GENETIC DISEASES

By

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- Genetic diseases are classified into four types:

Chromosomal disorders

Mitochondrial disorders

Monogenic disorders

Multigenic (multifactorial) disorders

Chromosomal disorders

- Results from alterations in chromosomal **numbers** or **structure**, which is also called **chromosome aberrations**.

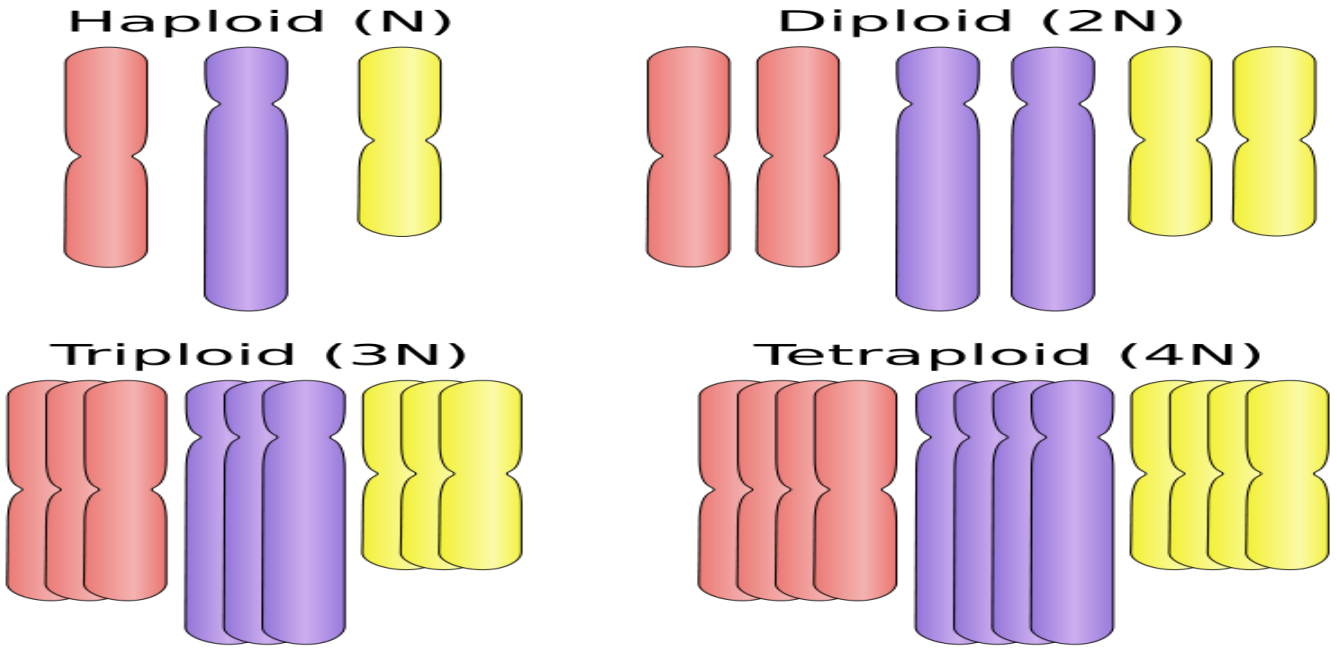
Numerical changes

- **Polyploidy**: when the changes involves a set number of chromosomes(numerical change in the whole set of chromosomes)
- **Aneuploidy**: in which the changes is limited to the number of individual chromosomes (numerical change in part of the chromosome set) .

- True polyploidy rarely occurs in humans, but it may occur in some tissues (especially in the liver) while aneuploidy is more common.

- Human polyploidy appears in the form of triploidy, with 69 chromosomes (also called 69, XXX), and tetraploidy with 92 chromosomes (also called 92, XXXX).
- *The letter x is used to represent the number of chromosomes in a single set.*

- Triploidy, is usually responsible for 17 % of spontaneous abortions. The main causes of this mutation is due to fertilization with a diploid spermatocyte or egg or the fertilization of normal egg with two sperms.

