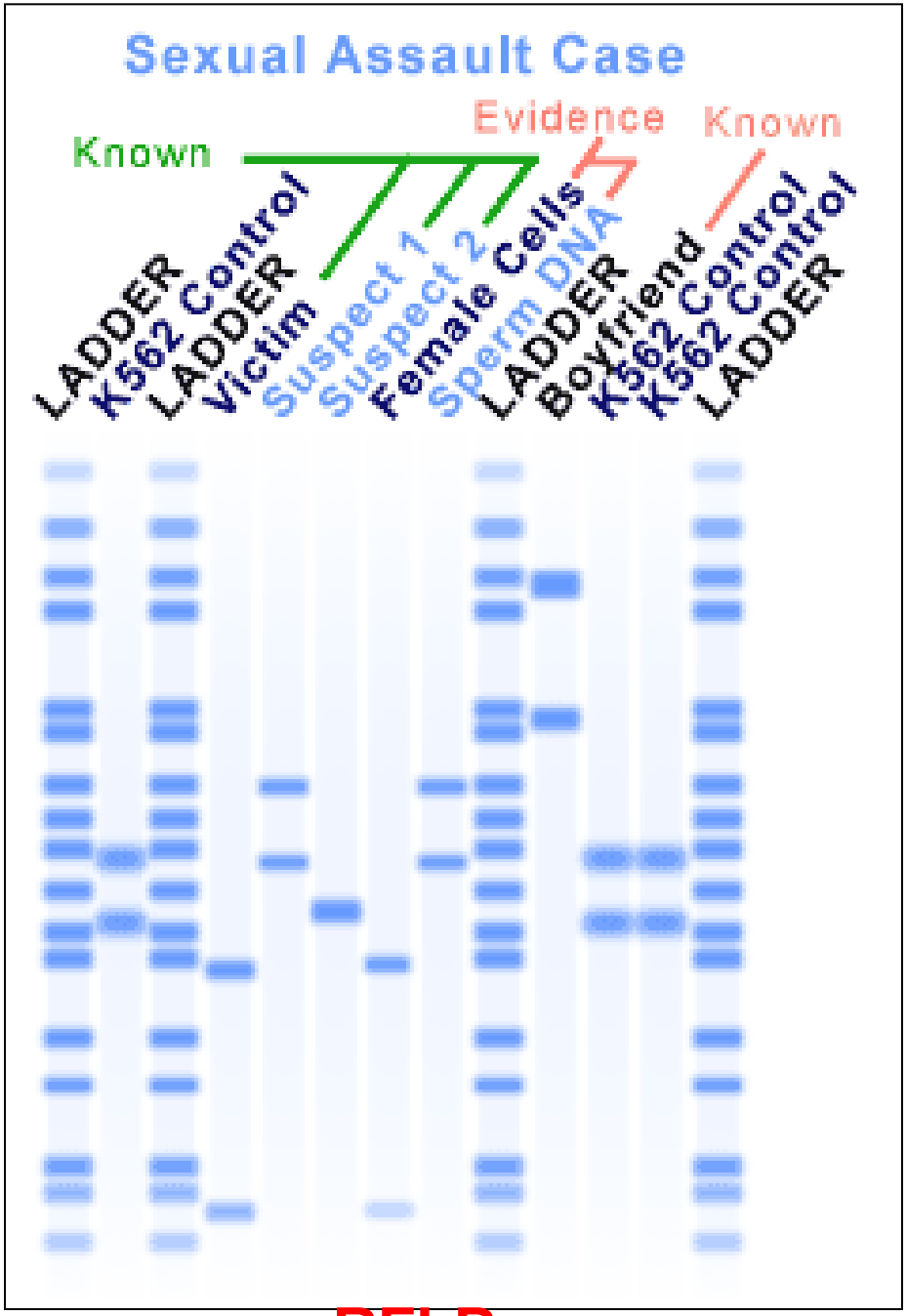
**Detection of Polymorphism:**

- Restriction Fragment Length Polymorphism (**RFLPs**)

(DNA is cut with restriction enzymes and fragments generated are separated and visualized on agarose gel)

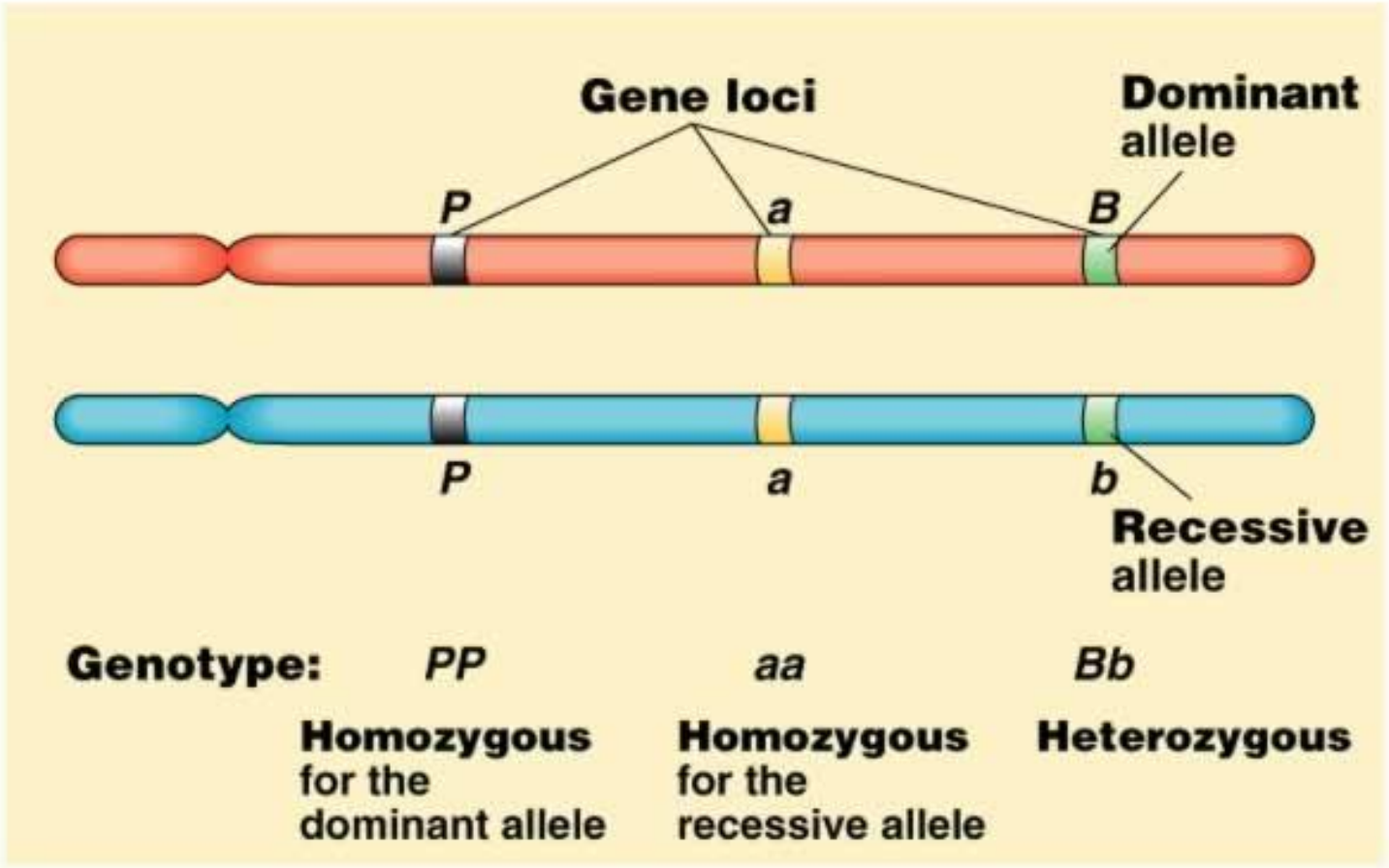
- Amplified fragment length polymorphism (**AFLPs**))

(DNA is isolated then specific sequences are amplified, to generate fragments of varying sizes then analyzed/separated and visualized on agarose gel)




RFLP

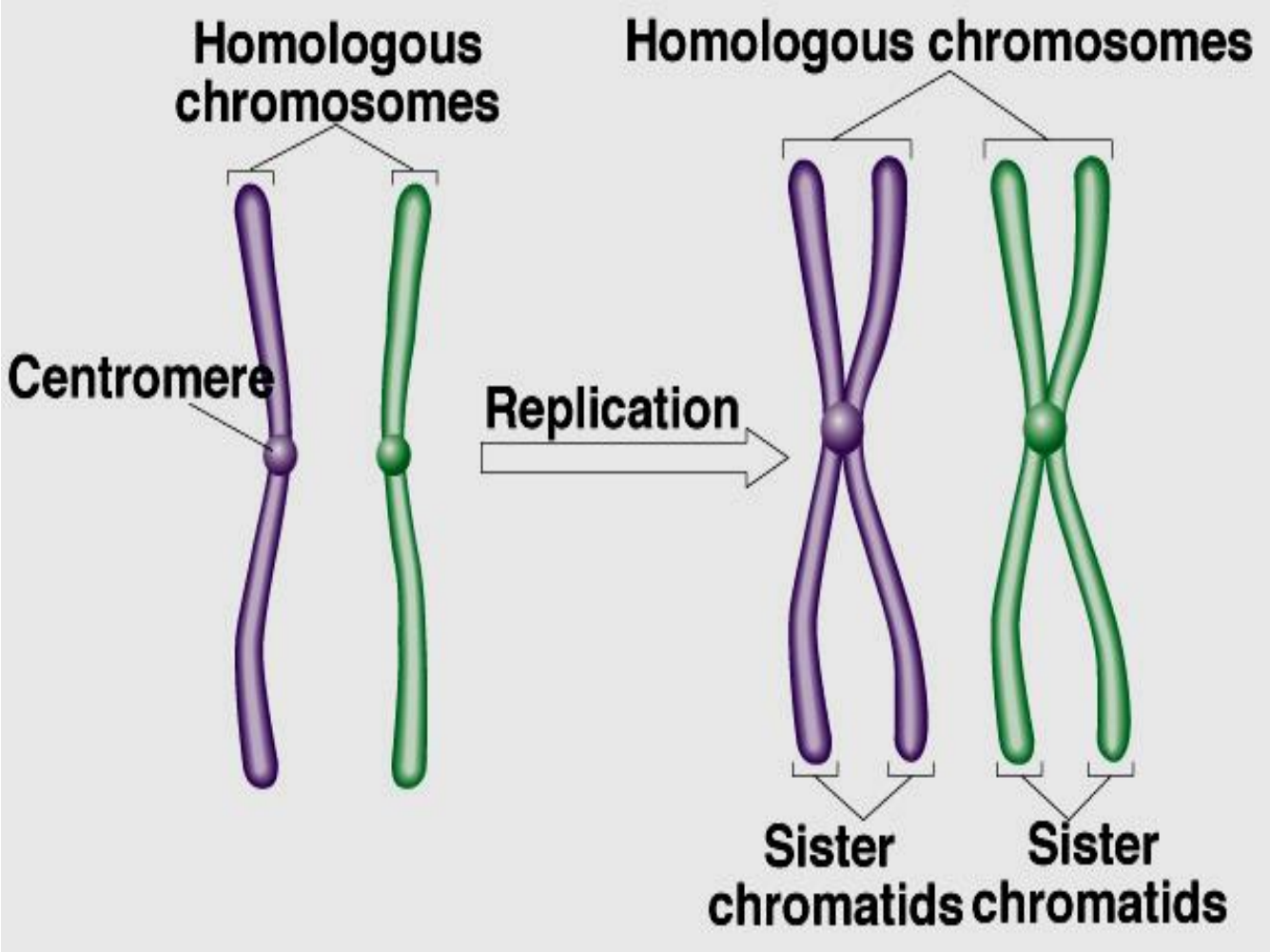
The chromosome pairs:



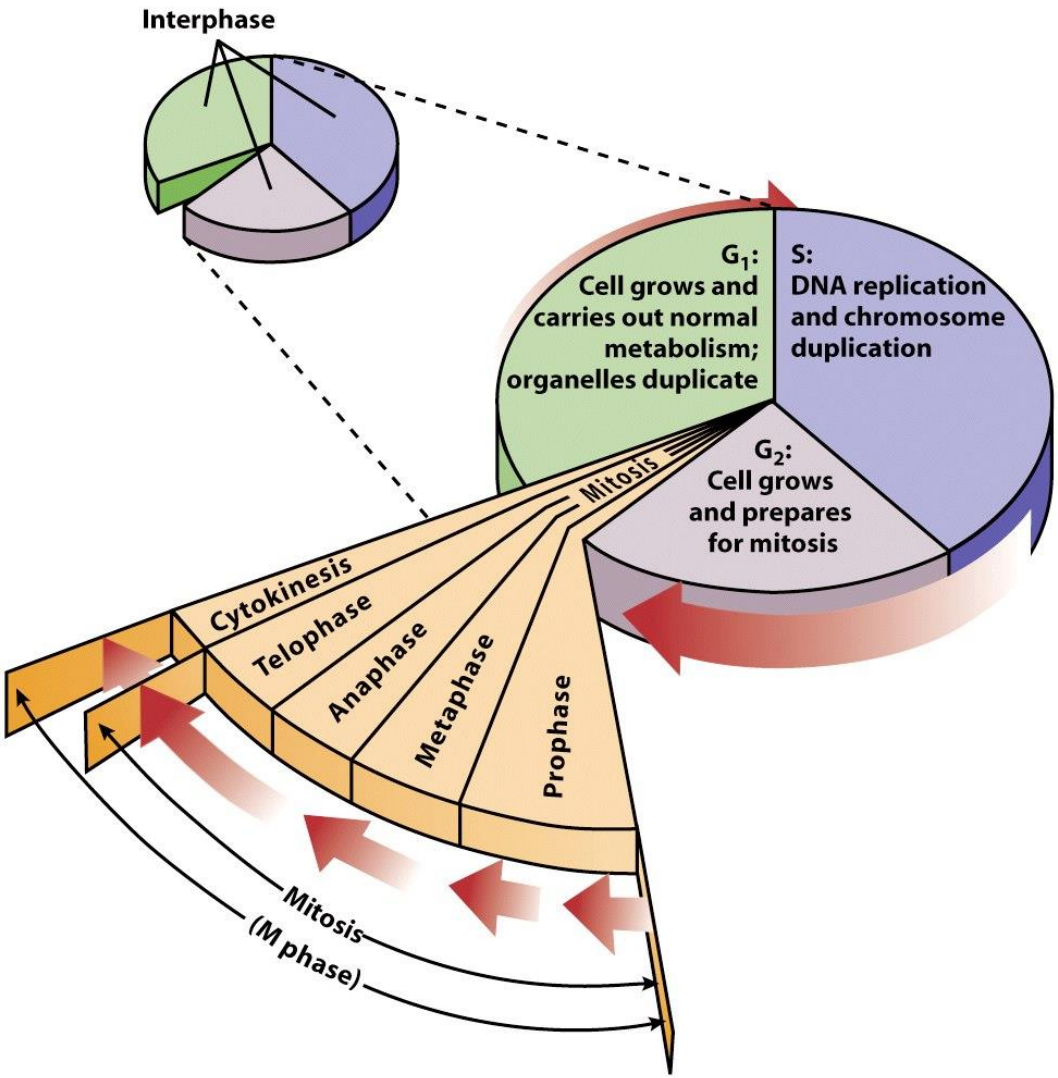

- Locus
  - Allele
    - Heterozygous (**Aa**)
      - Homozygous (**AA** or **aa**)

# How do chromosomes become **double stranded**?

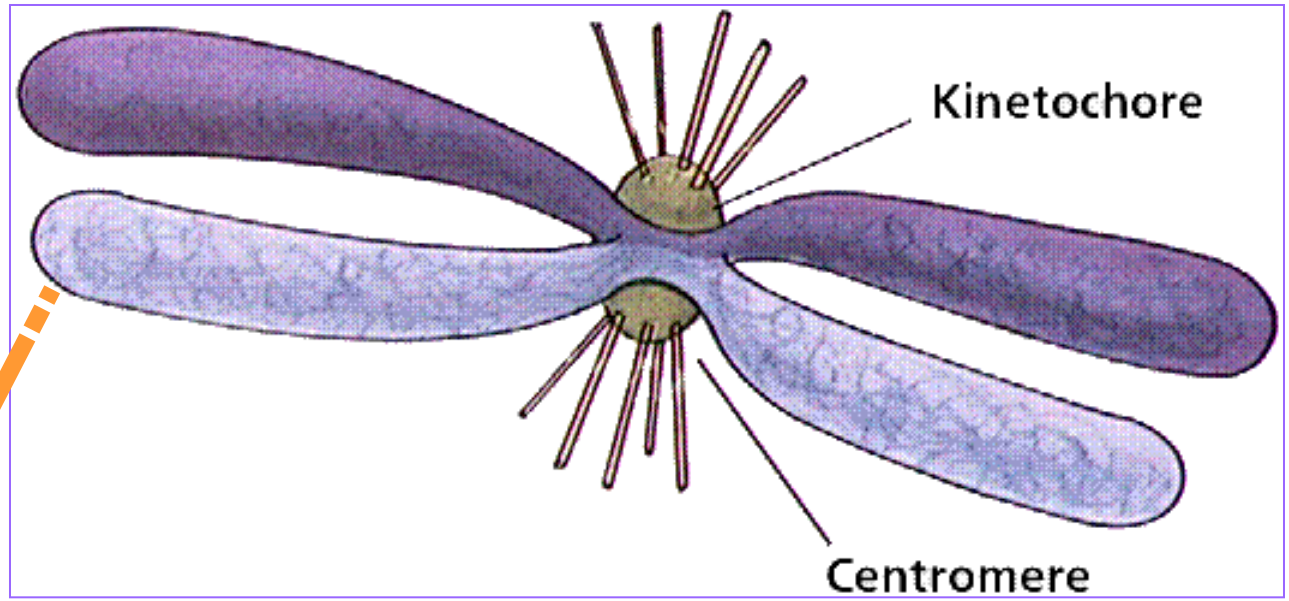
During the life of the cell, each chromosome of DNA **makes a copy of itself** prior to cell division to ensure each daughter cell gets a complete set



# Cell Cycle

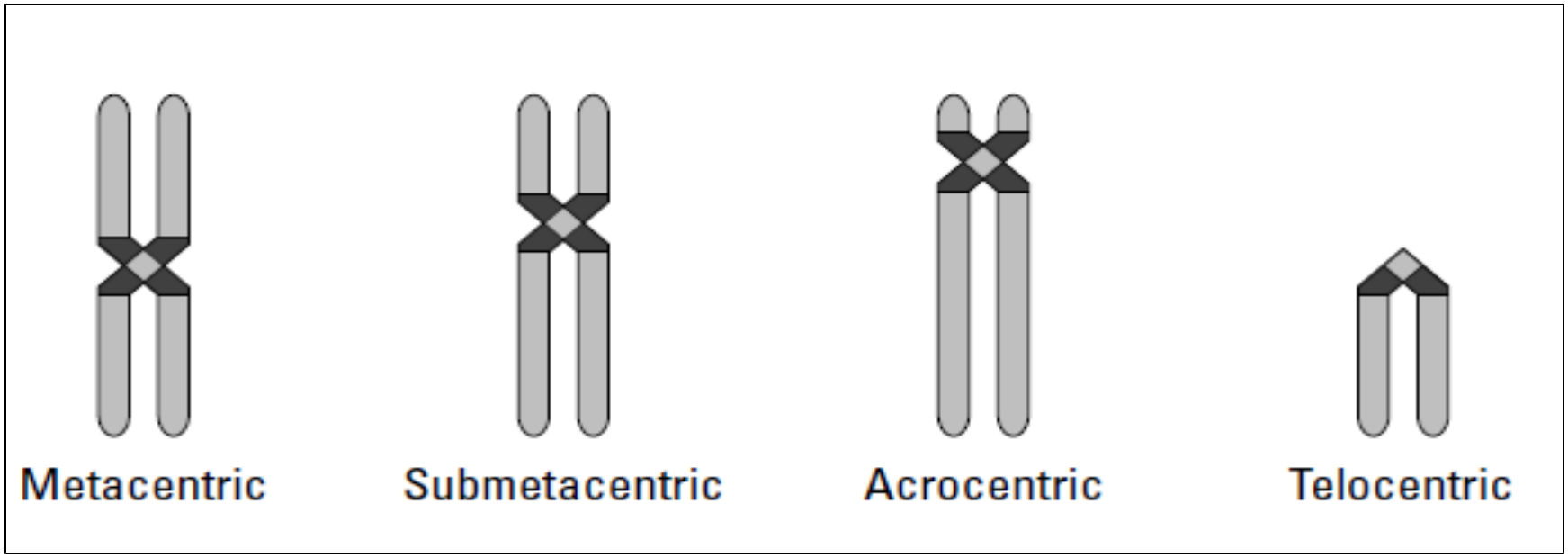

Interphase
G1:
Cell grows and carries out normal metabolism; organelles duplicate
S:
DNA replication and chromosome duplication
G2:
Cell grows and prepares for mitosis
Mitosis
Prophase
Metaphase
Anaphase
Telophase
Cytokinesis
Mitosis
(M phase)