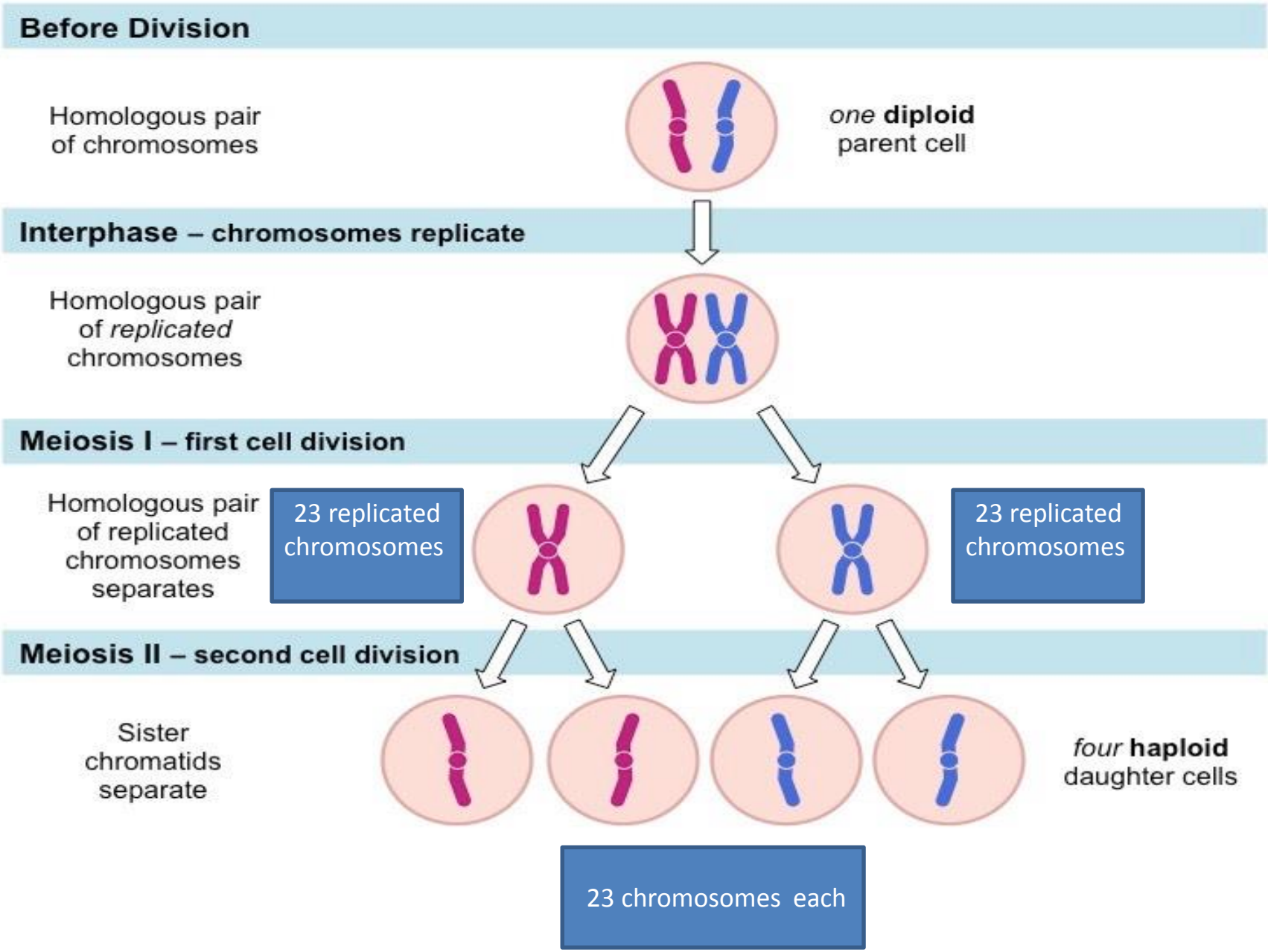


- **Human aneuploidy** is the result of adding an extra chromosome or losing a single chromosome which happens during cell division when chromosomes do not separate properly between the two new cells.

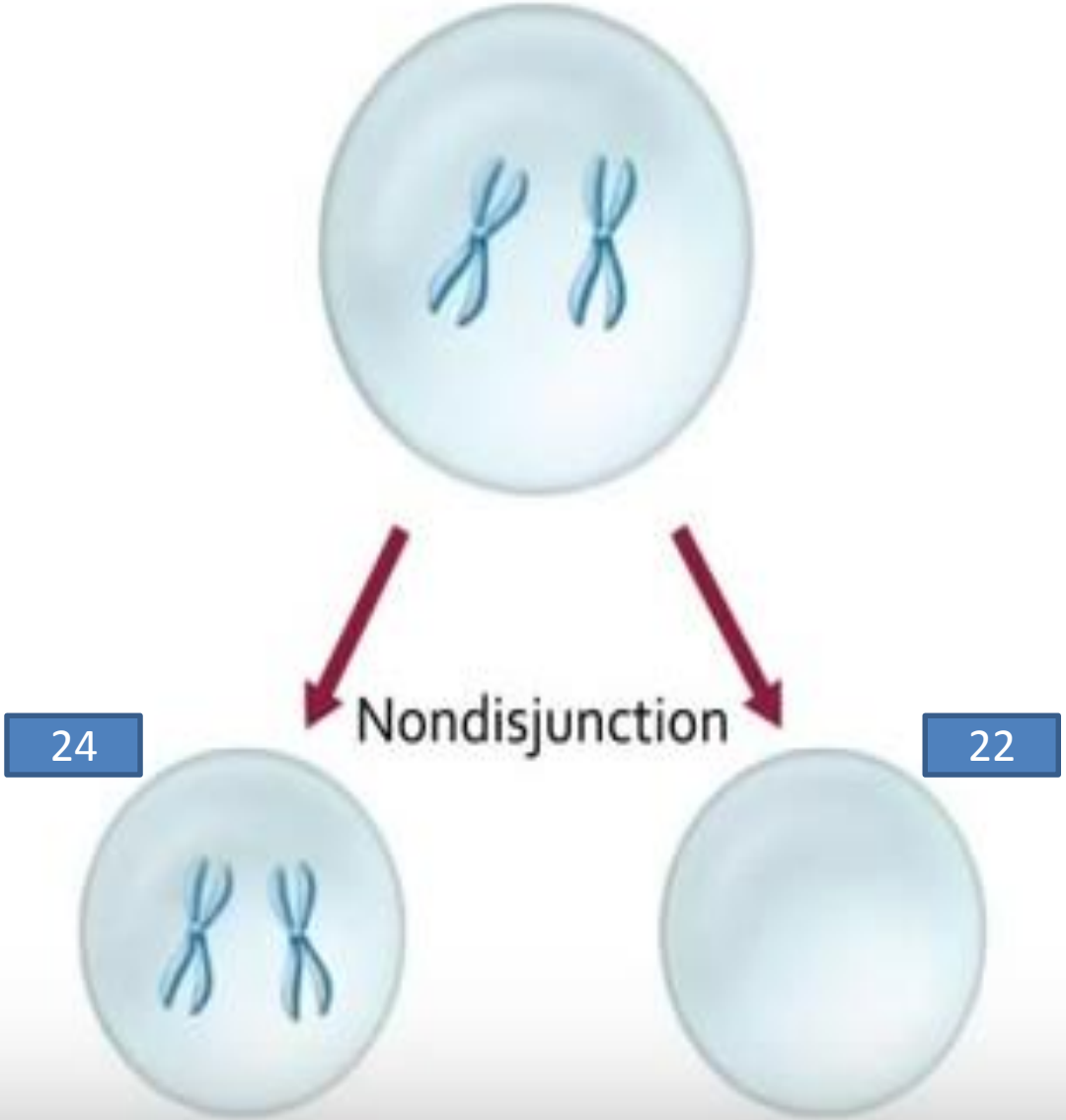
- The defect may take place in germ cells at birth leading to birth defects or may occur in somatic cells and associated with some cancer cells development.

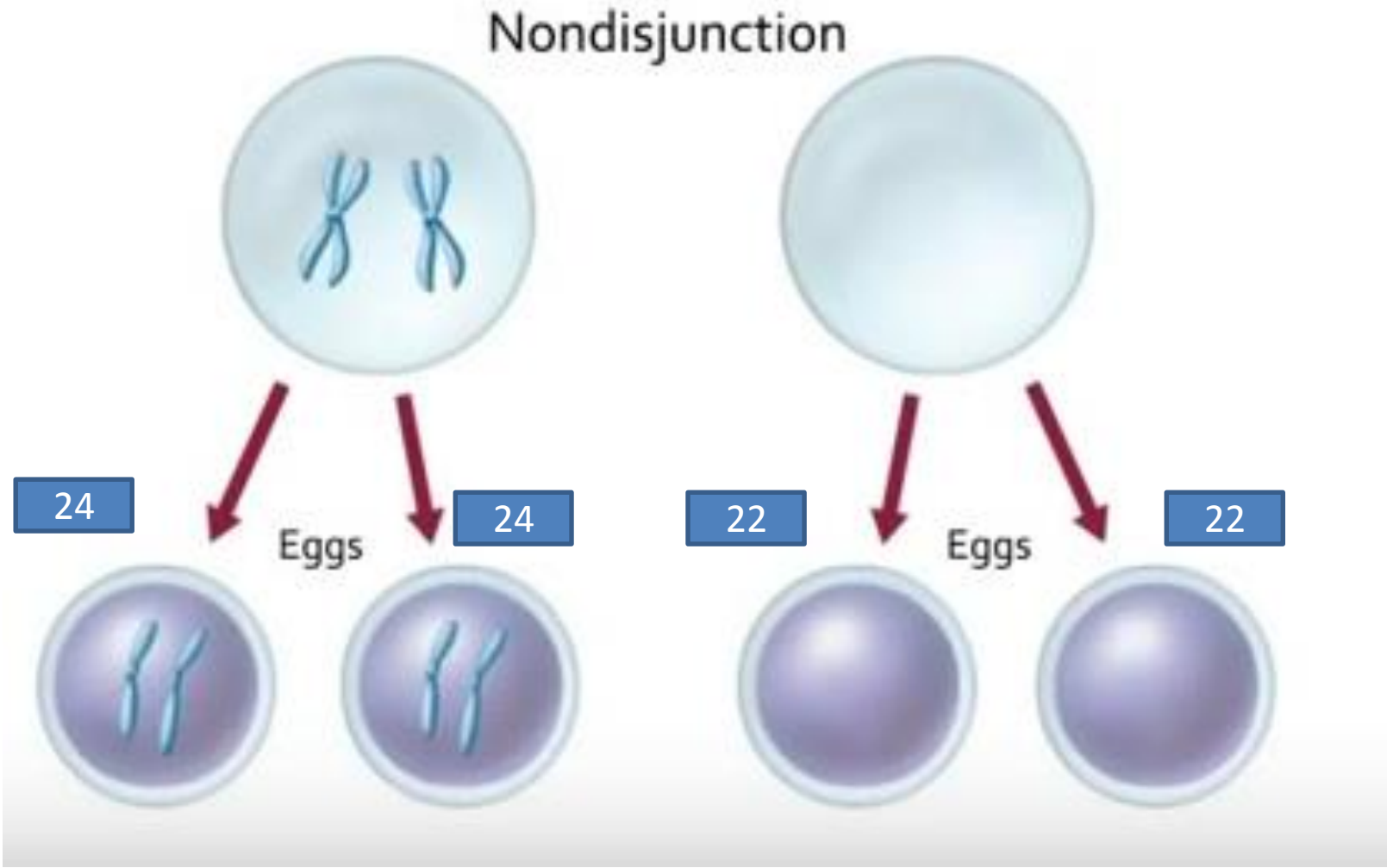
- **Nondisjunction** of chromosomes occurs when either homologues pairs fail to separate during anaphase I or sister chromatids fail to separate during anaphase II of meiosis.
- **Nondisjunction is the failure of homologous chromosomes (in meiosis I) or sister chromatids to separate properly (meiosis II and mitosis) during cell division.**
- The result is that single gamete has 2 copies of one chromosome and the other has no copy of that chromosome.

- If either of these gametes unites with another during fertilization, the result is aneuploidy , so that one trisomic cell will have one extra chromosome (2n +1). Another cell will be monosomic has one missing chromosome (2n -1) = mostly lethal


Before Division
Homologous pair of chromosomes
one diploid parent cell
Interphase – chromosomes replicate
Homologous pair of replicated chromosomes
Meiosis I – first cell division
Homologous pair of replicated chromosomes separates
23 replicated chromosomes
23 replicated chromosomes
Meiosis II – second cell division
Sister chromatids separate
four haploid daughter cells
23 chromosomes each