# Chromosome




Sister Chromatids

# Chromosome are classified based on the Locations of their Centromeres.




**Metacentric**: centromere in the middle, with arms of equal length.

**Acrocentric**: centromere near one end, with arms of very different lengths.

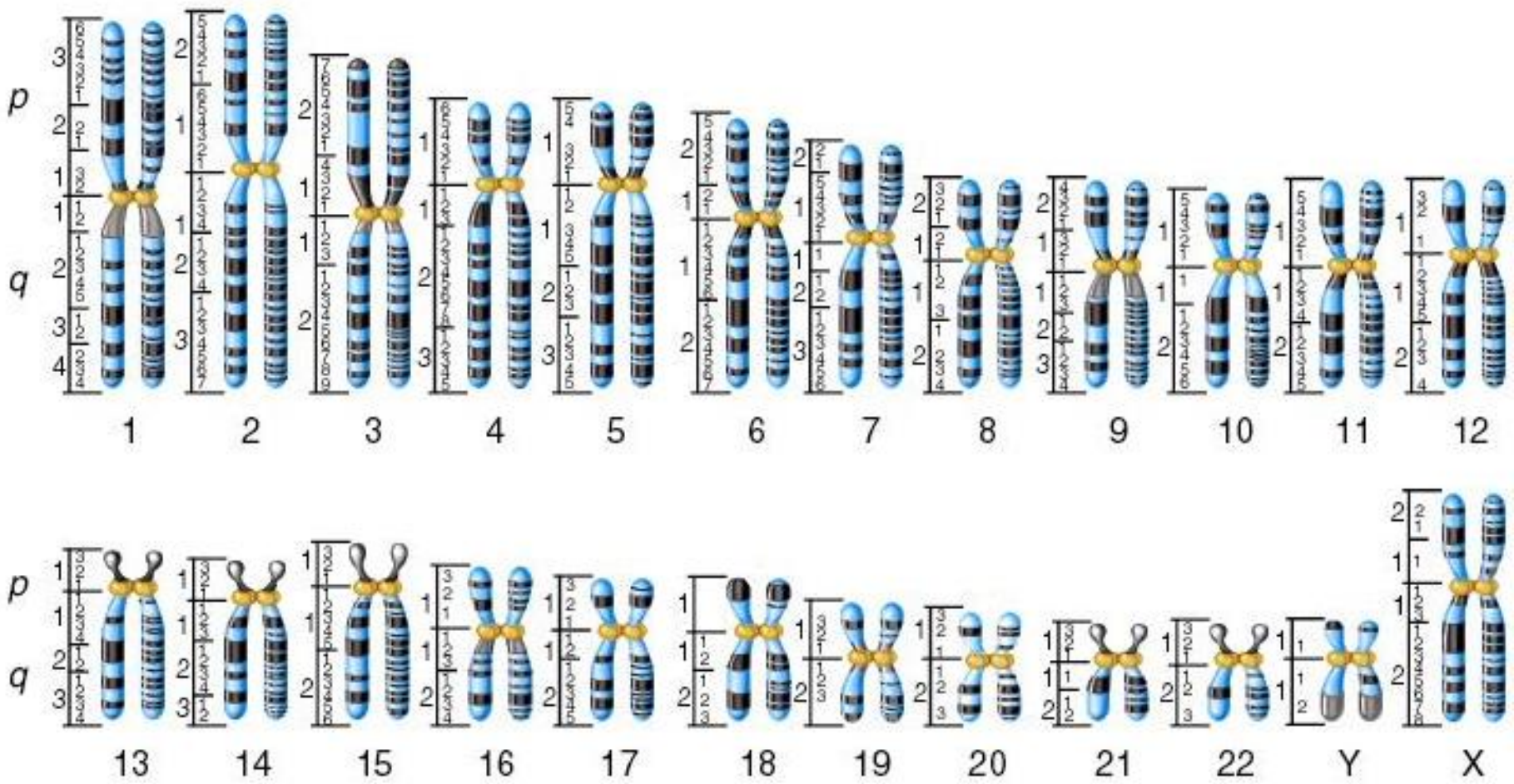
**Sub-metacentric**: centromere near the middle, with arms of slightly different lengths.

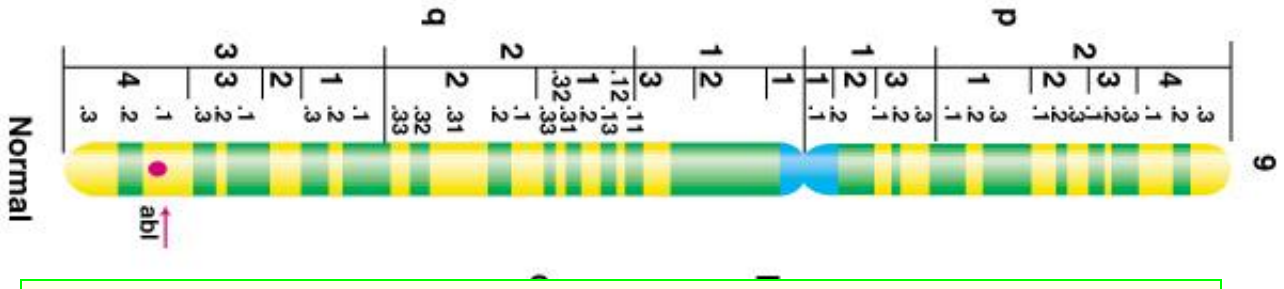
**Telocentric**: centromere at one end, with only 1 arm.

# G-Banded Metaphase Chromosomes

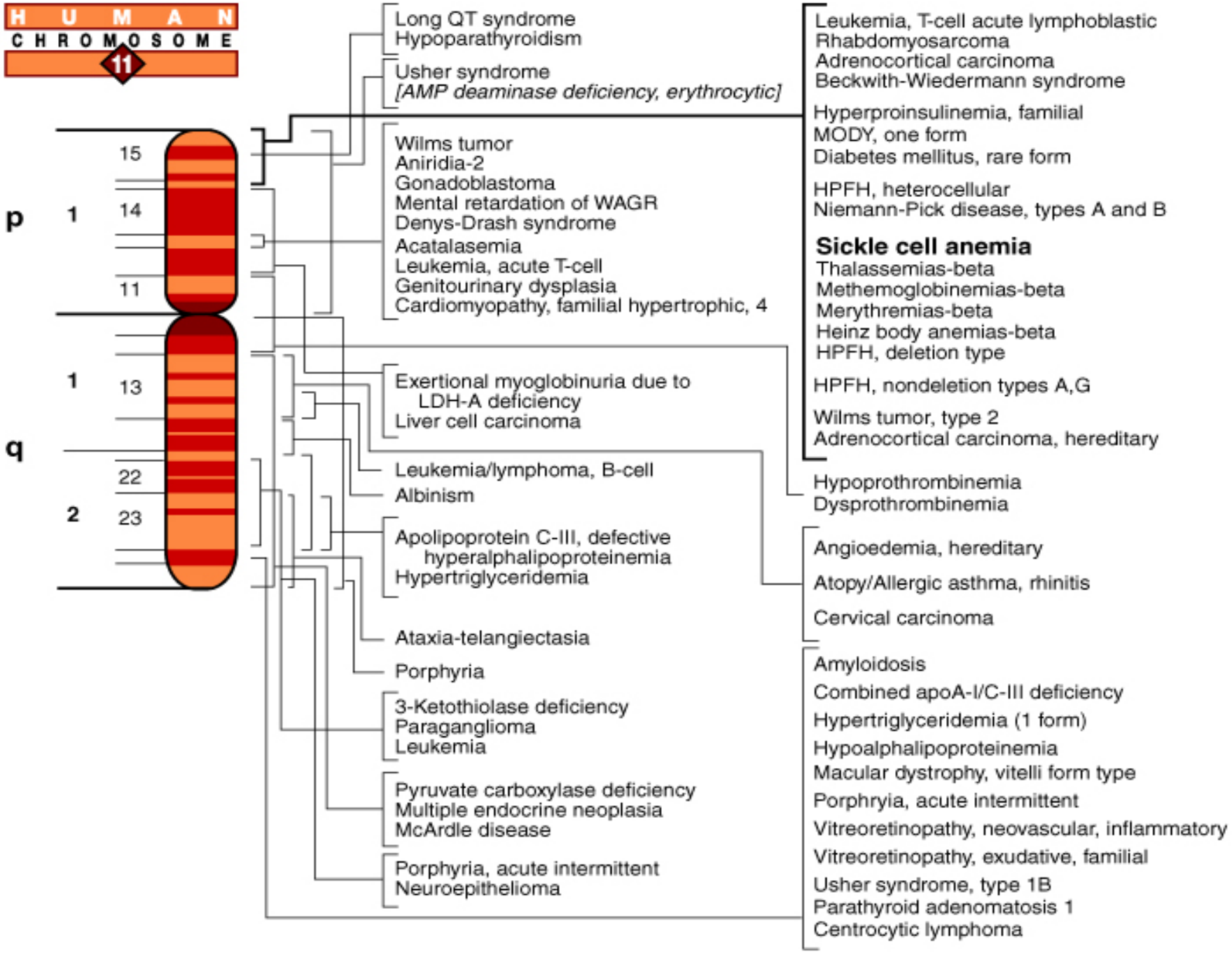
**The metaphase chromosomes are treated with trypsin (to partially digest the protein) and stained with Giemsa.**

**Dark bands that take up the stain are strongly A,T rich.**



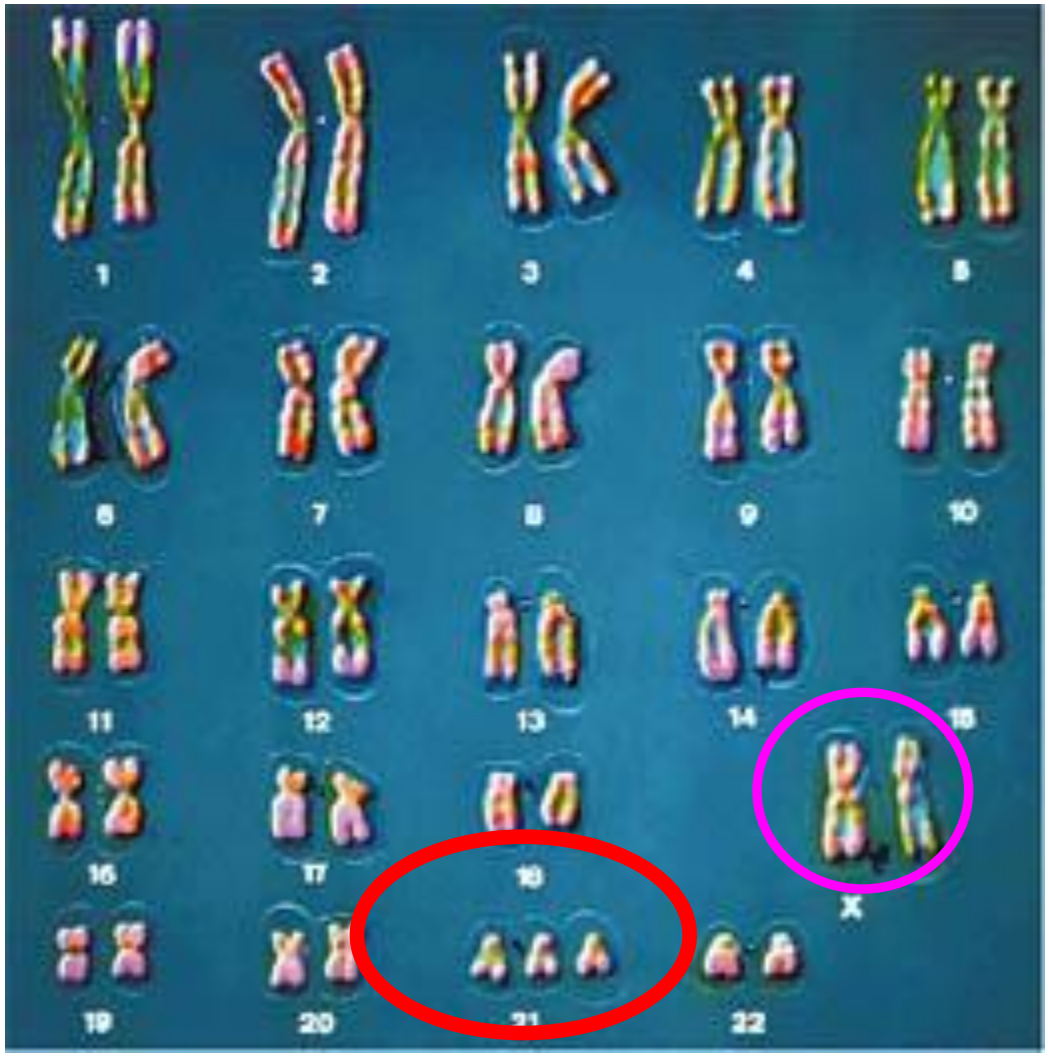



# Chromosome banding pattern



**Karyotype**

1. A visual display of the chromosomes arranged by size, shape, and banding pattern.
2. Used to identify aneuploidy conditions.




**Can you see the extra 21st chromosome?**

**Is this person male or female?**

# Chromosomes in eukaryotes and prokaryotes are different

| PROKARYOTES | EUKARYOTES |
| --- | --- |
| Single chromosome plus plasmids | Many chromosomes |
| Circular chromosome | Linear chromosomes |
| made only of DNA | Made of **chromatin**, a nucleoprotein (DNA coiled around histone proteins) |
| Found in **cytoplasm** | Found in a **nucleus** |
| Copies its chromosome and divides immediately afterwards | Copies chromosomes, then the cell grows, then goes through mitosis to organise chromosomes in two equal groups |

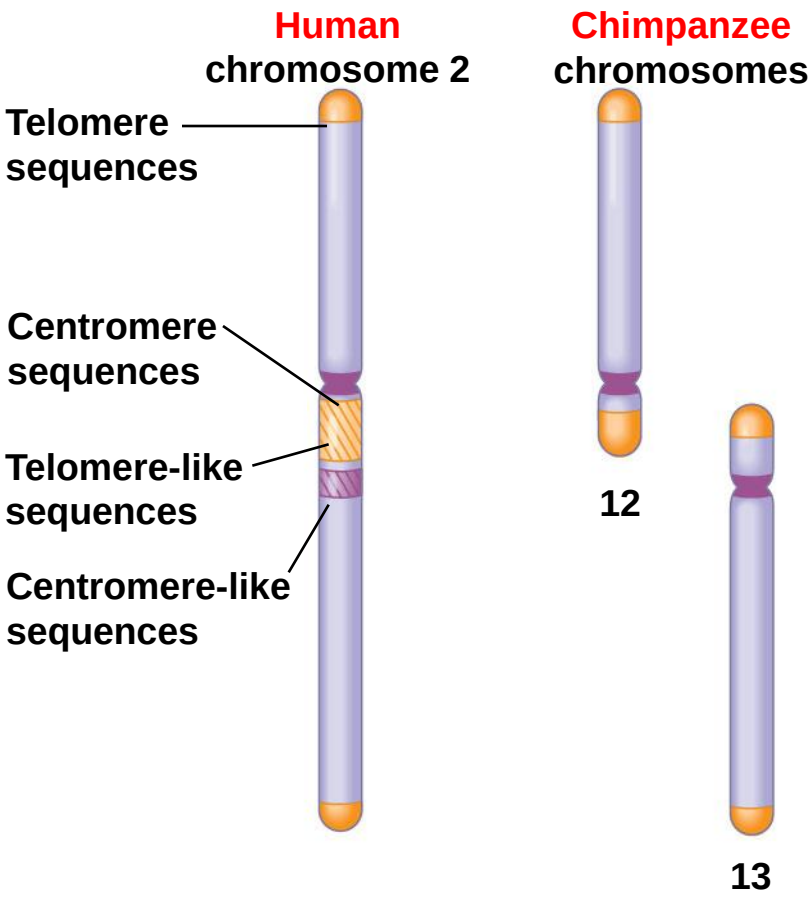
# Chromosome number and ploidy condition in commercially important crop species

| Common name | Haploid | Chromosome no. (X) | Ploidy | |
|---|---|---|---|---|
| alfalfa | 8 | 32 | 4X | **Tetraploid** |
| Apple | 17 | 34 | 2X | **Diploid** |
| Oats | 13 | 52 | 4X | **Tetraploid** |
| Wheat, durum | **7** | 28 | **4X** | **Tetraploid** |
| Wheat, bread | **7** | 42 | 6X | **Hexaploid** |
| Barley | 7 | 14 | 2X | **Diploid** |
| Strawberry | **7** | 56 | 8X | **Octaploid** |
| **Humans** | **23** | **46** | **2X** | **Diploid** |

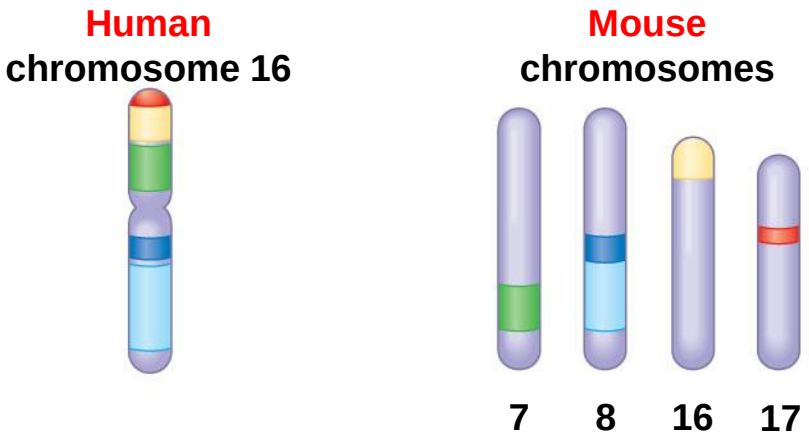
| Organism | Number of chromosomes |
|---|---|
| pea plant | 14 |
| sun flower | 34 |
| cat | 38 |
| puffer fish | 42 |
| human | 46 |
| dog | 78 |

| | |
|---|---|
| Chimp | 48 |
| Orangutan | 48 |
| Gorilla | 48 |
| | |
| Gibbons | 44 |
| Siamang | 50 |
| | |
| Colobus | 44 |
| Green Monkey | 60 |
| Baboon | 42 |
| Owl Monkey | 54 |
| Squirrel Monkey | 44 |
| | |
| Ringtailed Lemur | 56 |
| Black Lemur | 44 |

# Related chromosome sequences among mammals.




(a) Human and chimpanzee chromosomes




(b) Human and mouse chromosomes

# Human evolution

Humans are classified within the superfamily Hominoidea (with **gibbons**, **orangutans**, **gorillas** and **chimpanzees**).