Meiosis I

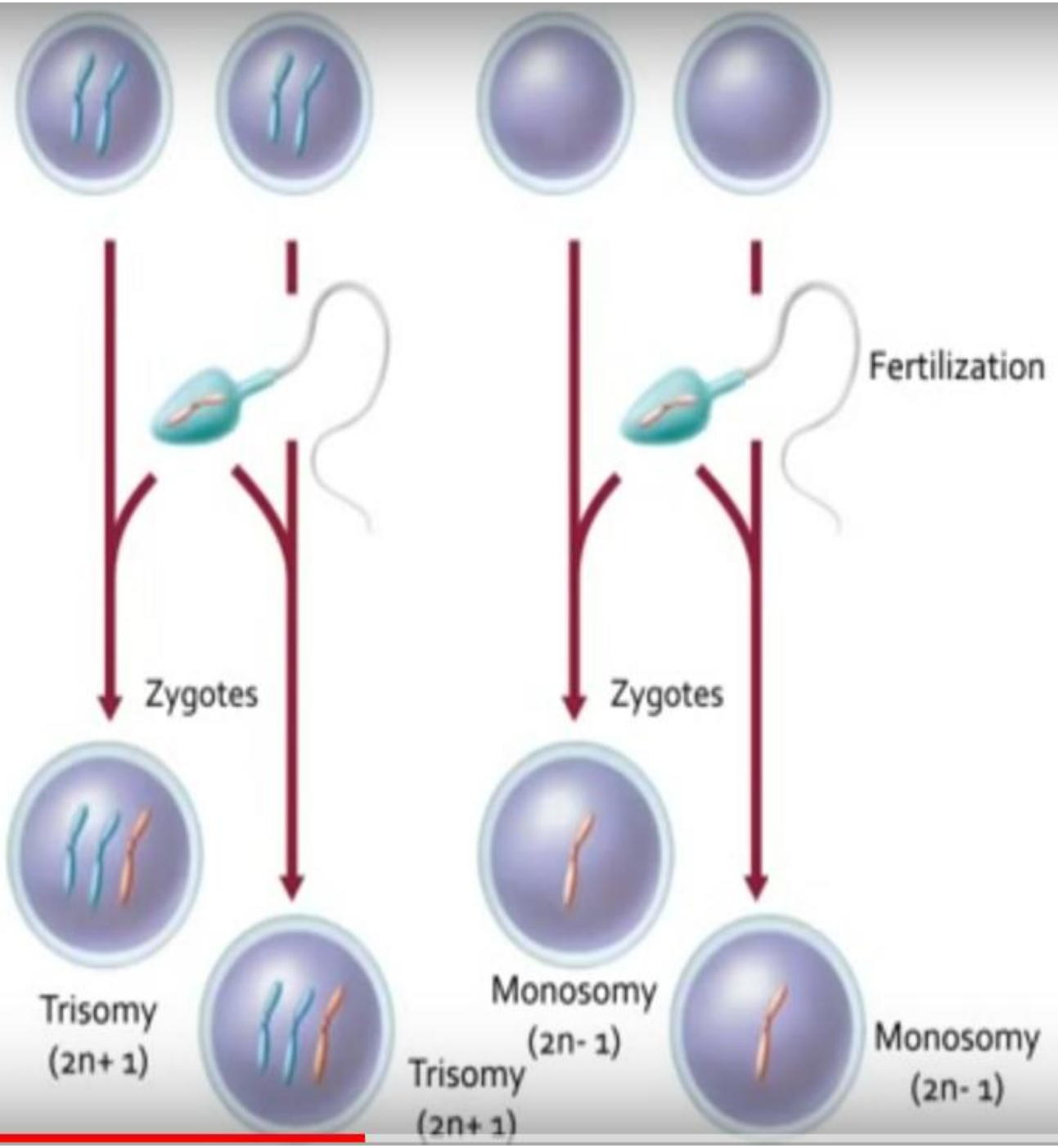


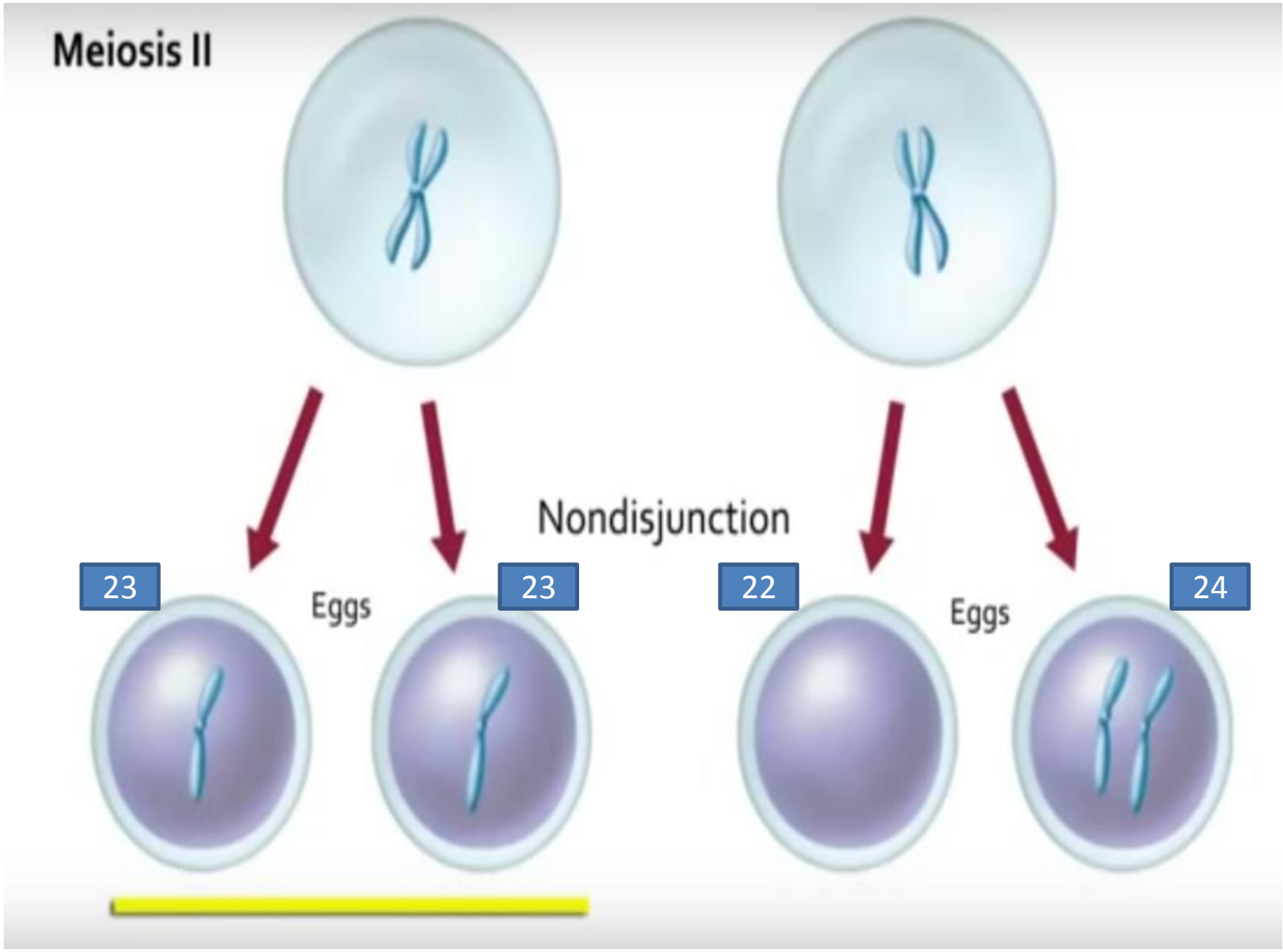

Nondisjunction
24
Eggs
24
22
Eggs
22

Meiosis I

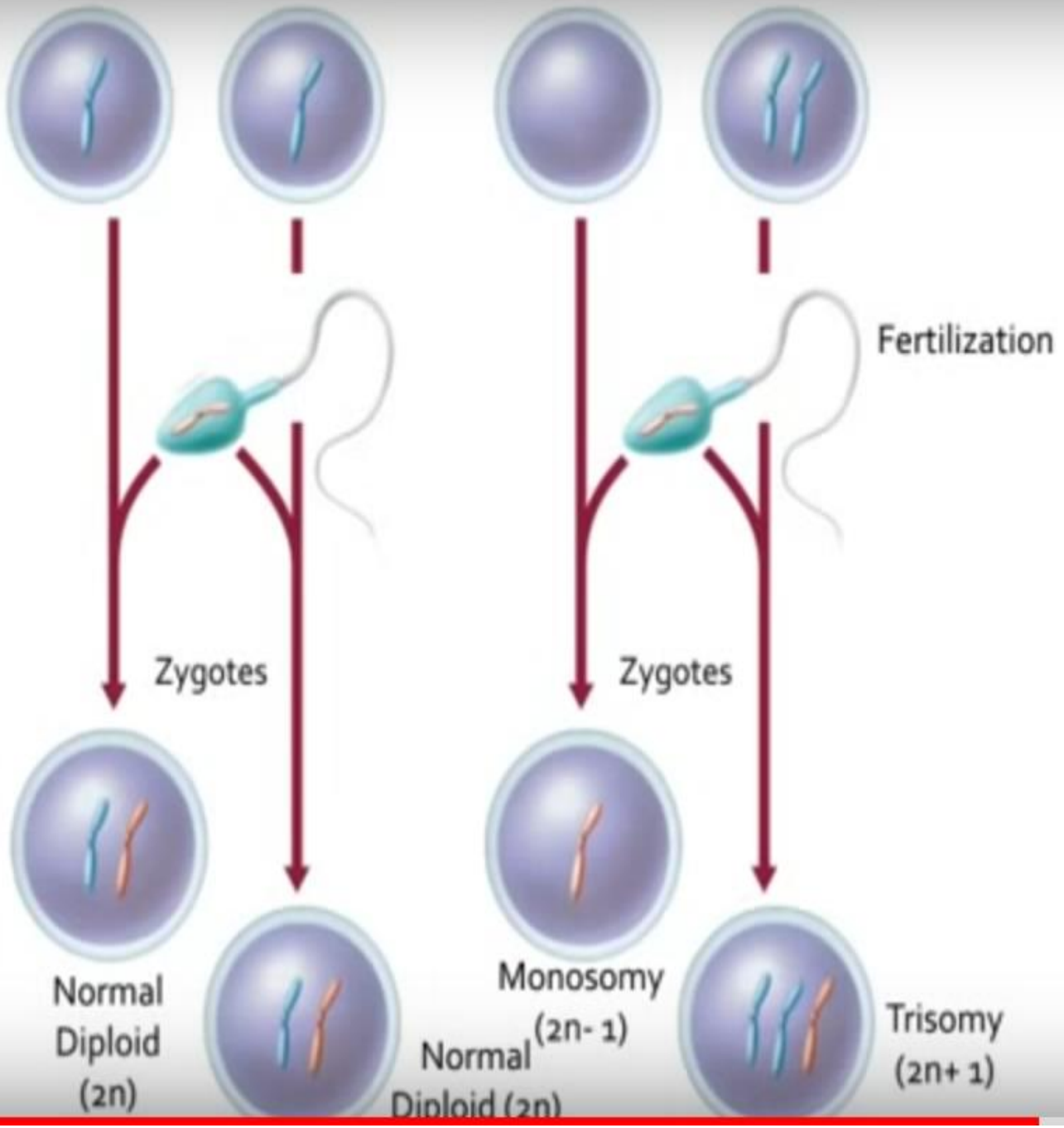
Trisomy or Monosomy:

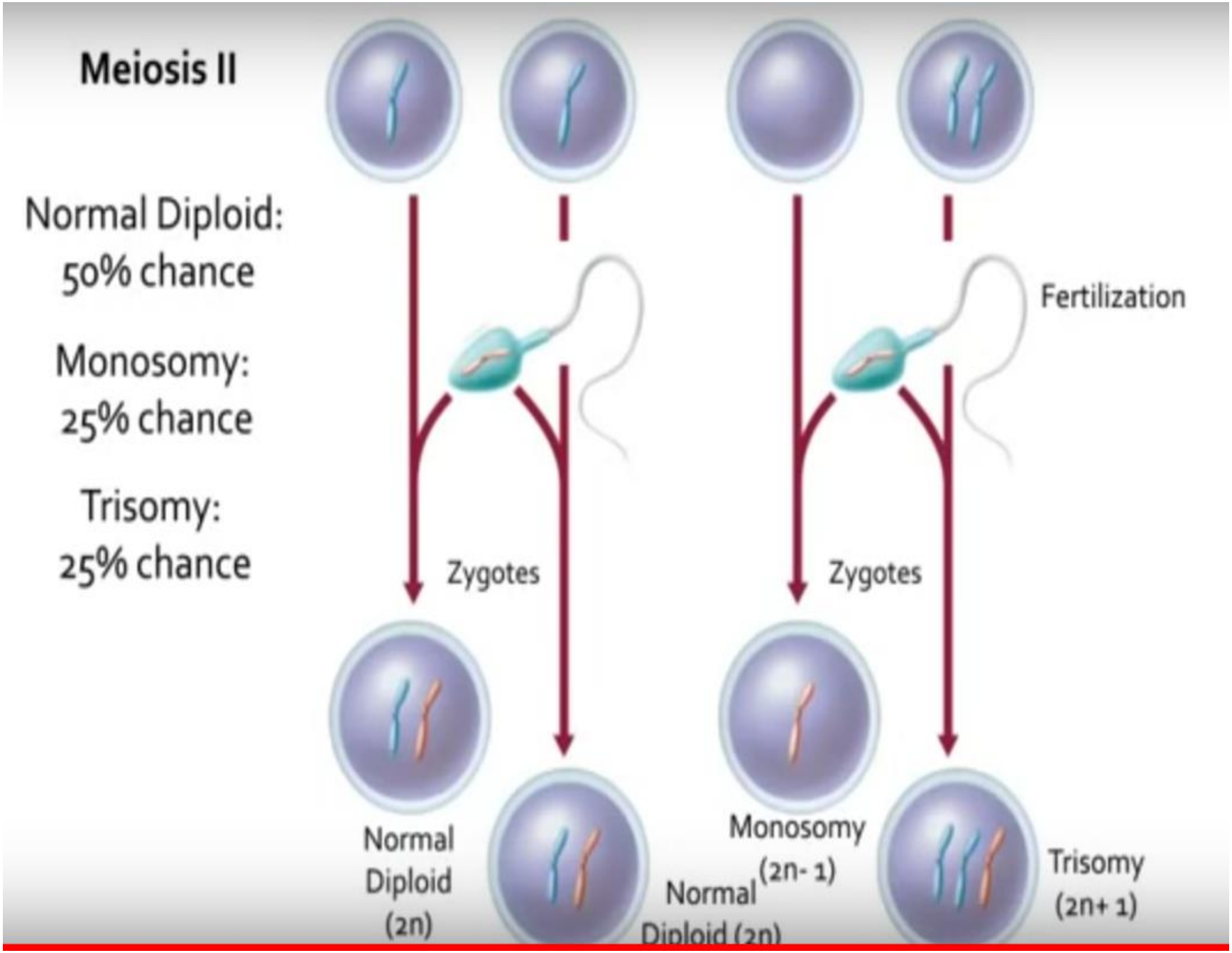
100% Chance




Meiosis II
Nondisjunction
23
Eggs
23
22
Eggs
24

Meiosis II


Fertilization
Zygotes
Zygotes
Normal
Diploid
(2n)
Normal
Diploid (2n)
Monosomy
(2n- 1)
Trisomy
(2n+ 1)


Meiosis II
Normal Diploid:
50% chance
Monosomy:
25% chance
Trisomy:
25% chance
Fertilization
Zygotes
Zygotes
Normal
Diploid
(2n)
Normal
Diploid (2n)
Monosomy
(2n- 1)
Trisomy
(2n+ 1)

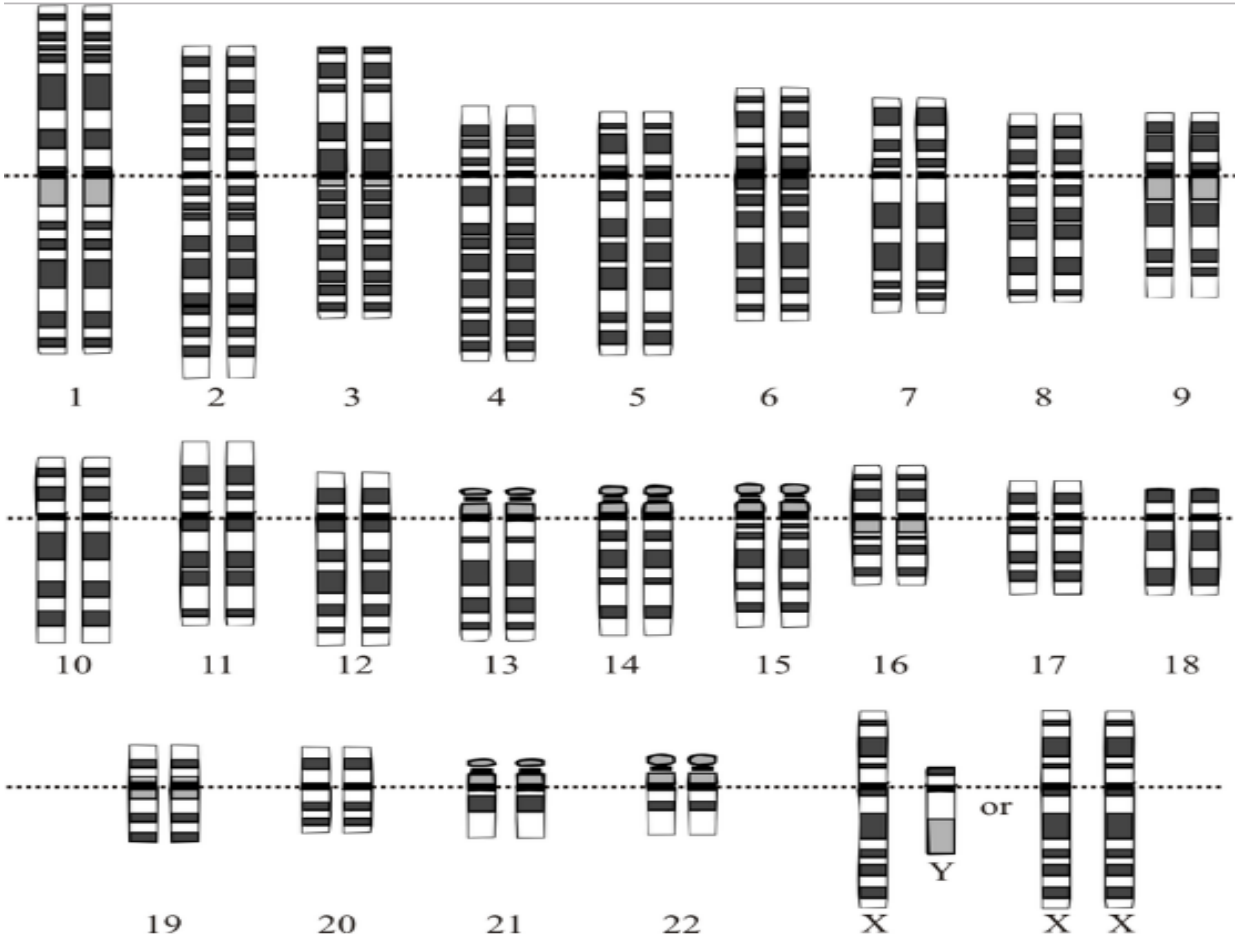
- The frequency of nondisjunction is quite high in humans, but the results are usually so damaging to the growing zygote that miscarriage occurs very early in the pregnancy.