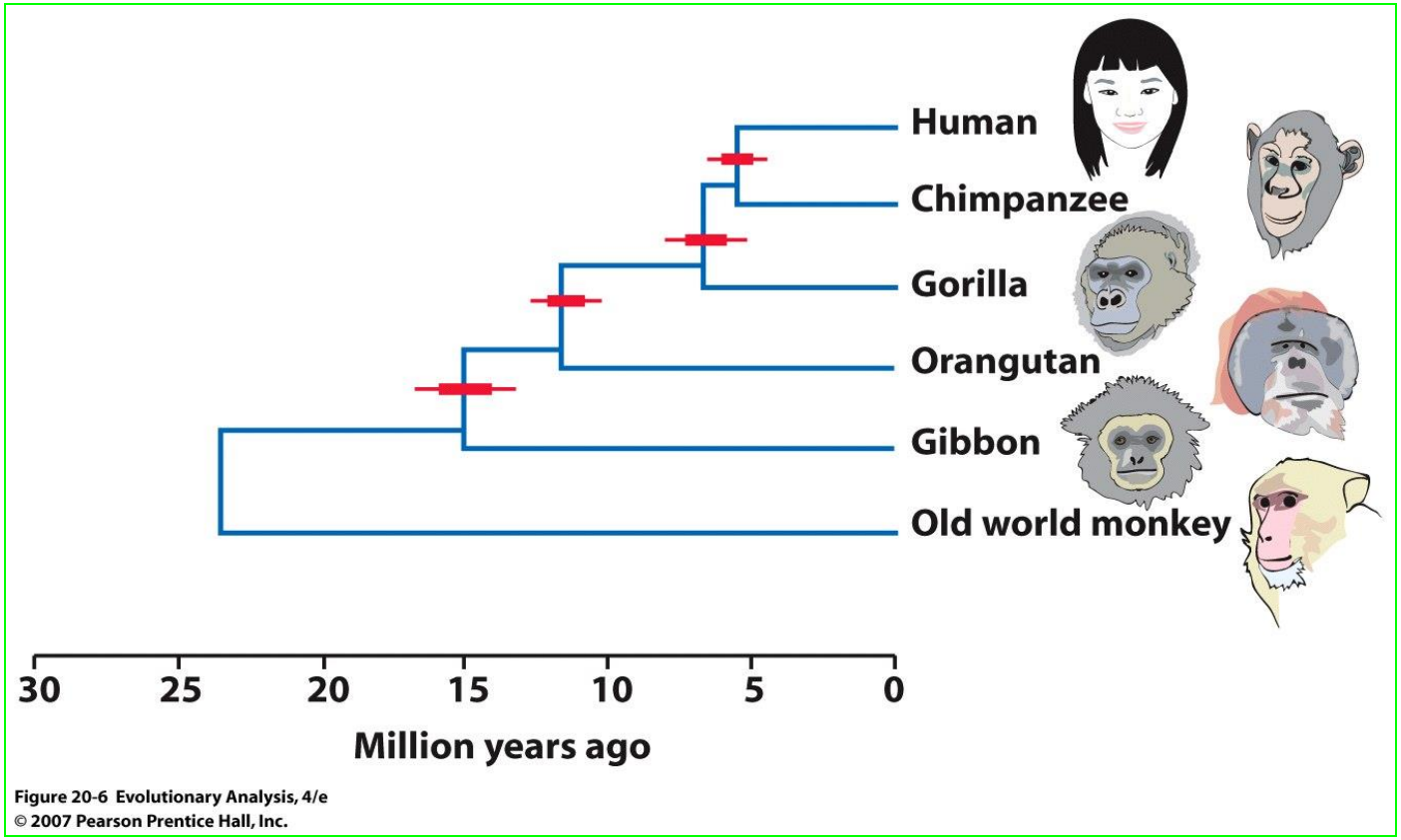



Figure 20-6 Evolutionary Analysis, 4/e

# Hybrids

**Horse** **X** **Donkey**

**Mule**

Horse (**64** chromosomes) x donkey (**62** chromosomes)

= Mule = (**32**+**31**) = **63** **(Odd No.)** Chromosomes - **Sterile**

Haploid = ?

# Mendel's Laws of Heredity:

1. Inherited traits are controlled by **versions of genes** that occur in pairs.
   - The two versions are called ***alleles*.**
   - ***Alleles*** control the ***traits*.** *E.g., Height trait (or gene) there is a* ***'tall' allele*** *and a* ***'short'*** **allele**.
2. An organism has **2 alleles** for **each trait total**.
   - One allele for each trait is inherited from each parent. **[These are found at a given locus] – DIPLOID**

NB: The two alleles may be drawn from a gene pool with more than two alleles in a population *eg* 3, 4, 5 etc

3. One allele may hide/ mask the presence of the other - The ***principle of dominance.*** [ Dominant (**R**) *vs* recessive (**r**) ]

4. Alleles are separated during meiosis **I** - the ***law of segregation.***

# Terminology

***Homozygous*** *- both alleles for a trait are the same (AA; aa)*

***Heterozygous*** *- the alleles for trait are different (Aa)*

***Genotype*** *- the actual genetic makeup for a trait (AA; Aa; aa)*

***Phenotype*** *- the way in which the genotype is expressed (tall; short)*

***Dominant*** *- the allele that **masks** the presence of the other (AA; Aa)*

***Recessive*** *- the allele that is masked by the other (aa)*

# General features of the eukaryotes

Some of the general features of eukaryotes that **distinguish** them from prokaryotes are**:-**

- Eukaryotes include many **multicellular** organisms**,** in addition to **unicellular** organisms.
- Eukaryotes have
  - ✓ **a membrane-bound nucleus,**
  - ✓ **intracellular organelles,** ***and***
  - ✓ **a cytoskeleton**
- Most eukaryotes undergo **sexual** reproduction
- The genome **size** of eukaryotes spans a wider range than that of most prokaryotes
- Eukaryotic genomes have a **lower gene density.**
- Prokaryotes are **haploid**; **eukaryotes** have varying **ploidy**
- Eukaryotic genomes tend to be organized into **linear chromosomes** with a **centromere** and **telomeres**.

# Locating Genes along Chromosomes

- Mendel's **"hereditary factors"** are genes.
- Genes are located on **chromosomes** - **[Locus / Loci]**.
- The location of a particular gene can be seen by **tagging** isolated chromosomes with a **fluorescent dye** that highlights the gene.

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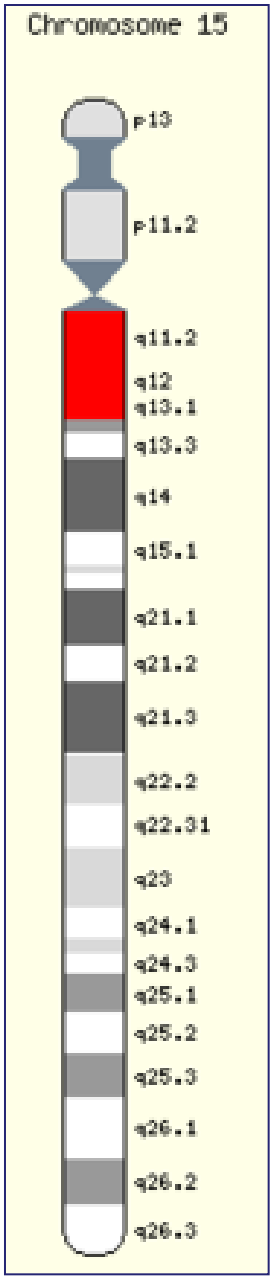
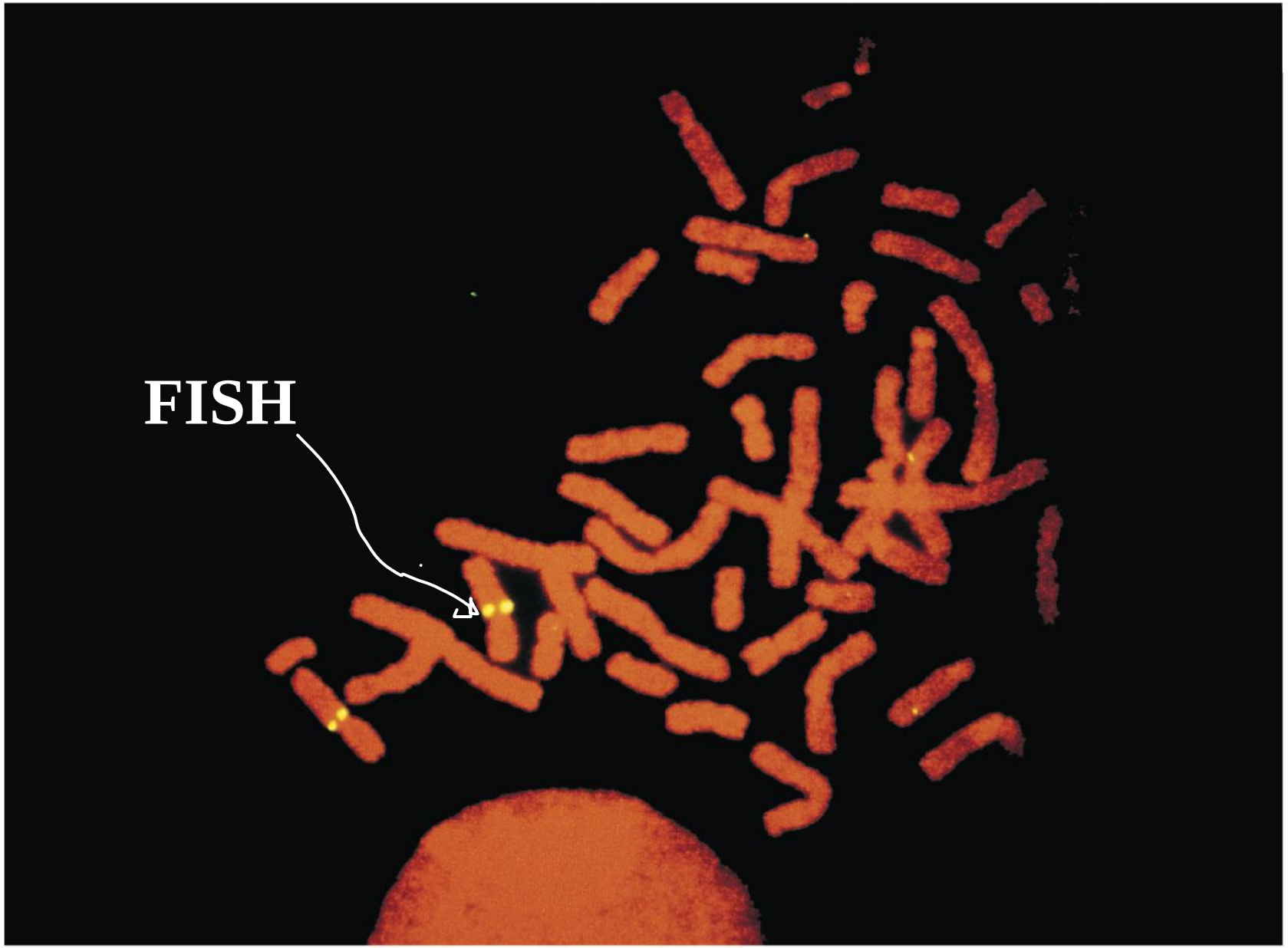
- ✓ **Genome** - is an organism's complete set of DNA, including all of its genes.
- ✓ Each **genome** contains all of the information needed to **build** and **maintain** that organism.
- ✓ In humans, a copy of the entire **genome** - more than **3 billion** DNA base pairs - is contained in all cells that have a nucleus.

# Chromosome #15

tagging



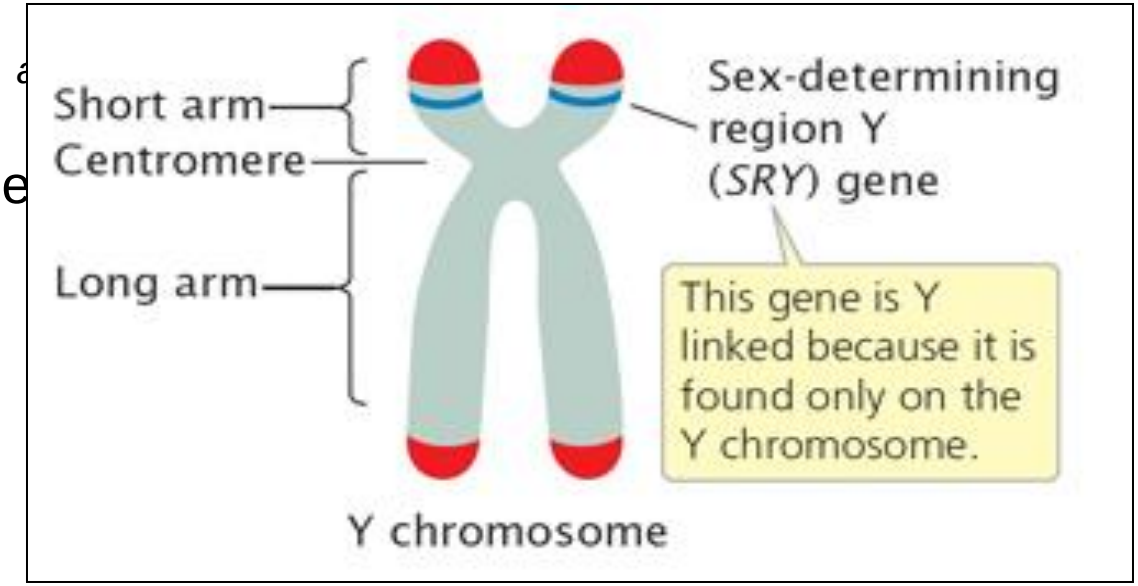


# Mendelian inheritance has its physical basis in the behavior of chromosomes

- **Mitosis** and **meiosis** were first described in the late 1800s.
- The **chromosome theory of inheritance** states:
  - genes have **specific loci** (**positions**) on chromosomes.
  - Chromosomes undergo **segregation** and **independent** assortment.
- **The behavior of chromosomes during meiosis can account for Mendel's laws of segregation and independent assortment.**

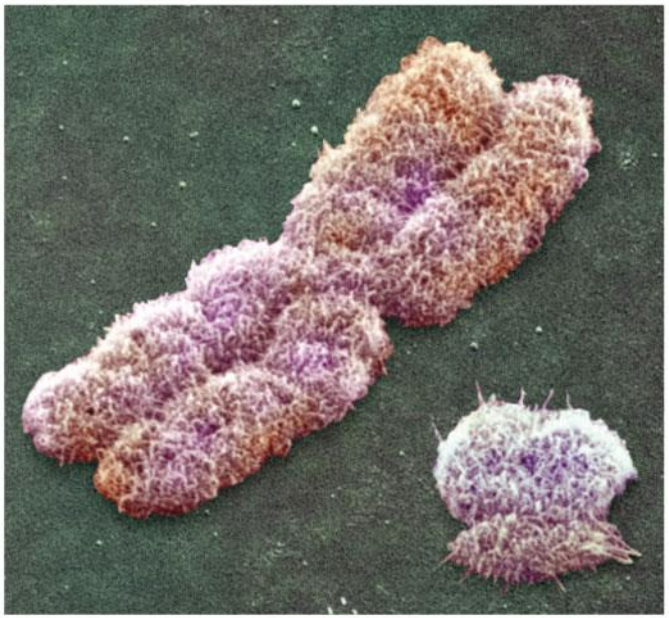
# In humans and other animals, there is a **chromosomal basis** of **sex determination**

- In **humans** and other **mammals**, there are **two** sex chromosomes:
  - a larger **X** chromosome
  - a smaller **Y** chromosome

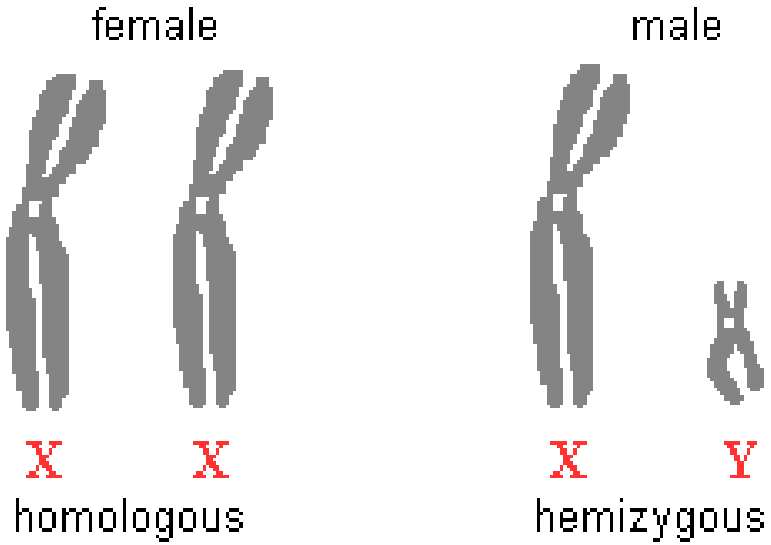



- The ***SRY* gene** (***S****ex-determining* ***r****egion* ***Y***) on the **Y** chromosome codes for a protein that directs the development of **male anatomical features.**

# X and Y Chromosomes








## Sex-Linked Genes

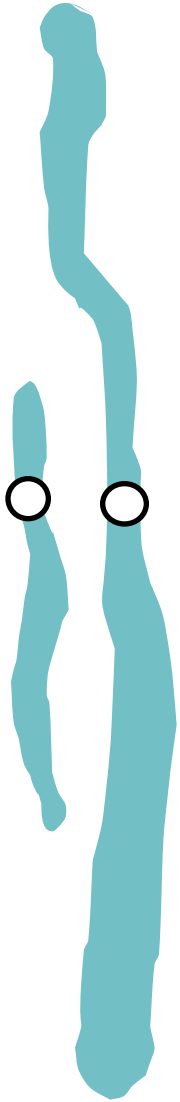
- Genes unrelated to gender on the **X** chromosome.
- Females have **two X** chromosomes (so they can be heterozygous or homozygous for each of these genes)
- Males have **one copy** of the sex-linked genes. Thus, the male is referred to as **hemizygous**.

**X** = 900-1600 genes
**Y** = 70-200 genes

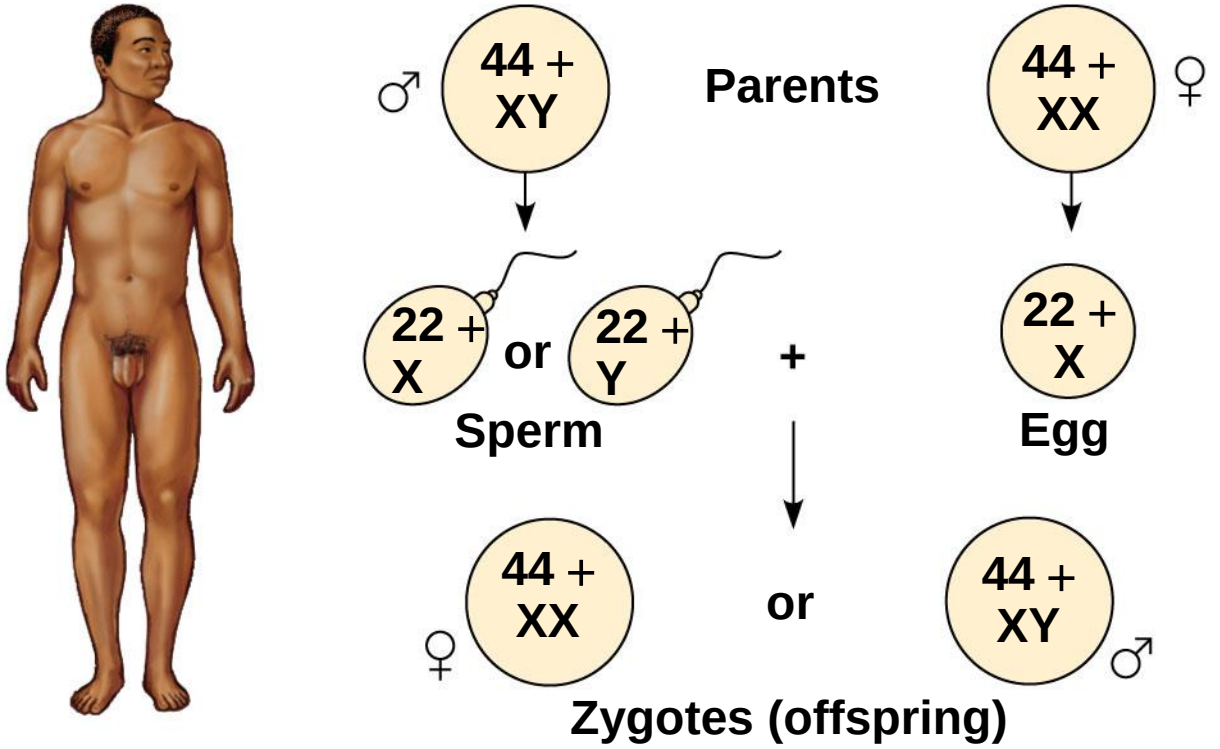
# Sex linkage

## X and Y are homologous chromosomes

- X and Y are an **exception** to the homology definition.
- Human **X**-chromosome is larger than **Y** and has about **2000** genes compared to about **450**.
- X and Y are homologous because they pair up during meiosis I.
- Pairing is due to a small area of homology around the centromere.



- The Y-chromosome lacks many genes found on its homologous X-chromosome.
- This leads to a pattern of inheritance called **sex linkage**.
- In XX females, a recessive allele on one X can be masked by a dominant allele on the other X.
- In XY males, a recessive allele on the X has no second copy to mask its effects.




(a) The X-Y system


(b) The X-0 system



**Other animals have different methods of sex determination.**

Sex chromosome composition in birds, butterflies, moths and some fish is opposite that of mammals, with the male the homogametic sex (**ZZ**) and the female heterogametic (**ZW**). Z-linked genes behave like X-linked genes in mammals, but the sexes are reversed.

76 + ZW ♀

76 + ZZ ♂

**(c) The Z-W system**

32 (Diploid) ♀

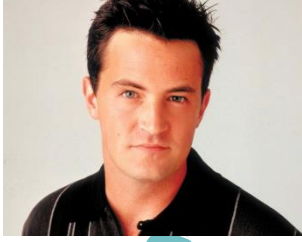
16 (Haploid) ♂

**(d) The haplo-diploid system**

# Sex Determination Chart

Not every animal has the same sex chromosomes.

| Type | Example | Male | Female | Homogametic | Heterogametic |
|---|---|---|---|---|---|
| XY | Humans & Fruit Flies | XY | XX | Female | Male |
| 2N/ N | Bees | N | NN | Male and Female | -- |
| XO | Grasshopper | XO | XX | Female | Male |
| ZW | Birds | ZZ | ZW | Male | Female |
| ZO | Chickens | ZZ | ZO | Male | Female |



# Chromosomal sex determination

## SRY gene

- Default setting for human embryonic development is to become female (hence male nipples!).
- Y-chromosome has a gene called SRY (**S**ex determining **R**egion of **Y**-chromosome).
- SRY controls the development of male genitalia and male characteristics.
- SRY is a ‘master switch’ which produces a transcription factor to switch on other genes.
- Many of these genes are on the autosomes but are only transcribed in males due to SRY control.
- XX male due to SRY translocated to X-chromosome.
- XY female due to SRY deleted from Y-chromosome.

# Environmental sex determination

## Temperature affects sex ratio in reptiles

- In turtles and crocodiles, the level of expression of some genes is affected the temperature during a sensitive period in development.
- For some reptiles, there is trend in the effect of temperature on the sex ratio.
  - In Hermann's Tortoises, below 31°C is all males and above 32°C is all females.
- In other reptiles, the extremes cause the production of one sex while the intermediate temperature produces the other sex.
  - In Mississippi Alligators, males only develop at 32–34°C while females are produced at temperatures below 32°C and above 34°C.

- A gene that is located **on either** sex chromosome is called a **sex-linked gene.**

- Genes on the **Y** chromosome are called **Y**-linked genes; there are **few** of these.

- Genes on the **X** chromosome are called **X-linked genes** (there are many genes)

# Inheritance of X-linked Genes

- **X** chromosomes have genes for **many** characters **unrelated to sex**, whereas the **Y** chromosome mainly encodes genes related to sex determination.
- **X**-linked genes follow specific patterns of inheritance
- **For a recessive X-linked trait to be expressed**
  - A female needs two copies of the allele (**homozygous**)
  - A male needs only **one copy** of the allele (**hemizygous -** have no allelic counterparts)**
- **X-linked recessive disorders** are much more **common** in **males** than in **females**

- Some **disorders** caused by recessive alleles on the **X** chromosome in humans
  - Color blindness (mostly **X**-linked)
  - **Duchenne muscular dystrophy**
  - **Hemophilia**

# X - Inactivation in Female Mammals

- In mammalian females, **one** of the two **X** chromosomes in each cell is **randomly inactivated** during **embryonic** development.

  = NOT PARMANENTLY =

- The inactive **X** condenses into a **Barr body.**

# Dosage compensation

## X-chromosome inactivation

- Males are **heterogametic** (with only one X-chromosome) while females are **homogametic** (two X-chromosomes).
- Despite this, female cells do not have a **double-dose** of gene products from their X-chromosomes.
- In females, one X-chromosome is **partially inactivated** early in embryonic development.

- The regions inactivated are those that are lacking on Y-chromosome.

  (Deacetylation of histones, methylation of bases.)

- The inactivated X-chromosome shows up as a highly condensed region on the inside of the nuclear membrane – a **Barr body**.

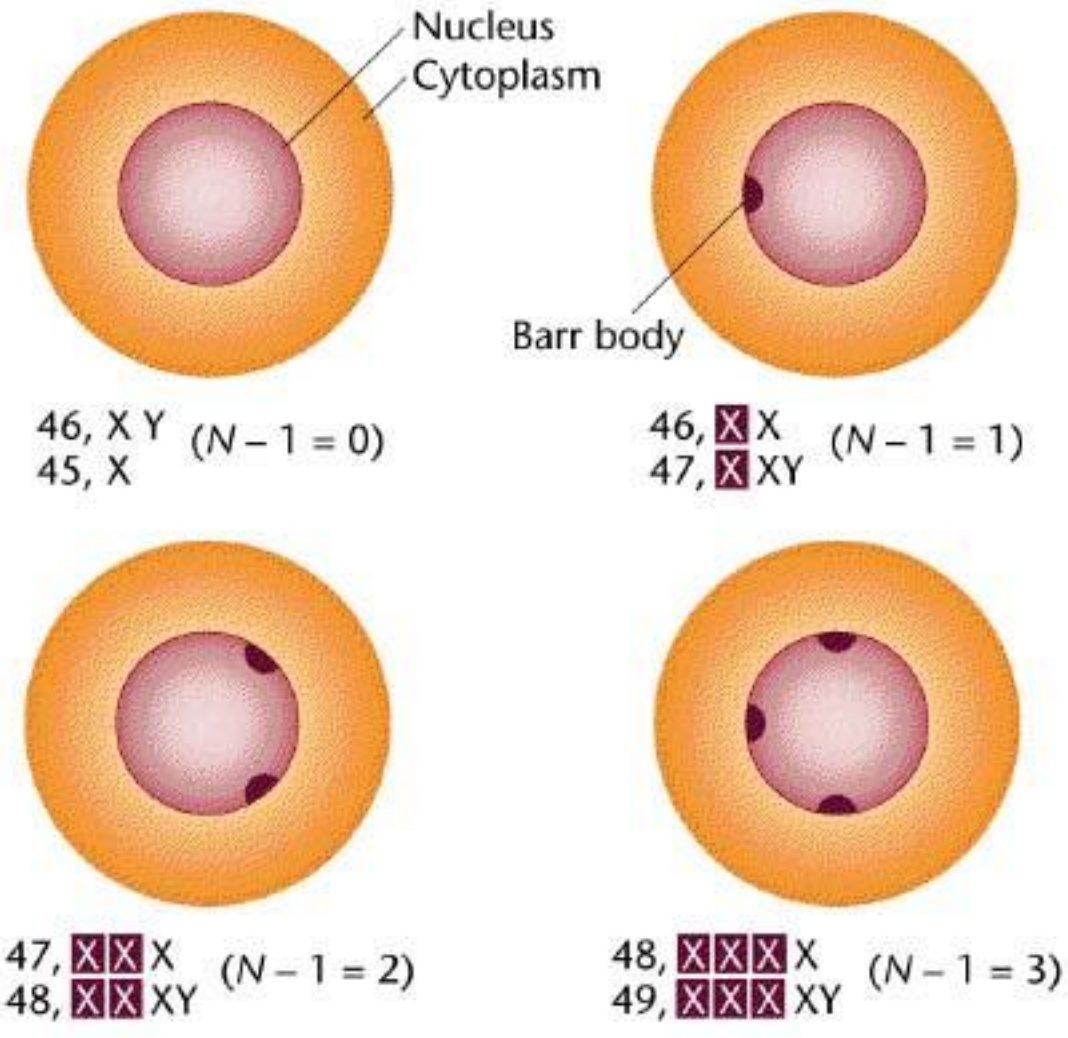
# Dosage Compensation

- Shouldn't **XX** females produce **twice** the amount of **X**-linked gene products as **XY** males?

No!=

- Because **XX** females "**compensate**" by **inactivating** one of their **X** chromosomes to make a **single** "dosage" of **X**-linked genes.

# **Barr Bodies** are **Inactivated X** Chromosomes in Females

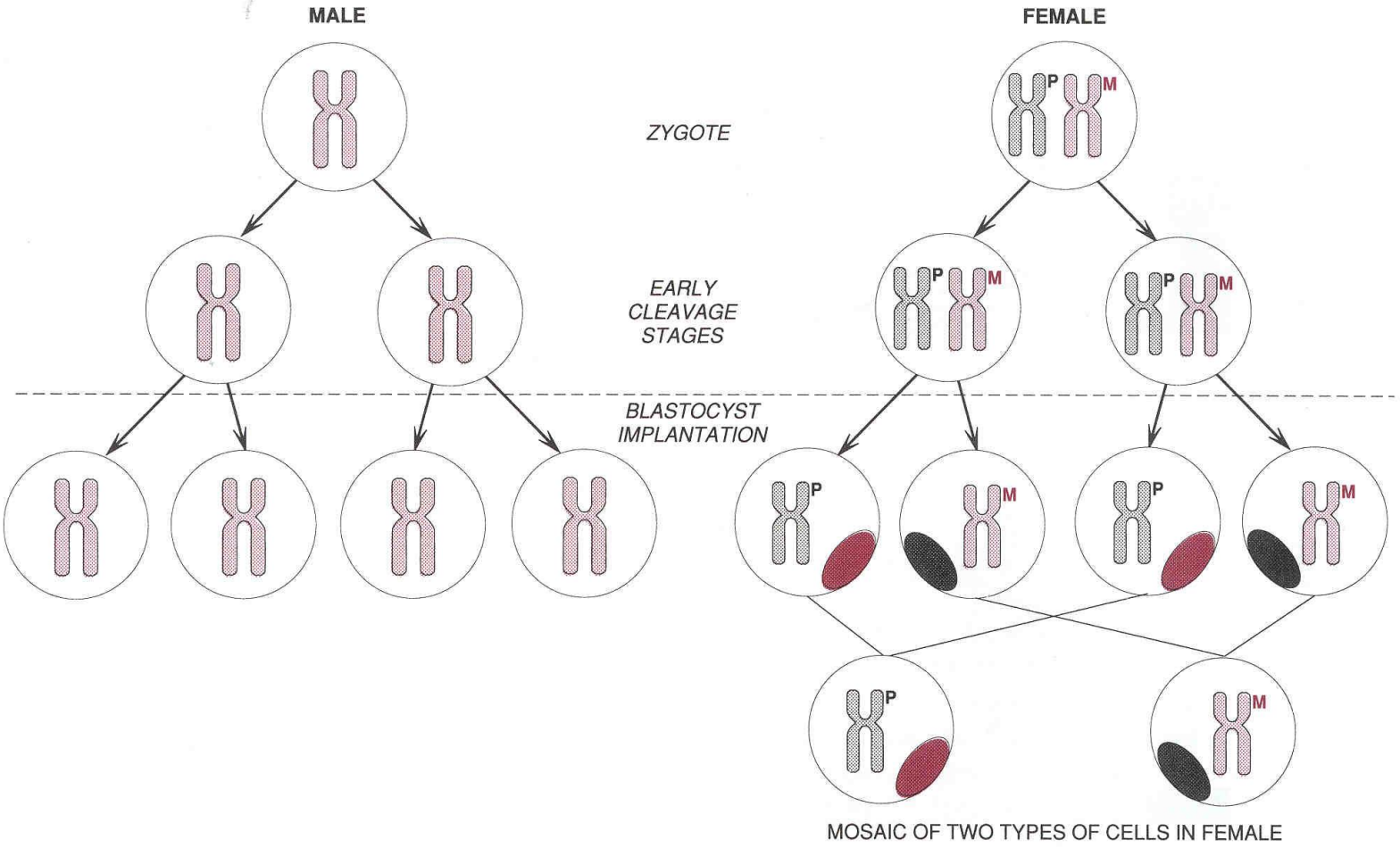


# The Lyon Hypothesis of X Inactivation

- Proposed by **Mary Lyon** and **Liane Russell** (**1961**)
- **Inactivation** of **X** chromosome occurs **randomly** in somatic cells during **embryogenesis**.
- Progeny of the embryonic cells bearing the inactivated **X** chromosome all have same inactivated as original, creating **mosaic** individual

**NB :** **X**-inactivation is **reversed** in the **female germline**, so that all oocytes contain an active **X** chromosome.