- The abnormality in chromosomes number may occur in **somatic** or **sex** chromosomes.

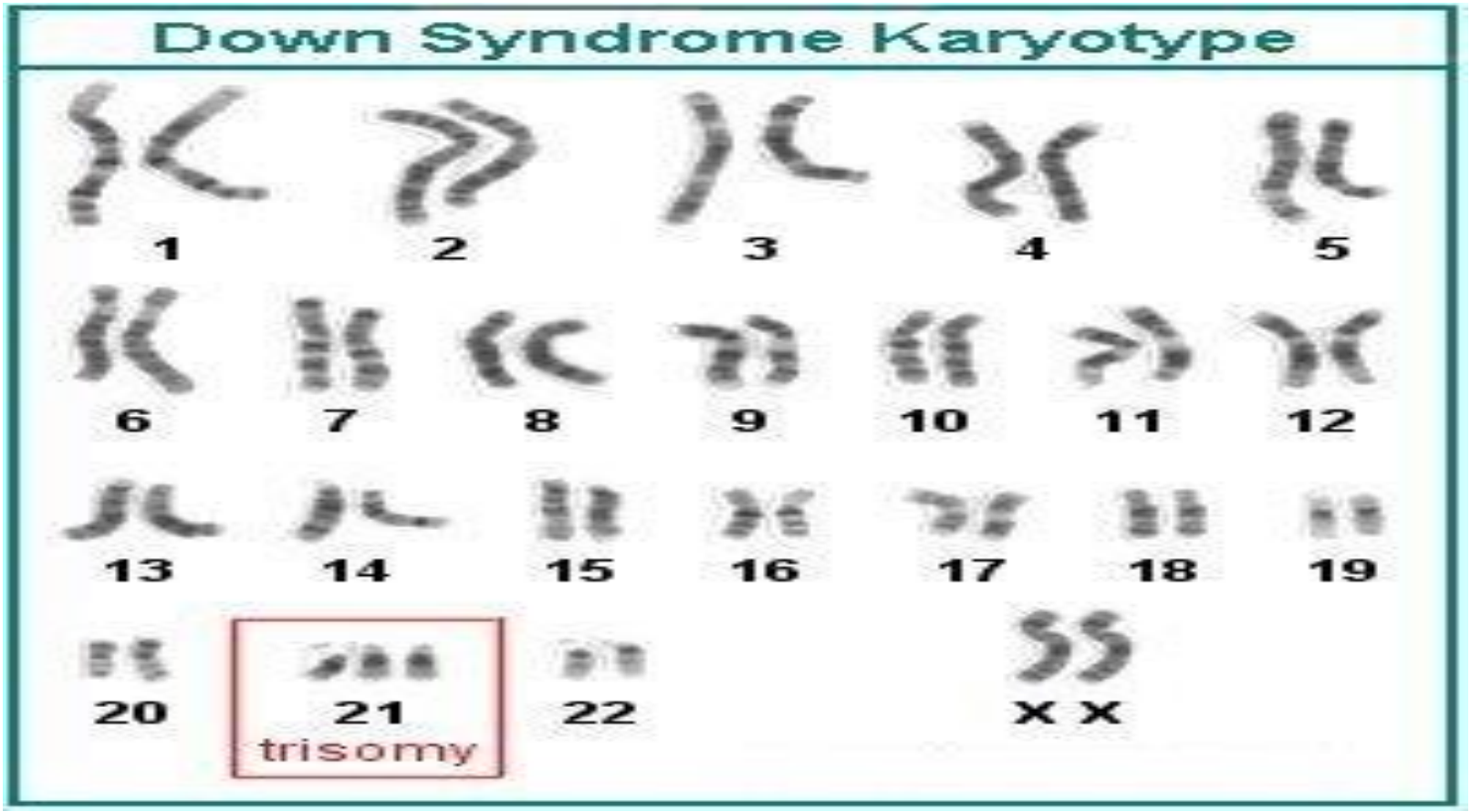
Human disorders due to chromosome alterations in autosomes (Chromosomes 1-22)

- There are only 3 examples of trisomies that result in a baby that can survive for a time after birth; while other trisomies can be very severe and the baby usually dies in utero.
- **A. Down syndrome (trisomy 21)**:
- The result of an extra copy of chromosome 21.
- People with Down syndrome are 47, 21+.

- Down syndrome affects 1:700 children and alters the child's phenotype either moderately or severely: characteristic facial features, short stature; heart defects susceptibility to respiratory disease, shorter lifespan prone to developing early leukemia.
- Often the patients are sexually underdeveloped and sterile, with some degree of mental retardation.
- Down Syndrome is correlated with age of mother but can also be the result of nondisjunction of the father's chromosome 21.



Normal human Karyotype.