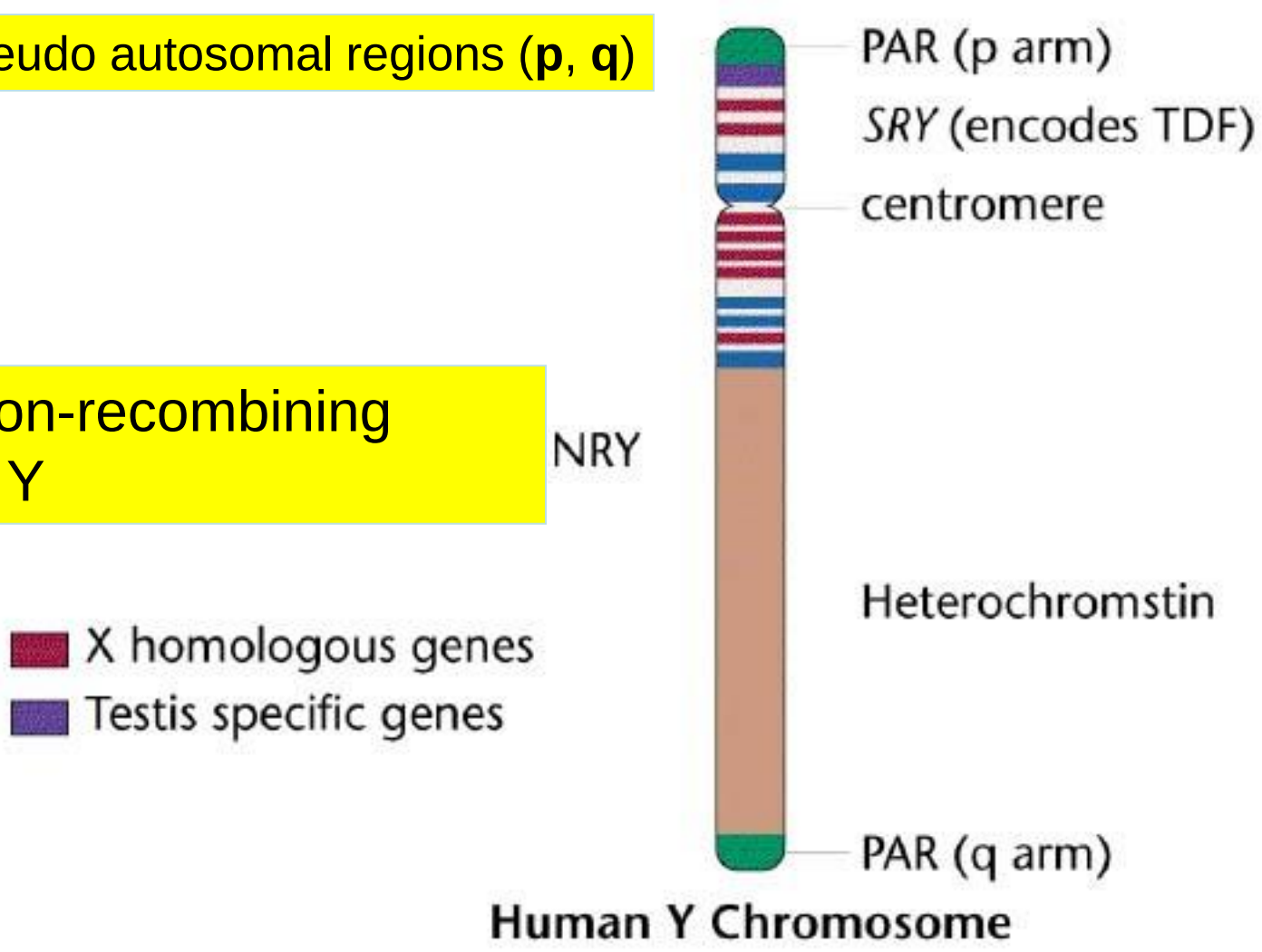
# X-inactivation



# The Human Y Chromosome

**PAR** – Pseudo autosomal regions (**p**, **q**)

**NRY** is non-recombining region of Y

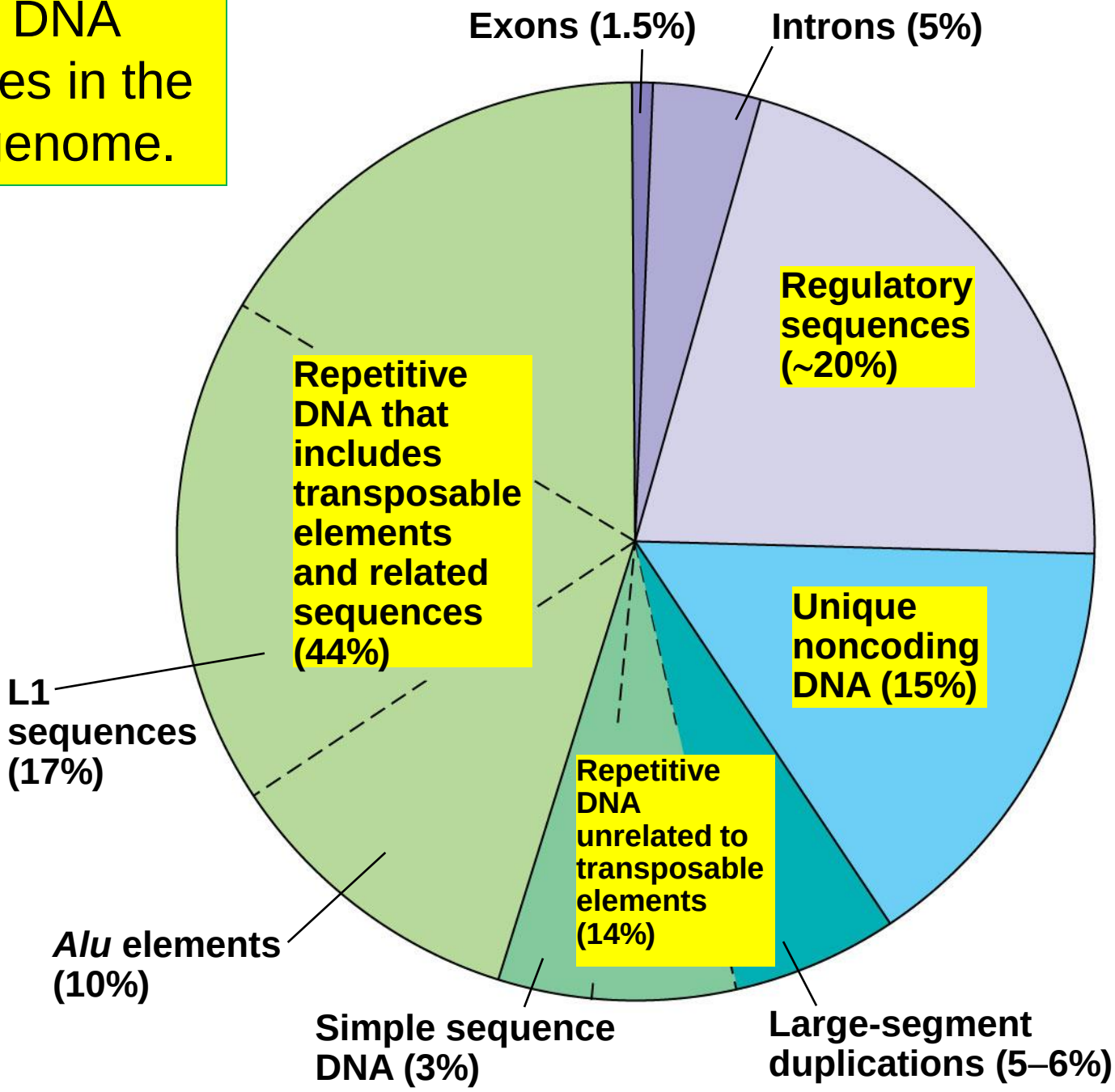



Human Y Chromosome

# The Human genome...

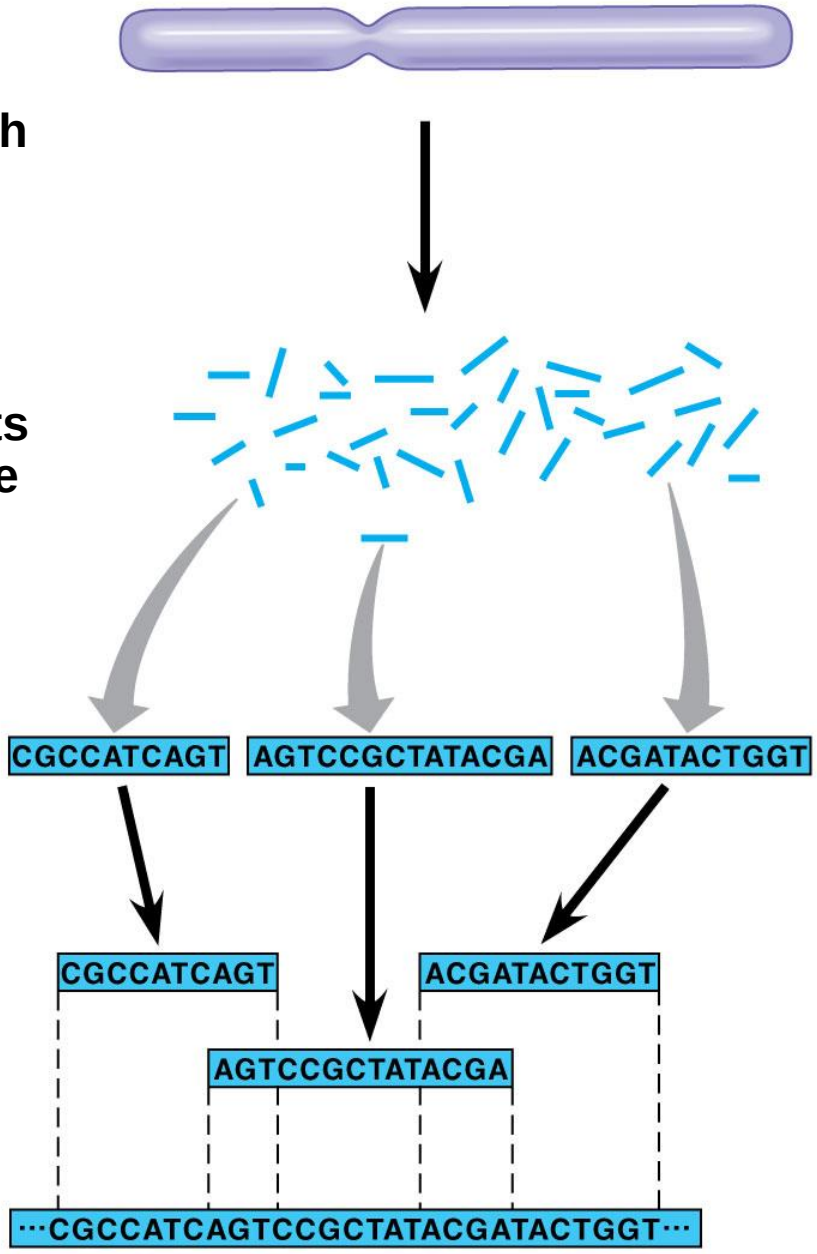
- **3 billion** base pairs
- about **30000+** genes
- **23** chromosome pairs → **46** chromosomes
- **25 %** of the DNA is gene related
- Only **5 %** encodes proteins
- Genes include **exons** and **introns** – **split genes**
- Beside coding sequences also additional secuences are found

Types of DNA sequences in the human genome.



Scientists use bioinformatics to analyze genomes and their functions

1. Cut the DNA into overlapping fragments short enough for sequencing.
2. Clone the fragments in plasmid or phage vectors.
3. Sequence each fragment.
4. Order the sequences into one overall sequence with computer software.






Whole-genome shotgun approach to sequencing.

# Variations of chromosome number or structure

Cause some genetic disorders

- **Large-scale chromosomal alterations in humans and other mammals often lead to spontaneous abortions (miscarriages) or cause a variety of developmental disorders.**

# (A) Variations in Chromosome Number (PLOIDY)

**When the number deviates from wild type (especially in animals), this is chromosomal mutations.**

1. **EUPLOIDY**: An organism or cell is **euploid** when it has one complete set of chromosomes, or exact multiples of complete sets.

**(2*n*, 3*n*, 4*n* …) of the normal haploid (*n*)chromosomal number**

- **In an organism, the polyploidy (euploidy) can arise from two main types:**

**(i) Autopolyploidy**

» The multiplication of one basic set of chromosomes (are derived from within a **single species** ).

**(ii) Allopolyploidy**

» The combination of genetically distinct, but similar chromosome sets.(arise via hybridization between **two species**).

**{CAUSED by**: Nondisjunction during meiosis and mitosis**}**

# Variations in Chromosome Number (PLOIDY)

*cont.*

2. **ANEUPLOIDY:** Results from variations in the number of individual chromosomes (not sets), so that the chromosome number is NOT an exact multiple of the haploid set of chromosomes.

ie **Gain** or **Loss** of less than a complete set of haploid chromosomes

# Types of Aneuploidy

- **Nullisomy:** loss of both members of a homologous pair of chromosomes. ***2n* − 2**
- **Monosomy:** loss of a single chromosome. ***2n* − 1**. zygote has only one copy of a particular chromosome instead of two (**diploid**)
- **Trisomy:** gain of a single chromosome. ***2n* + 1**. zygote has **three copies of a particular** chromosome instead of two (**diploid**)
- **Tetrasomy:** gain of two homologous chromosomes.

  ***2n* + 2**

**Offspring with this condition have an abnormal number of a particular chromosome.**

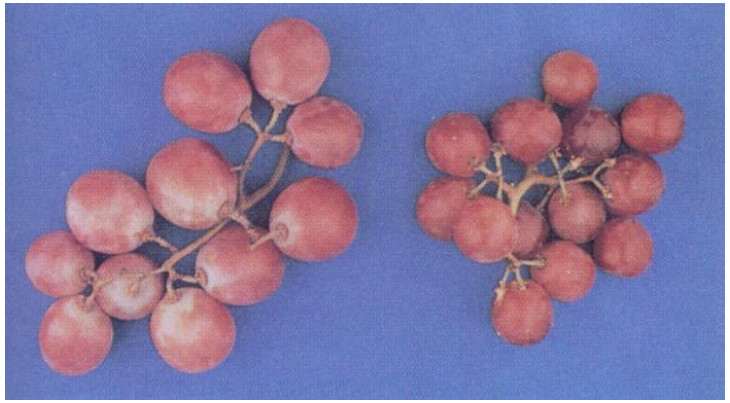
# Causes of Aneuploidy:

- ✓ Deletion of centromere during mitosis and meiosis.
- ✓ Robertsonian translocation.
- ✓ Nondisjunction during meiosis and mitosis.

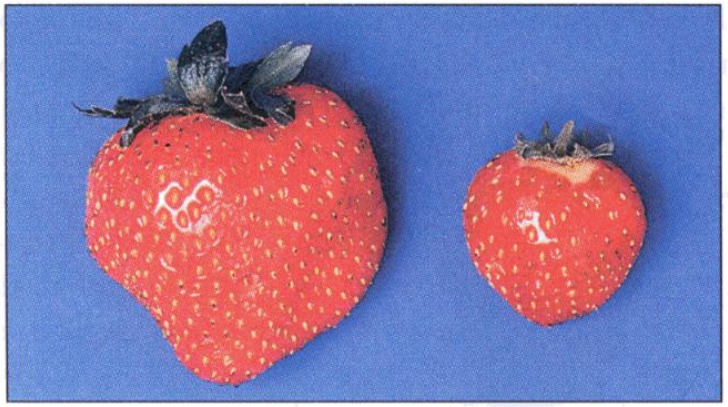
# Autopolyploidy (euploidy) Applications

**NB**: Polyploidy is **common in plants**, but not animals. **Plants tolerate** such genetic changes better than animals do.

- Treating a plant with **colchicine** often produces **autopolyploidy**, resulting in plants with larger flowers and/or fruit,

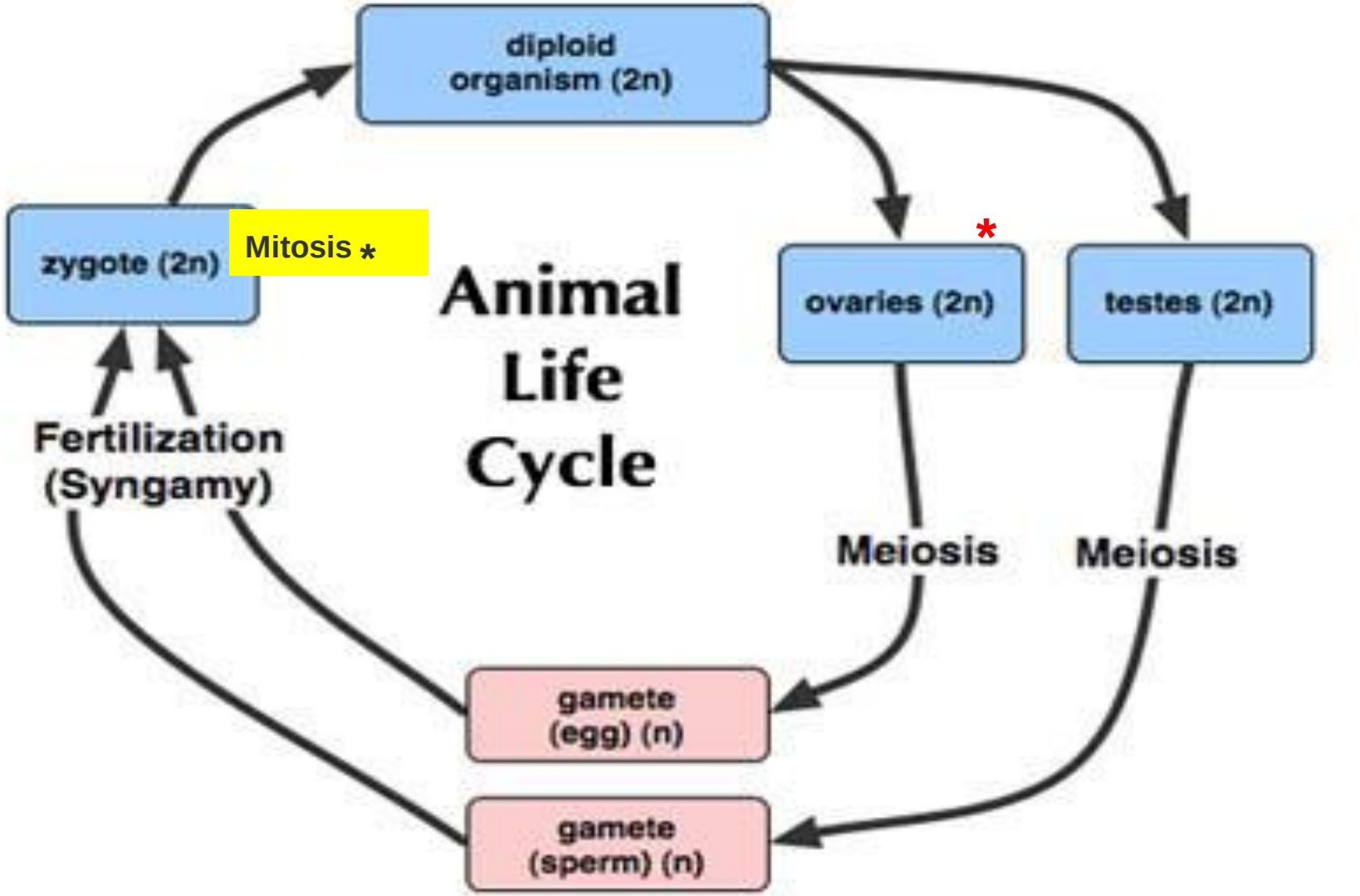


*4n* *2n*



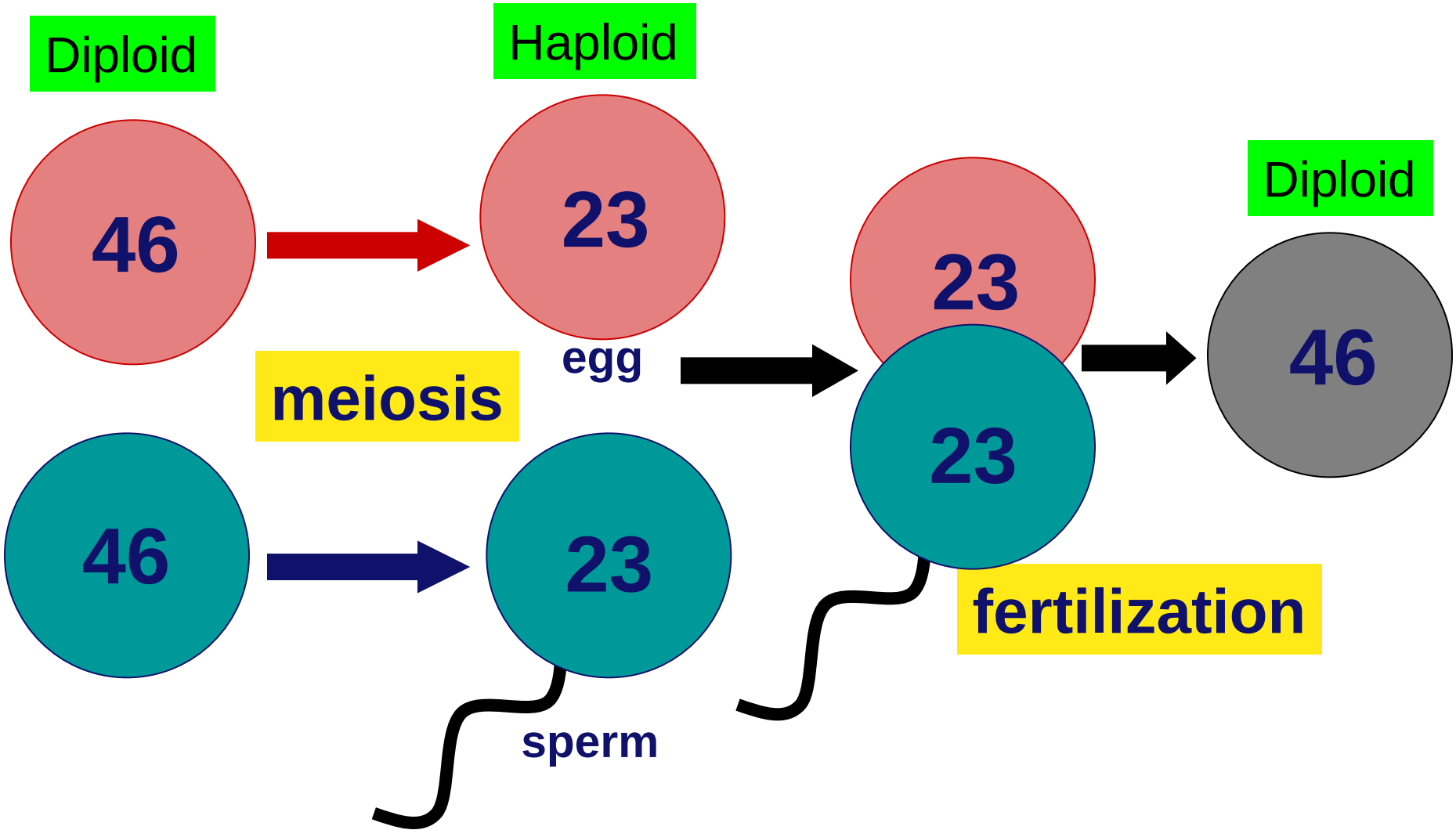
*8n* *2n*

# Meiosis & Sexual Reproduction: Life Cycle



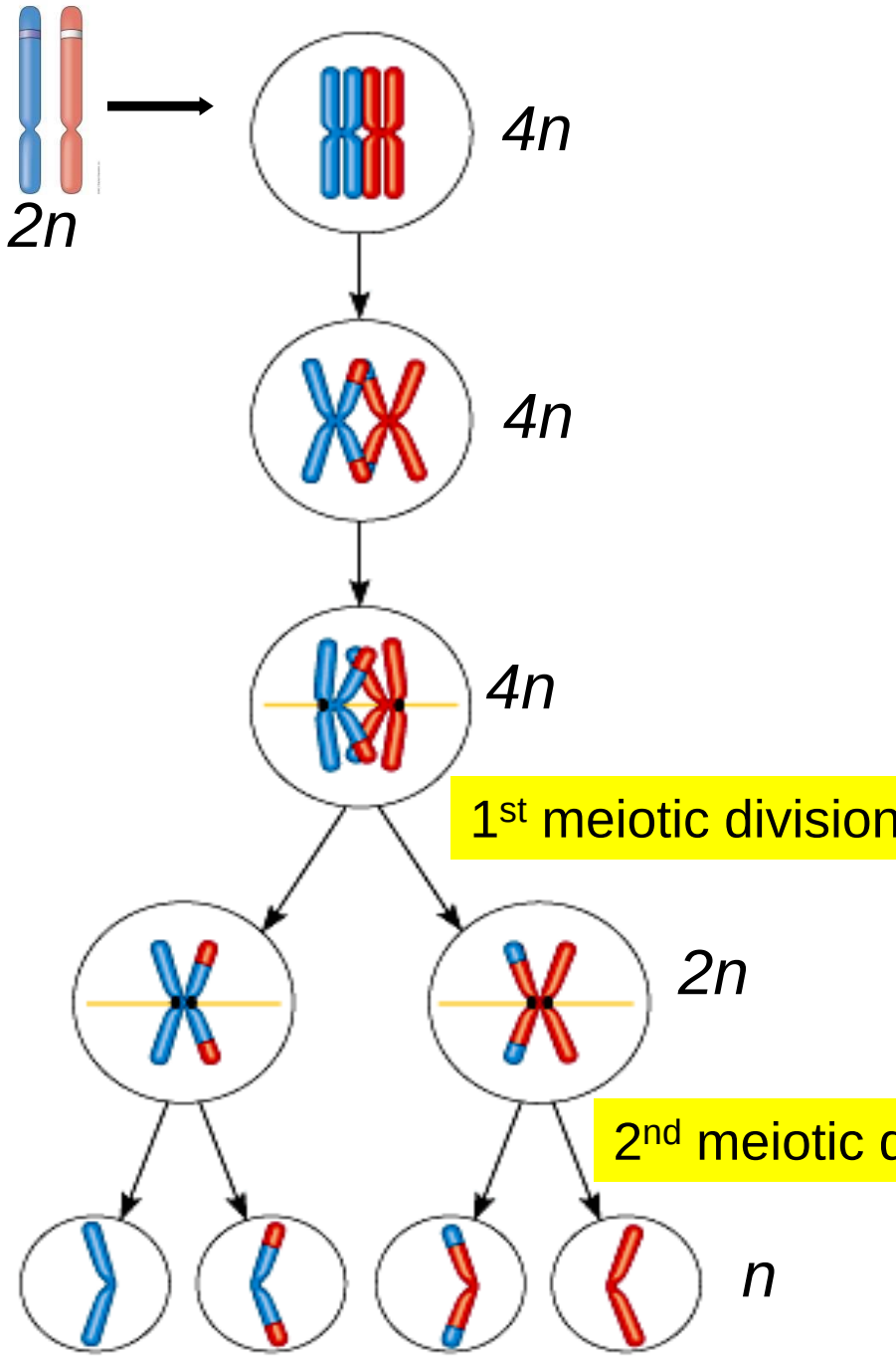
# Sexual reproduction

- Reduce **46** chromosomes → **23** chromosomes
  - **halves** the number of chromosomes

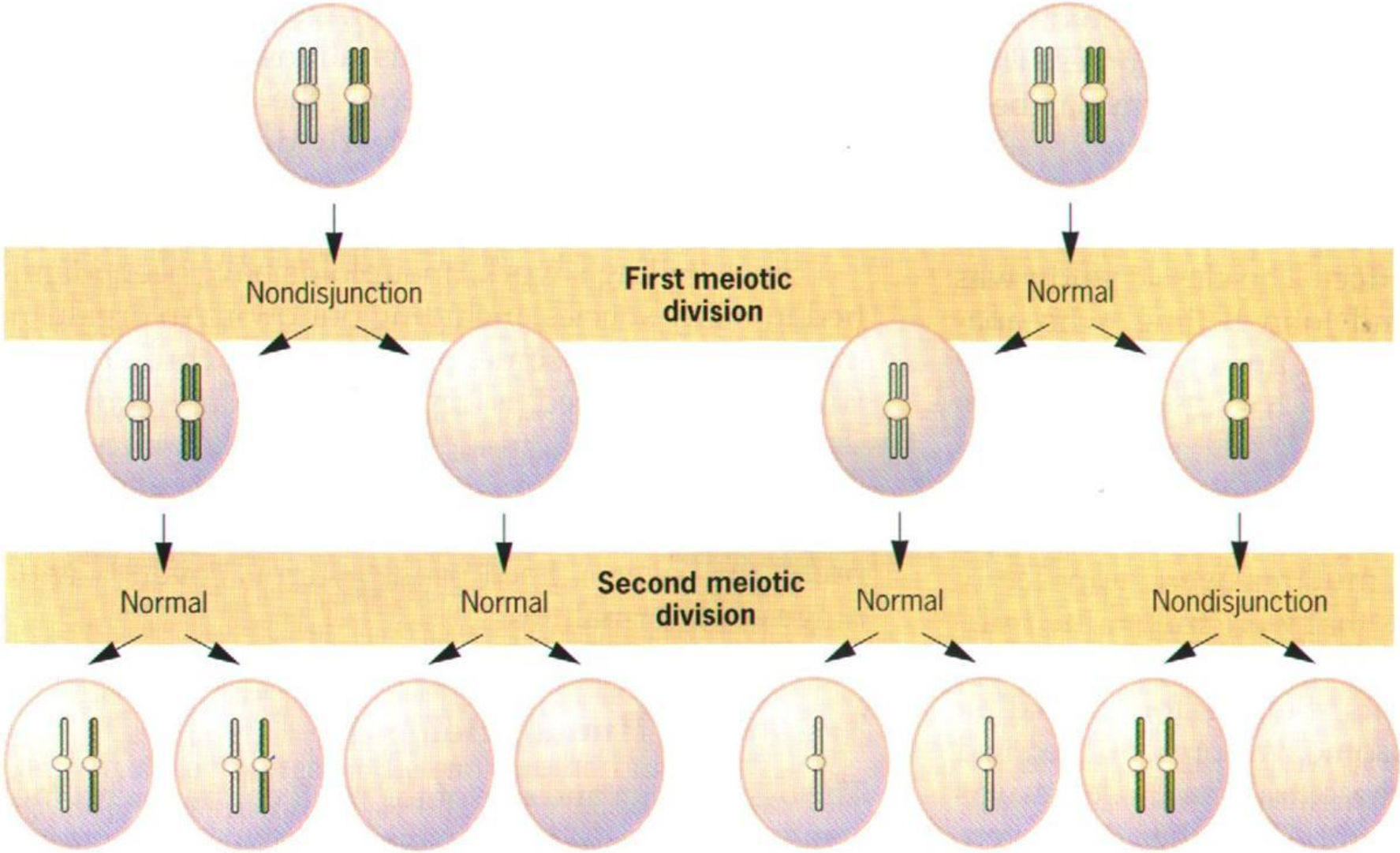


# Crossing over

- **During Prophase 1**
  - homologous pairs swap pieces of chromosome
  - sister chromatids intertwine
  - crossing over



# Effect of Nondisjunction




**Nondisjunction** of homologous chromosomes in meiosis I

**Non-disjunction** of sister chromatids in meiosis II

# Mitosis *vs* Meiosis

- **Mitosis**
  - **1** division
  - daughter cells genetically **identical** to parent cell
  - produces **2 cells**
  - 2n → **2n**
  - produces **cells for growth & repair**
  - no crossing over

- **Meiosis**
  - **2** divisions
  - daughter cells genetically **different** from parent
  - produces 4 cells
  - 2n → **1n**
  - produces **gametes**
  - **crossing over**

**Mutations**

- Mutation – sudden **genetic change** (change in **base** pair sequence of **DNA**)
- Can be :

  **Harmful** mutations – organism **less able** to survive: genetic disorders, cancer, death

  **Beneficial** mutations – allows organism to **better survive**: provides **genetic variation**

  **Neutral** mutations – **neither** harmful nor helpful to organism
- Mutations can occur in 2 ways: **chromosomal** mutation or **gene/point** mutation

**Chromosomal mutation:**

- **less common** than a gene mutation
- more **drastic** – affects entire **chromosome**, so affects **many genes** rather than just one
- caused by failure of the **homologous** chromosomes to **separate** normally during **meiosis**
- **chromosome pairs** no longer look the same – too few or too many genes, different shape

- Having an **extra set** of chromosomes is **fatal** in **animals**, but in **plants** it makes them **larger** and **hardier**.

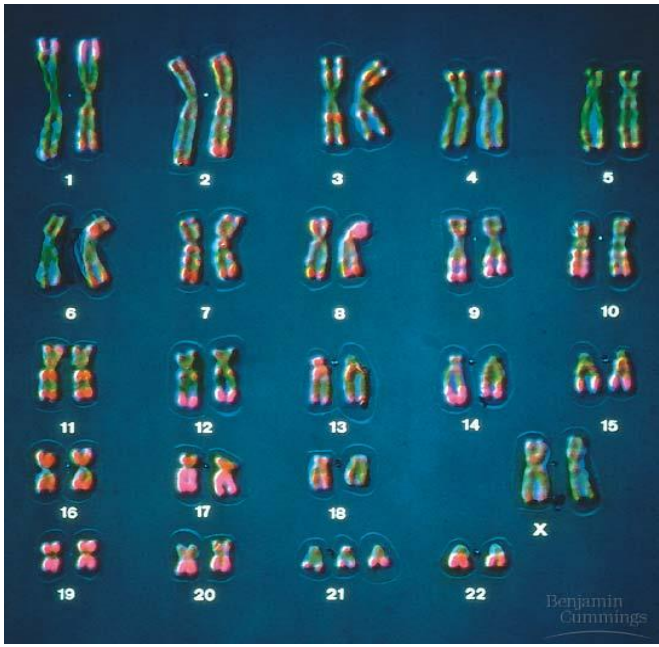
# Human Disorders Due to Chromosomal Number Alterations

- Alterations of chromosome number and structure are associated with some **serious disorders**.
- Some types of **aneuploidy** appear to upset the genetic balance less than others, resulting in individuals surviving to birth and beyond.
- These surviving individuals have a set of **symptoms**, or **syndrome**, characteristic of the type of aneuploidy.

- These abnormalities are caused by errors in the number or structure of chromosomes.
- Many children with a chromosomal abnormality have mental and/or physical birth defects.
- Some chromosomal abnormalities result in miscarriage or stillbirth.
- 50% of spontaneous abortion are chromosomal abnormal.

# *(i) Down Syndrome (Trisomy 21) [47, XX +21 ]*

- Delayed mental and social skills
- Decreased muscle tone at birth
- Asymmetrical or odd-shaped skull
- Small skull
- Small mouth with protruding tongue
- Broad short hands
- Increased risk of developing Leukemia and Alzheimer's later in life
- It affects about **one** out of every **700** children born in the United States.



# Effects of Aneuploidy in Humans

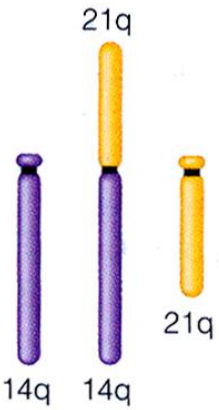
- **Autosomal aneuploids:**
  - **a)** **Autosomal monosomies** - are rarely found in humans, presumably because they are lost early in pregnancy.
  - **b)** **Autosomal trisomies** - account for about half of fetal deaths, and only a few are seen in live births. Most (trisomy-8, -13 and -18) result in early death, with only trisomy-21 (Down syndrome) surviving to adulthood.

## Down syndrome

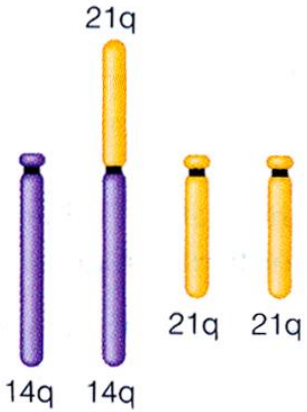
- Trisomy 21 is responsible for **Primary Down syndrome**, 75% random nondisjunction in egg formation
- **Familial Down syndrome**, Robertsonian translocation between chromosomes **14** and **21**

# Familial Down Syndrome


**a** Normal karyotype: two copies of 14q, two copies of 21q.

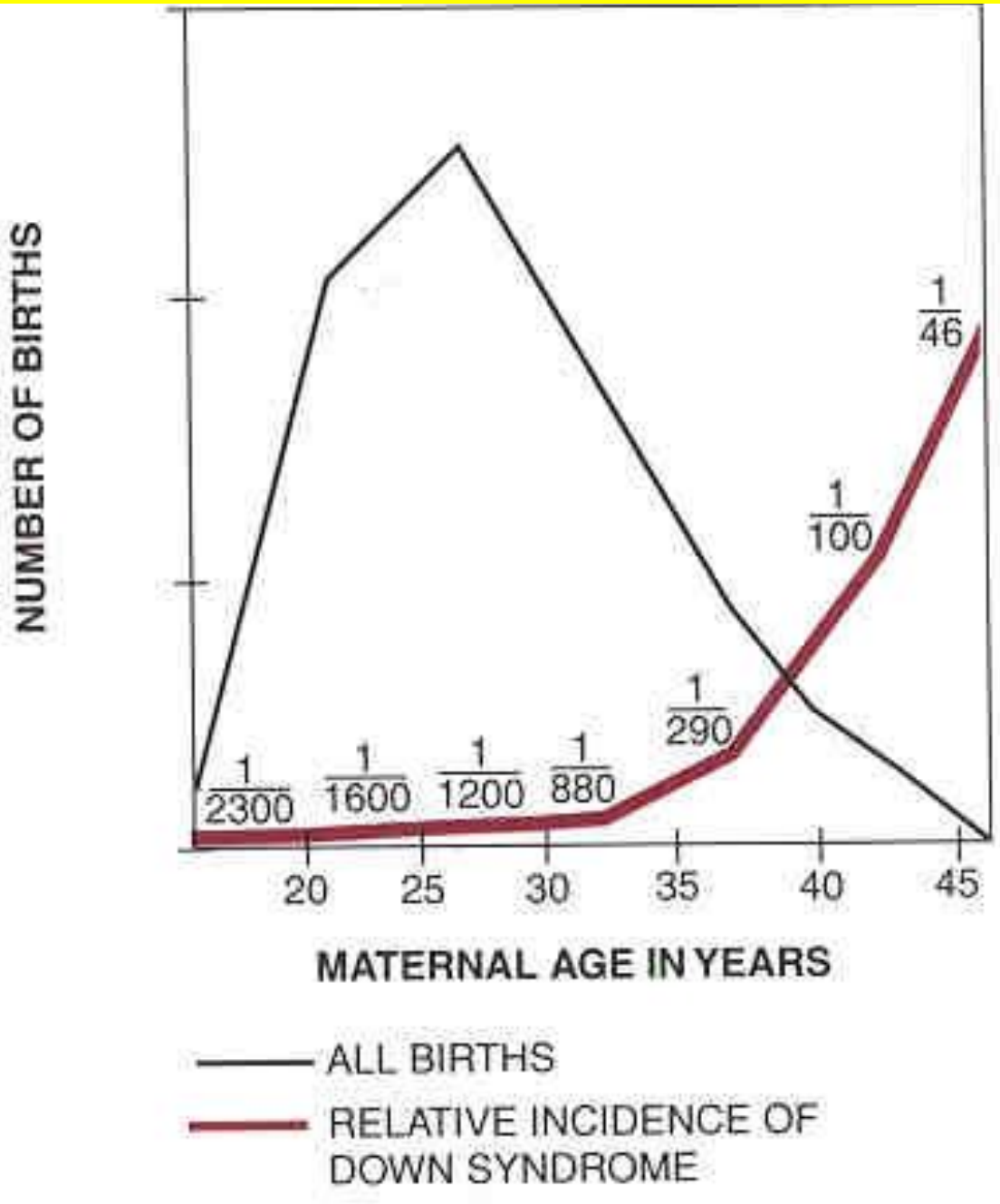



**b** Balanced translocation carrier: two copies of 14q, two copies of 21q.




**c** Translocation Down syndrome (trisomy 21q): two copies of 14q, three copies of 21q.

# Down syndrome - maternal age effect:



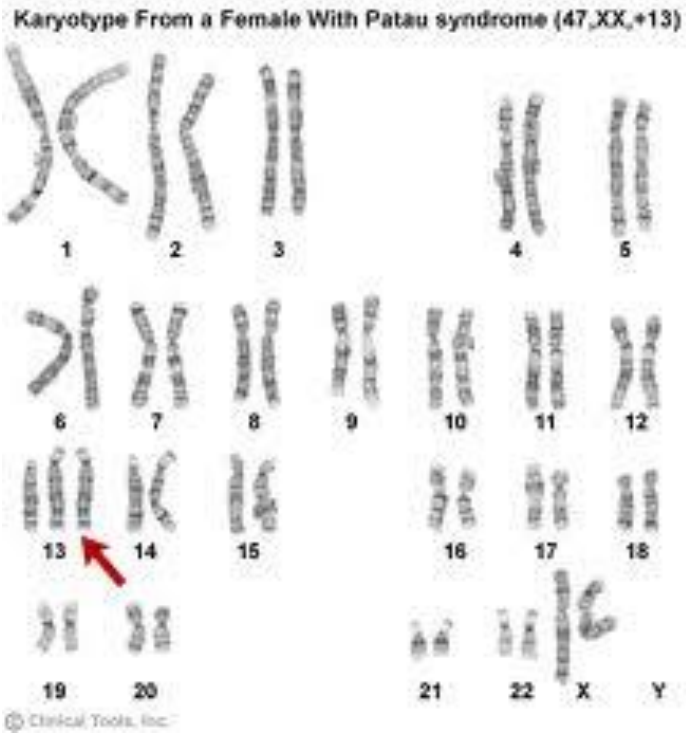

**A woman's chances of giving birth to a child with Down syndrome increase with age because older eggs have a greater risk of improper chromosome division. This association is because a woman?s eggs are as old as she.**

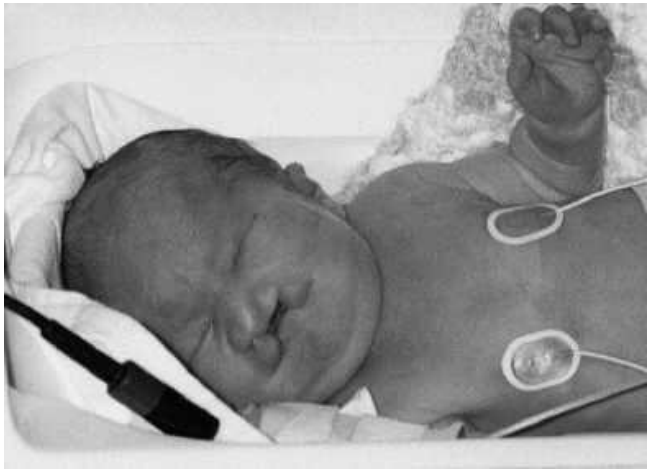
**Females have all of their eggs in the fetal stage therefore they are born with all the eggs they will have in their lifetime.**

**In males, sperm is made every 65-75 days therefore the sperm is not as old as the man.**

# Trisomy 13 : Patau Syndrome

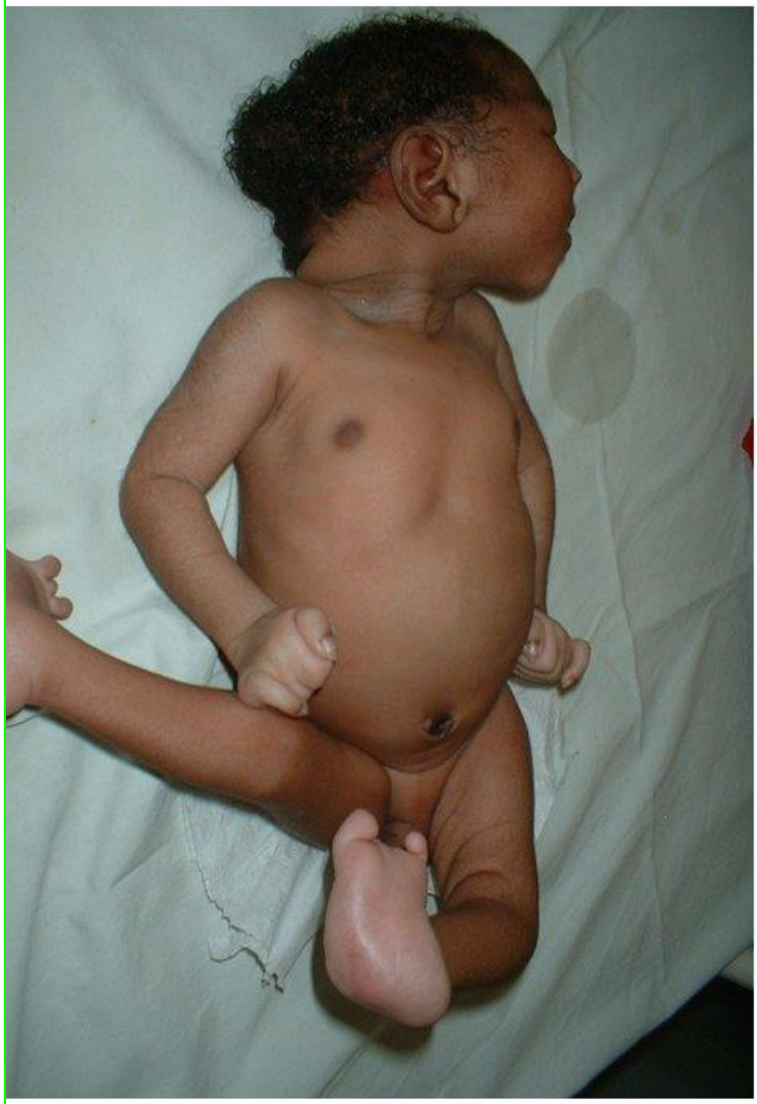
- Mental retardation, severe
- Seizures
- Small head
- Scalp defects
- Cleft lip and/or palate
- Eyes close set (hypotelorism) – may fuse
- Extra digits (**polydactyl**)
- Hernias
- Undescended testicle
- Children die in the first year of life



# Trisomy 18 : Edward's Syndrome

- Most children die in the first year of life, some have lived 10 years
- Fetuses identified with Trisomy 18 are often miscarried or aborted
- Growth deficiency
- Feeding difficulties
- Breathing difficulties
- Developmental delays
- Mental Retardation
- Overlapped, flexed fingers
- Webbing of the second and third toes
- Clubfeet
- Structural heart defects at birth



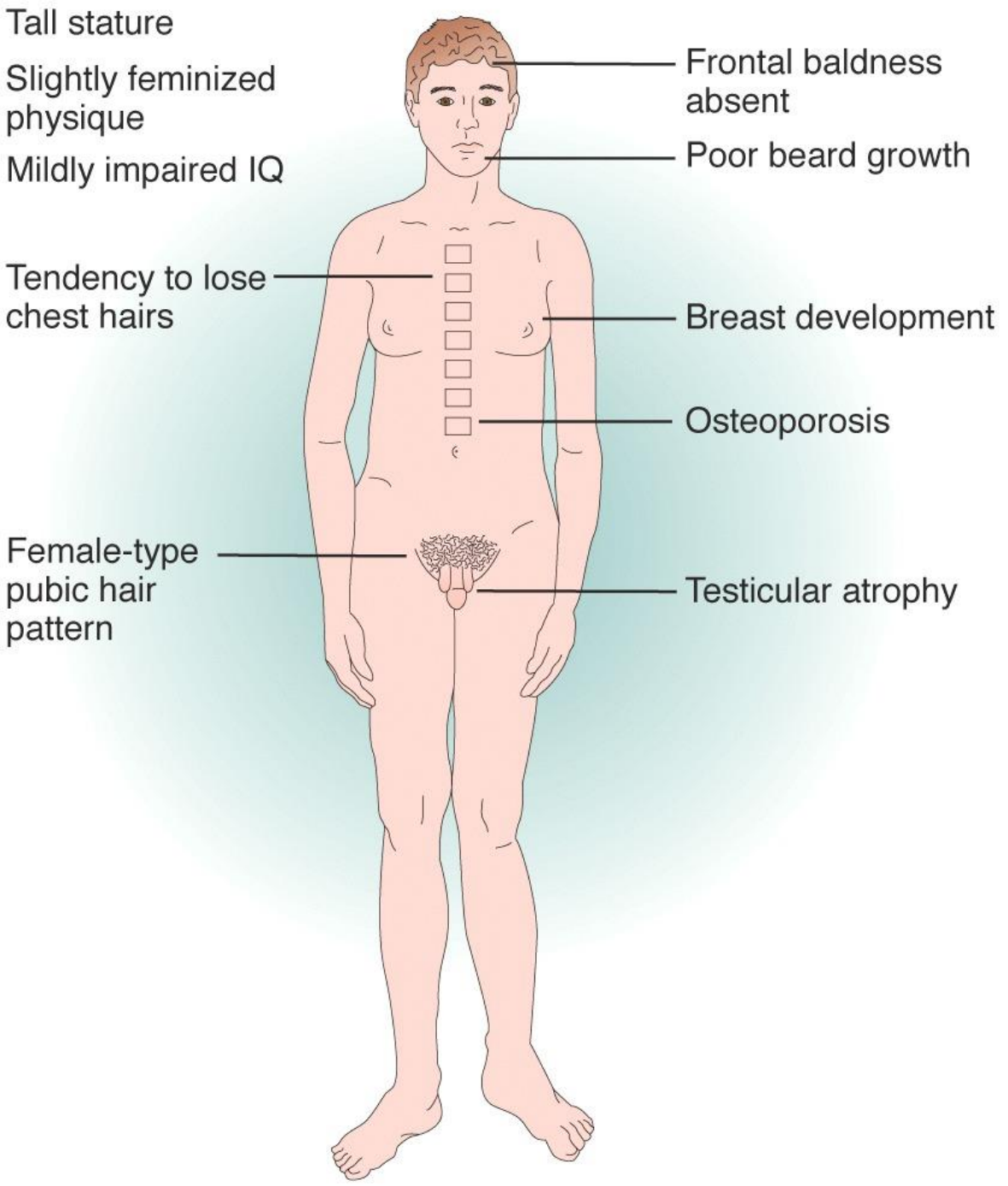
# *Aneuploidy of Sex Chromosomes*

- Nondisjunction of sex chromosomes produces a variety of aneuploid conditions. E.g.
  - **Klinefelter syndrome**
  - ***Turner syndrome***
  - **Sex chromosome aneuploidy is found more often than autosome aneuploidy, because Lyonization compensates for chromosome dosage.**

**Klinefelter's** syndrome – **47** chromosomes, **extra X** chromosomes (XXY)

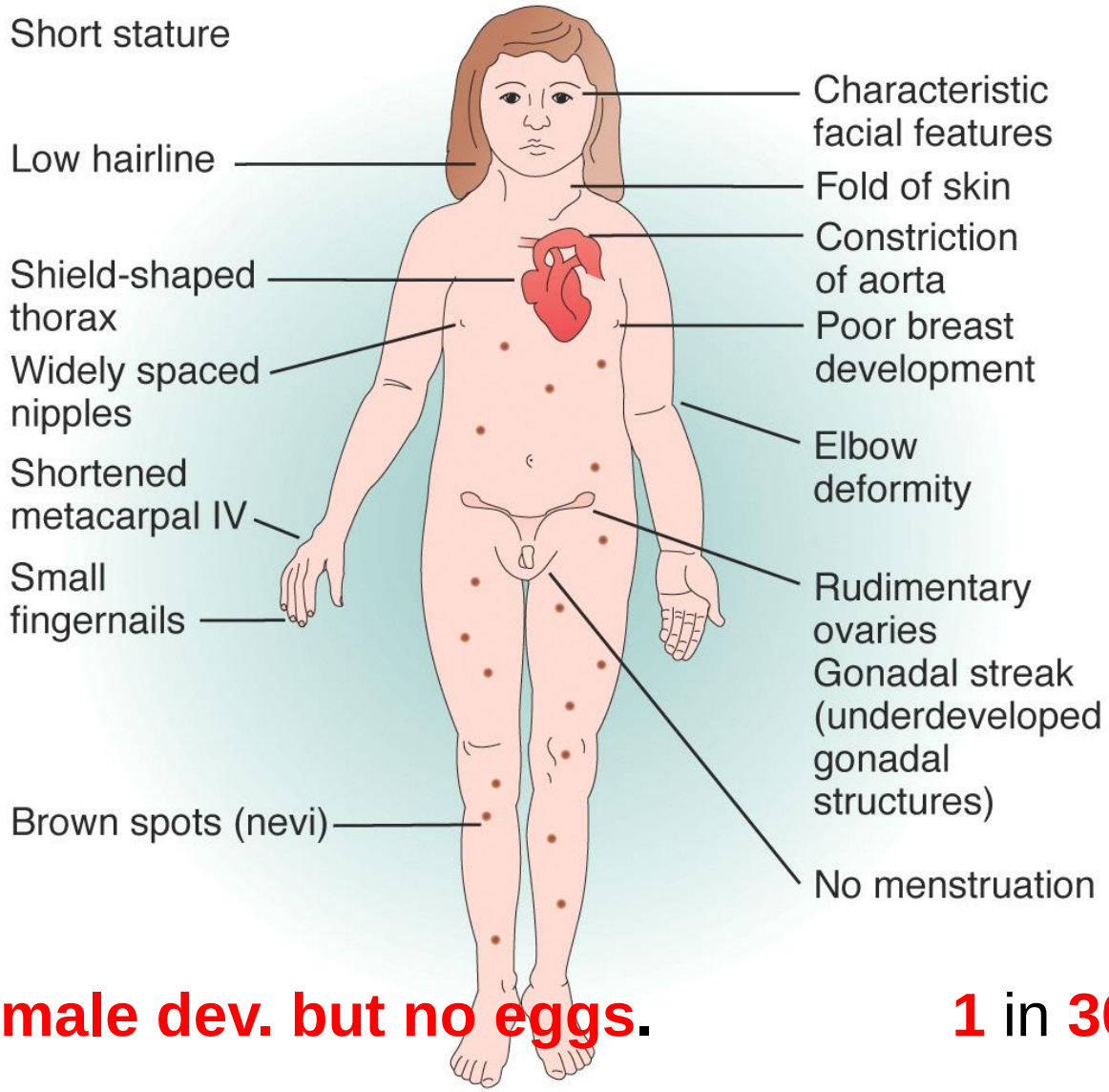
- **Boys** affected – low testosterone levels, underdeveloped muscles, sparse facial hair

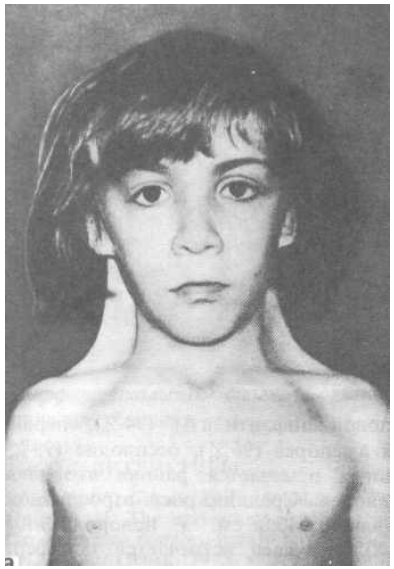
- **2** in **1000** male births



# (iii) Turner Syndrome (45, XO)

**Produces XO females, who are sterile; it is the only known viable monosomy in humans.**



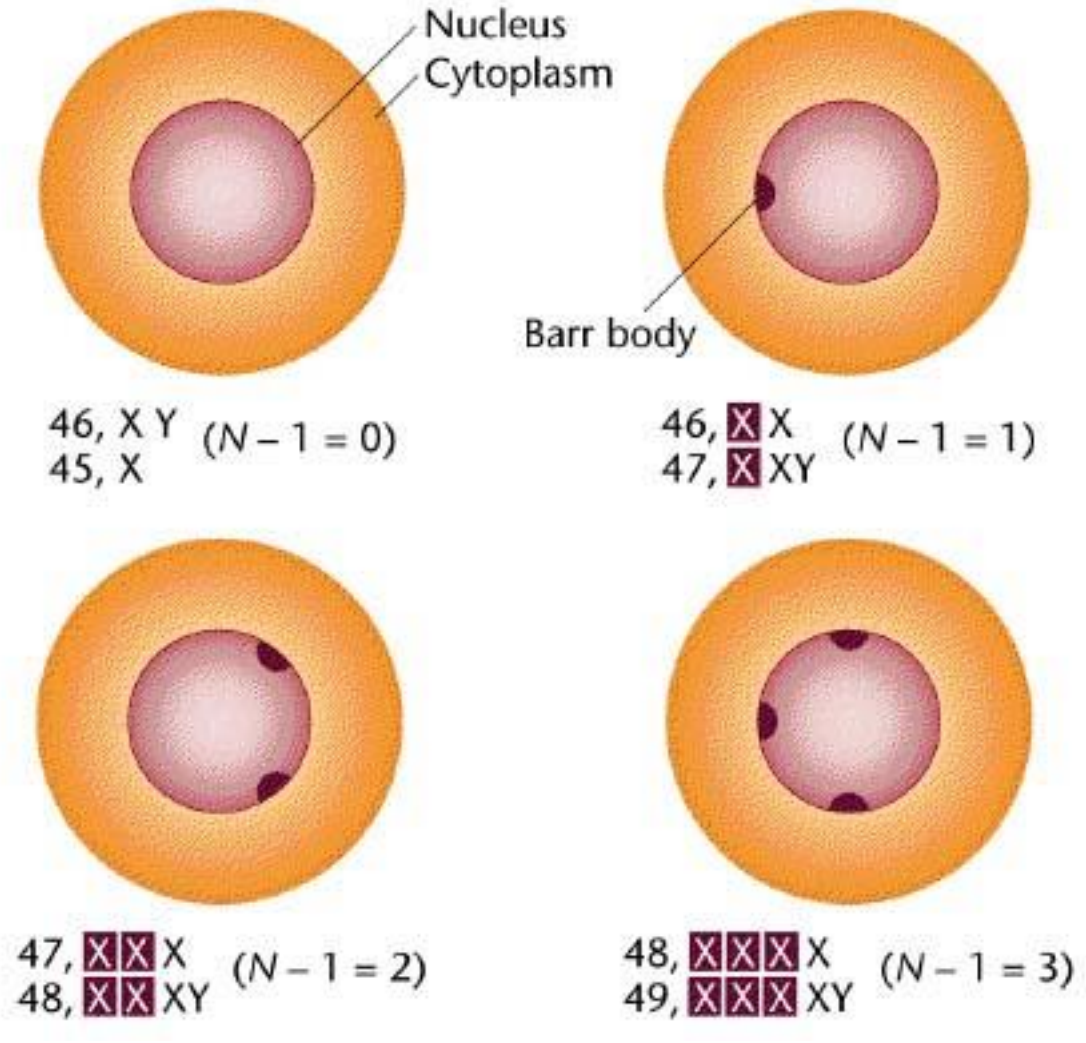



**Female dev. but no eggs.**

**1** in **3000** female births

# Barr Bodies are Inactivated X Chromosomes in Females

**&** in **Klinefelter syndrome**



# Cytological correlates of X-inactivation in mammals

Barr body:

- Present in **somatic XX** nuclei
- Not present in XY nuclei
- In X-chromosome aneuploids, all but one **X** become Barr bodies

| Females | Barr Bodies | Active X |
|---|---|---|
| XX | 1 | 1 |
| XO | 0 | 1 |
| XXX | 2 | 1 |
| XXXX | 3 | 1 |

| Males | Barr Bodies | Active X |
|---|---|---|
| XY | 0 | 1 |
| XXY | 1 | 1 |
| XXXY | 2 | 1 |

**Table 17-1** Chromosome Constitutions in a Normally Diploid Organism with Three Chromosomes (Identified as A, B, and C) in the Basic Set

| Name | Designation | Constitution | Number of chromosomes |
|---|---|---|---|
| ***Euploids*** | | | |
| Monoploid | *n* | A B C | 3 |
| Diploid | 2*n* | AA BB CC | 6 |
| Triploid | 3*n* | AAA BBB CCC | 9 |
| Tetraploid | 4*n* | AAAA BBBB CCCC | 12 |
| ***Aneuploids*** | | | |
| Monosomic | 2*n* – 1 | A BB CC | 5 |
| | | AA B CC | 5 |
| | | AA BB C | 5 |
| Trisomic | 2*n* + 1 | AAA BB CC | 7 |
| | | AA BBB CC | 7 |
| | | AA BB CCC | 7 |

**Table 17-1**
*Introduction to Genetic Analysis*, Tenth Edition

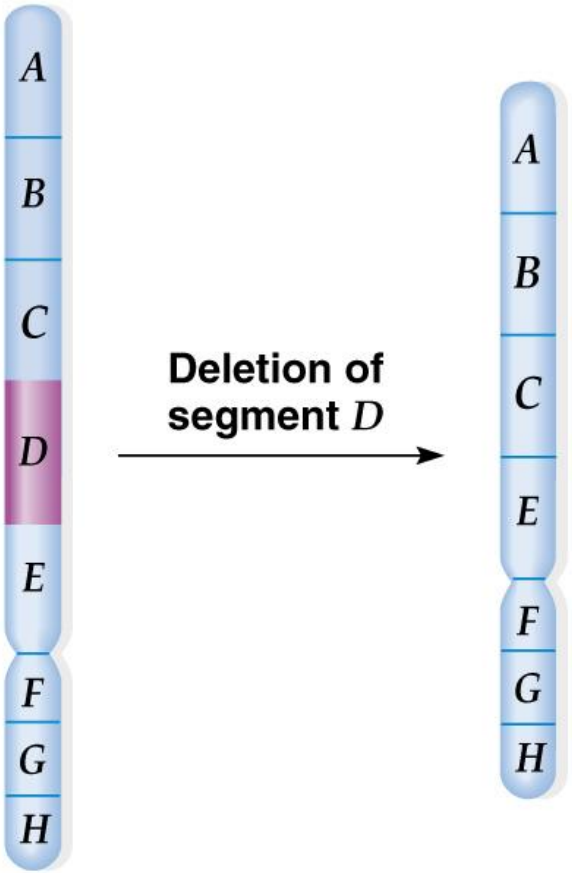
# Variations in Chromosome Structure

1. Mutations involving changes in chromosome structure occur in four common types:
   - ✓ **Deletions**.
   - ✓ **Duplications**.
   - ✓ **Inversions** (*changing orientation of a DNA segment*).
   - ✓ **Translocations** (*moving a DNA segment*).
2. All chromosome structure mutations begin with a **break** in the DNA, leaving ends that are not protected by **telomeres**, but are "**sticky**" and may adhere to other broken ends.

**Polytene chromosomes** (bundles of chromatids produced by DNA synthesis without mitosis or meiosis)

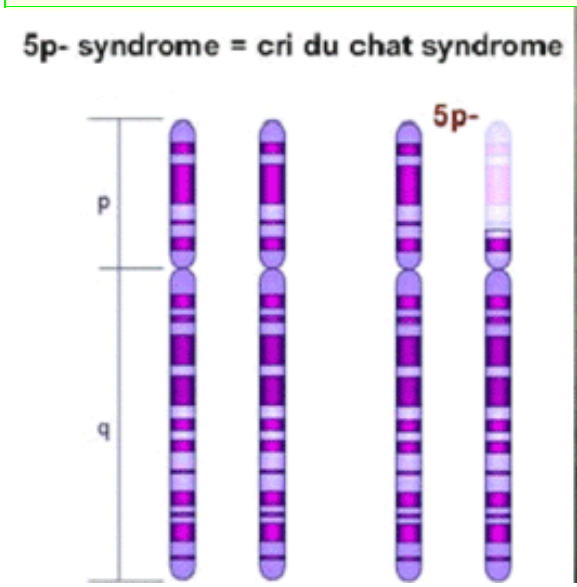
# Deletion

1. Part of a chromosome is missing.
   a. Deletions start with chromosomal breaks **induced** by:
      i. Heat or radiation (especially ionizing).
      ii. Viruses.
      iii. Chemicals.
      iv. Transposable elements.
      v. Errors in recombination.
   b. Deletions do not revert, because the **DNA is missing**.
2. Phenotype effect depends on what was deleted.
   a. A deletion in one allele of a **homozygous** wild-type organism may give a normal phenotype, while the same deletion in the wild-type allele of a **heterozygote** would produce a mutant phenotype.
   b. Deletion of the centromere results in an **acentric** chromosome that is lost, usually with serious or lethal consequences. (No known living human has an entire autosome deleted from the genome.)
   c. Large deletions can be **detected** by unpaired loops seen in karyotype analysis



# Deletion Syndromes

- **Cri du chat** (cat's cry): Deletion of a piece of short arm of chromosome **5 (46,XY, 5p-**)



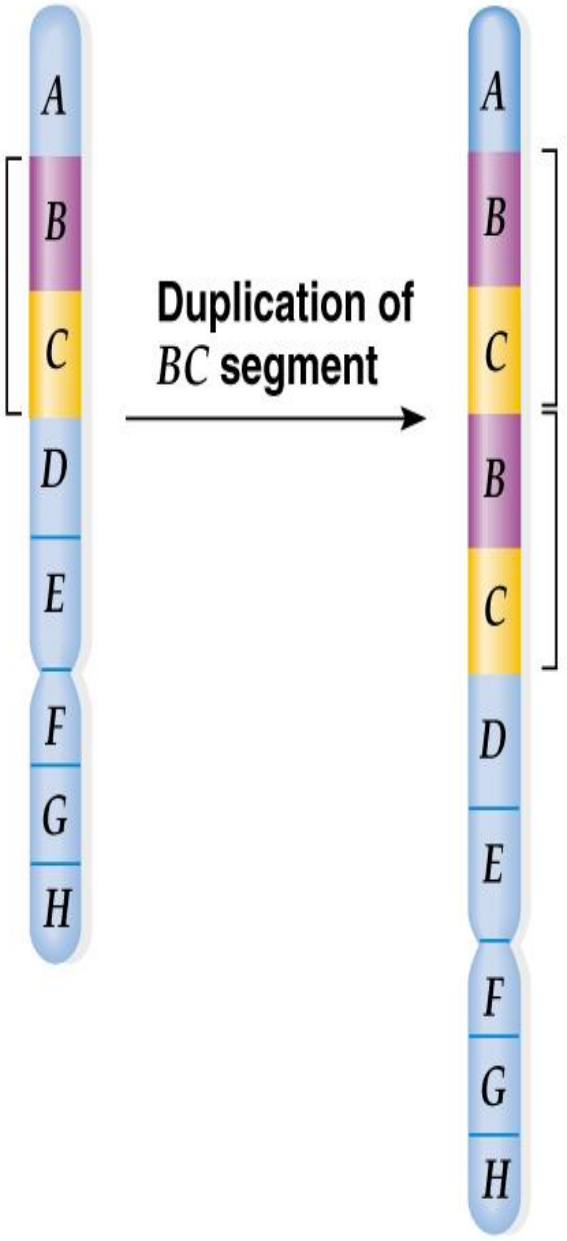

## Williams Syndrome:

- Spontaneous **deletion** on chromosome band **7q11.23**.
- Deletion removes more than **20 genes** that encode for different functions.
- Occurrence: **1** in **20,000**
- Problems associated with WS
  - Heart & Blood Vessel Defects
  - Supravalvular aortic stenosis
  - High blood pressure
  - Hypertension
  - Hypercalcemia
  - Vascular & Connective Tissue Deficiency-Gene that encodes for elastin is deleted
  - Kidney Defects

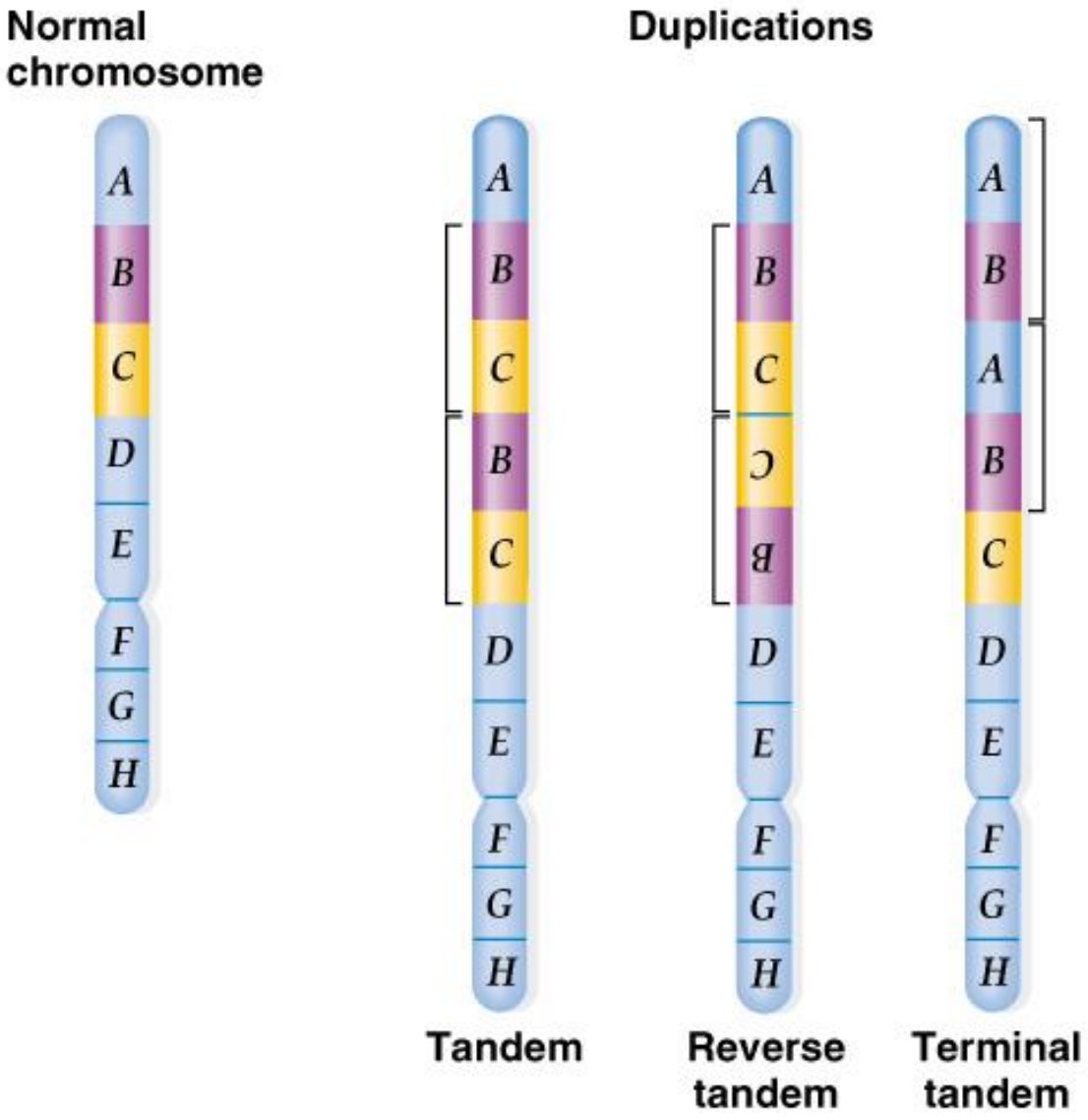
# Duplication

1. Duplications result from doubling of chromosomal segments, and occur in a range of sizes and locations

   - ❖ Tandem duplications are adjacent to each other.
   - ❖ **Reverse tandem** duplications result in genes arranged in the opposite order of the original.
   - ❖ Tandem duplication at the end of a chromosome is a terminal tandem duplication.
   - ❖ Heterozygous duplications result in unpaired loops, and may be detected cytologically.

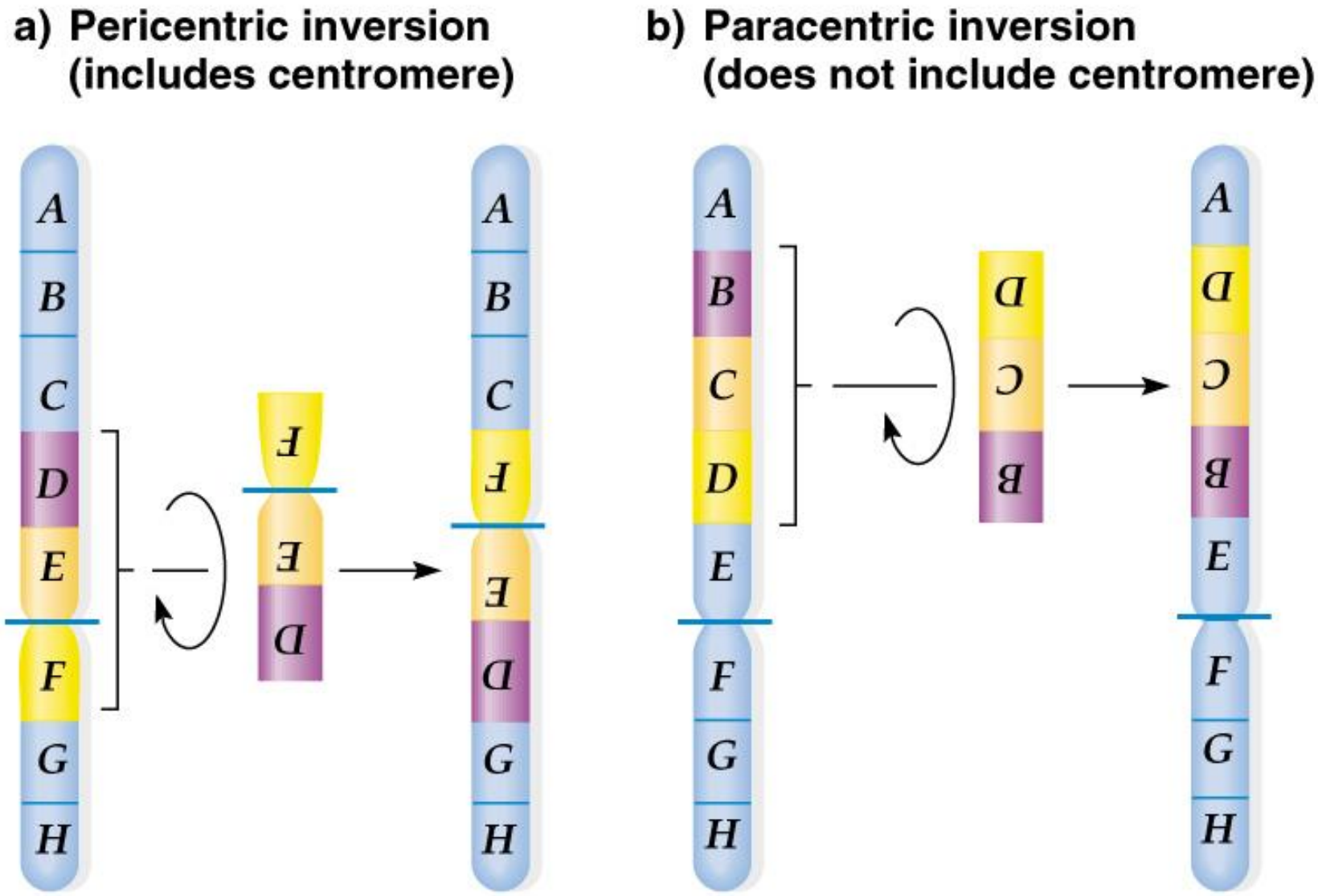


**Forms of chromosome duplications are tandem, reverse tandem, and terminal tandem duplications**



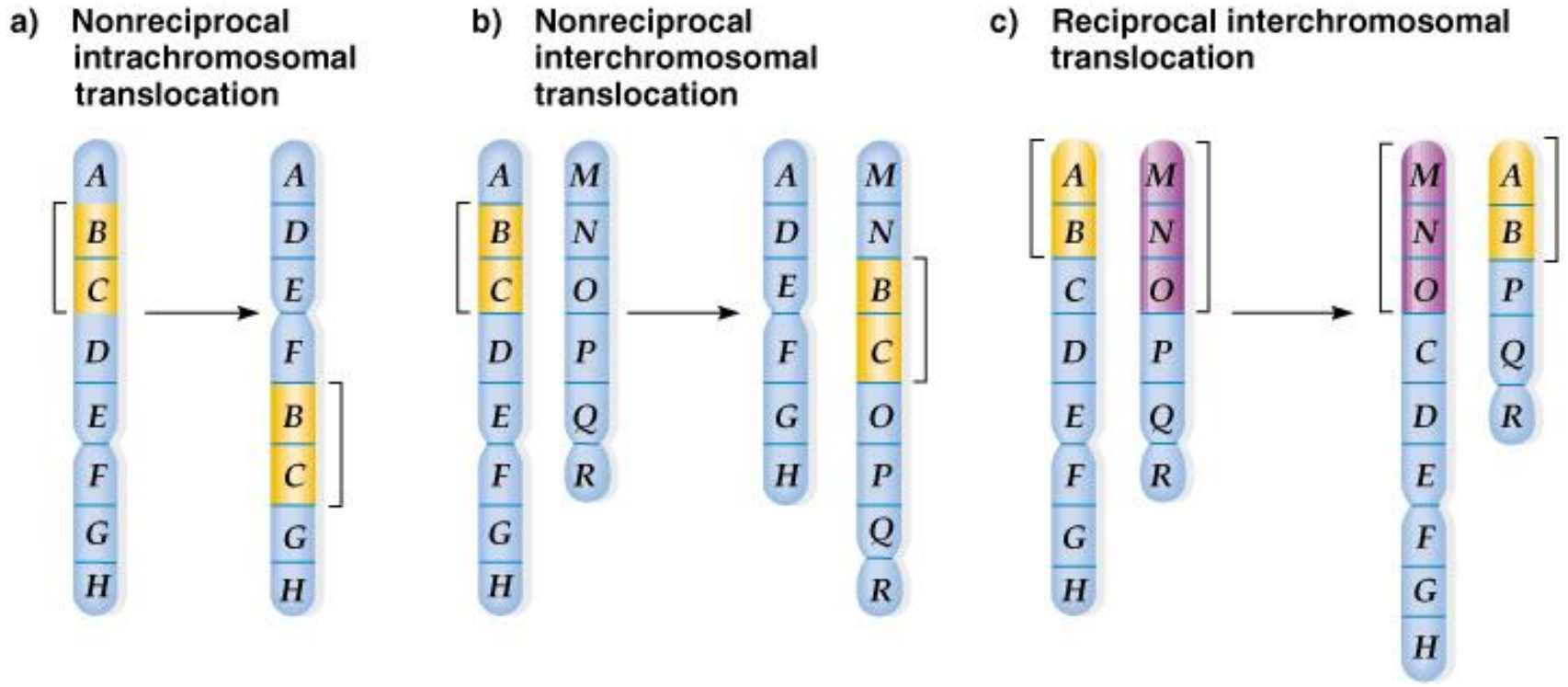
# Inversions:

**Reverses a segment within a chromosome.**

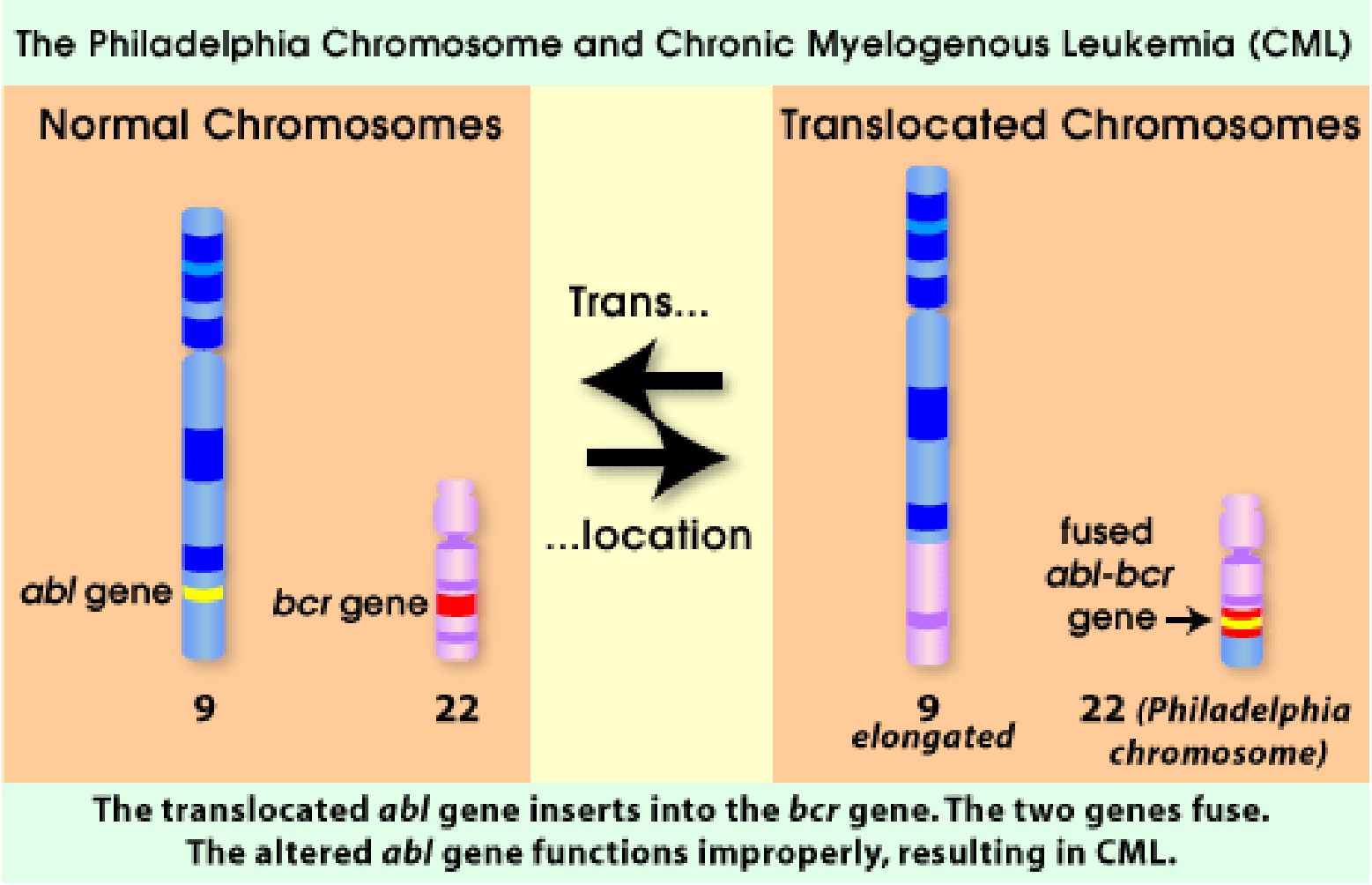


# Translocations

**Moves a segment from one chromosome to a non-homologous chromosome.**




**Balanced translocations**




- ABL gene encodes a tyrosine kinase enzyme. The BCR-ABL gene (***fusion***) encodes a protein with deregulated (**uncontrolled**) tyrosine kinase activity signaling cell division to be always on = **uncontrolled Myeloblasts cell division**.
- 90% of CML patients have the Philadelphia chromosome reciprocal translocation.

# Robertsonian translocations

Involves only the **acrocentric chromosomes** (chromosomes 13,14,15 and 21, 22), and results in the formation of a "**new**" chromosome consisting of the whole of the l**ong arms of the two acrocentrics involved**, which have been **fused together**.

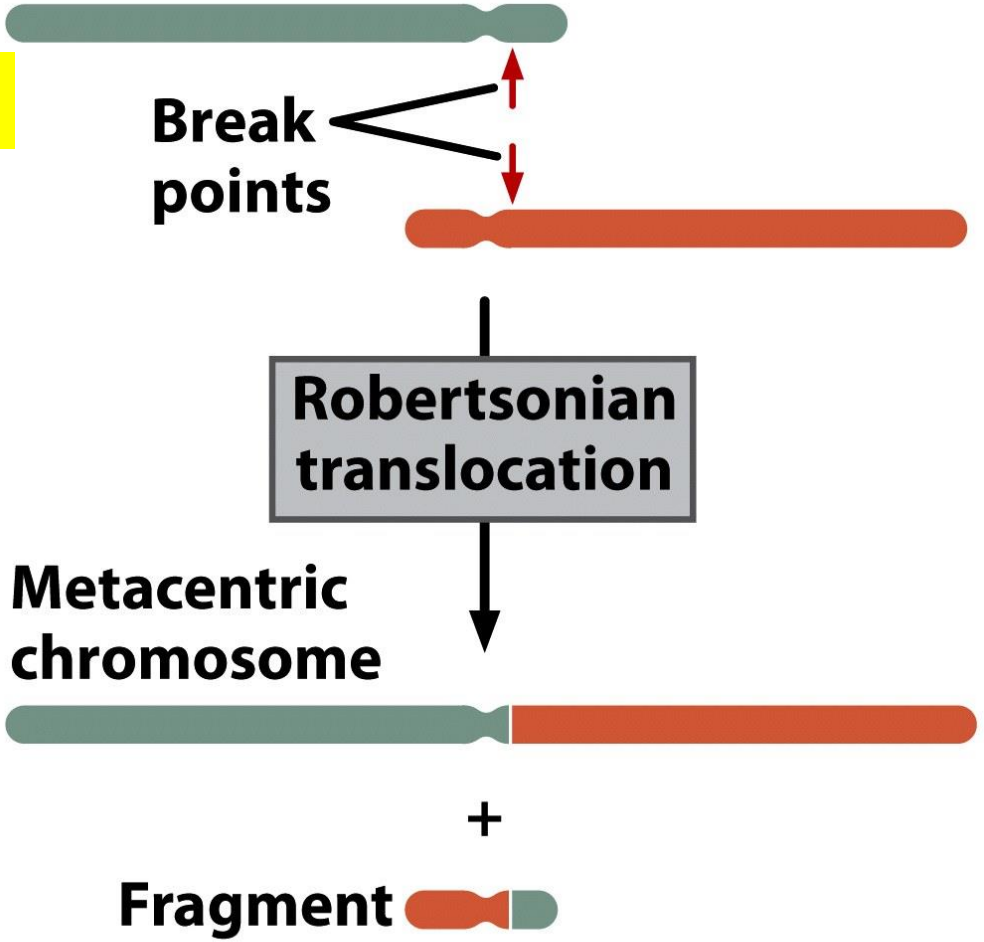



Figure 9-15
*Genetics: A Conceptual Approach, Third Edition*


The incidence of Robertsonian translocations in the general population is about **1** in **1000**.

**Burkitt lymphoma (BL)** involves a reciprocal translocation of chromosomes **8** and **14**.

- ✓ Reciprocal translocations between chromosomes 8 and 14 cause most cases of Burkitt's lymphoma.
- ✓ Induced by a virus, this disease is common in Africa.
- ✓ B cells are affected, and secrete antibodies as they proliferate.
- ✓ An oncogene on the tip of chromosome 8 becomes relocated next to an antibody gene enhancer region on chromosome 14.

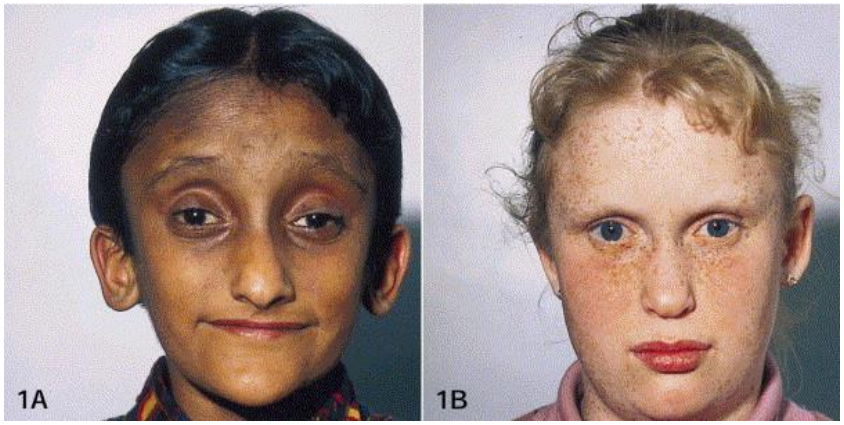
Sometimes **inversions** or **translocations** change phenotypic expression of genes by the position effect, for example, by moving a gene from **euchromatin** to **heterochromatin** (transcription generally occurs in euchromatin but not in heterochromatin).

# Translocation Syndromes

- **Alagille syndrome** – Chromosomes **2** and **20** exchange segments

Decreased number of hepatic ducts that leads to accumulation of bile in the liver. Eventually the liver may stop woking and this may necessitate a liver transplant.

As bile builds up in the liver causing damage, other organs may also be affected. This includes heart, kidneys, blood vessels, bones and eyes



# Amniocentesis and Karyotyping