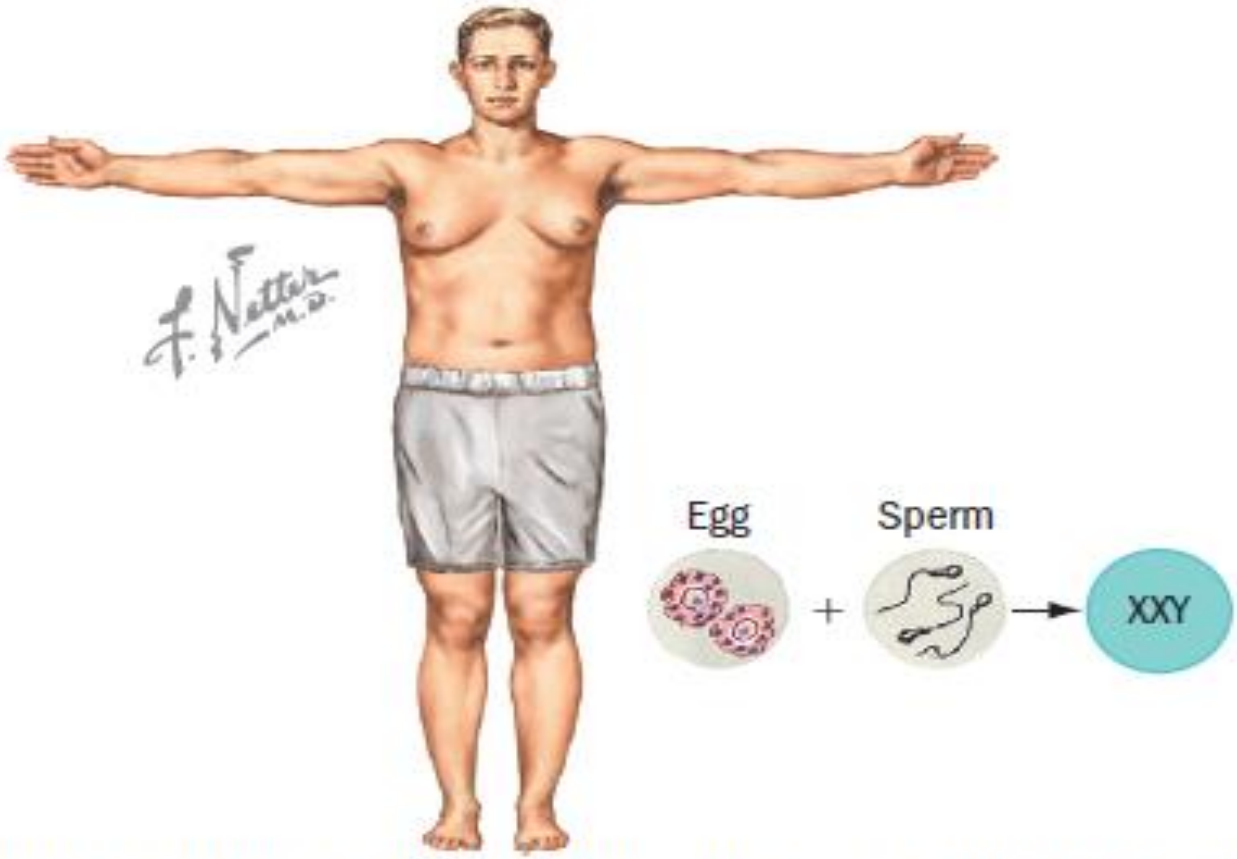
A karyotype is the number and appearance of chromosomes in the nucleus of an eukaryotic cell. Karyotypes describe the chromosome count of an organism and what these chromosomes look like under a light microscope. Attention is paid to their length, the position of the centromeres, banding pattern, any differences between the sex chromosomes, and any other physical characteristics.

- **B. Patau syndrome (trisomy 13):** serious eye, brain, circulatory defects as well as cleft palate. 1:5000 live births. Children rarely live more than a few months.

- **C. Edward's syndrome (trisomy 18):** almost every organ system affected 1:10,000 live births. Affected children generally do not live more than a few months.

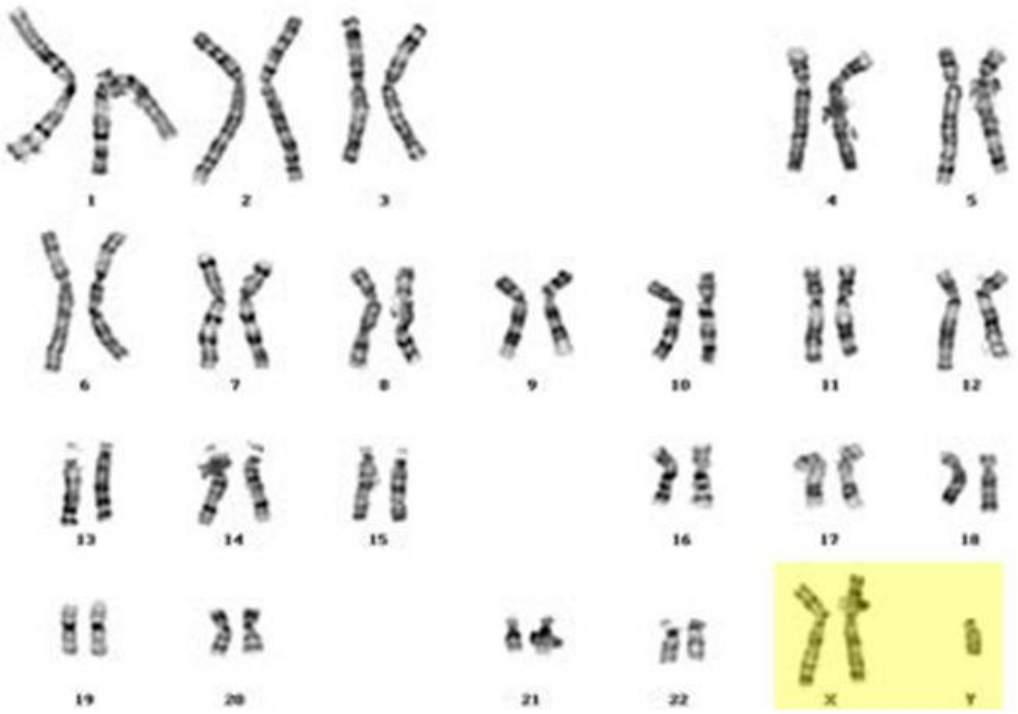
❖**Nondisjunction of the sex chromosomes** (X or Y chromosome) is potentially fatal, but many affected people can survive. There are 4 examples:

- **A. 47, XXY males(Klinefelter syndrome):** Male sex organs; unusually small testes, sterile. Breast enlargement and other feminine body characteristics. Normal intelligence.



Klinefelter's syndrome is an inherited disorder of males. Males have an extra X chromosome and don't develop normal male sexual characteristics of puberty; however, most men with Klinefelter's syndrome can live normal lives.

Klinefelter syndrome: Karyotype



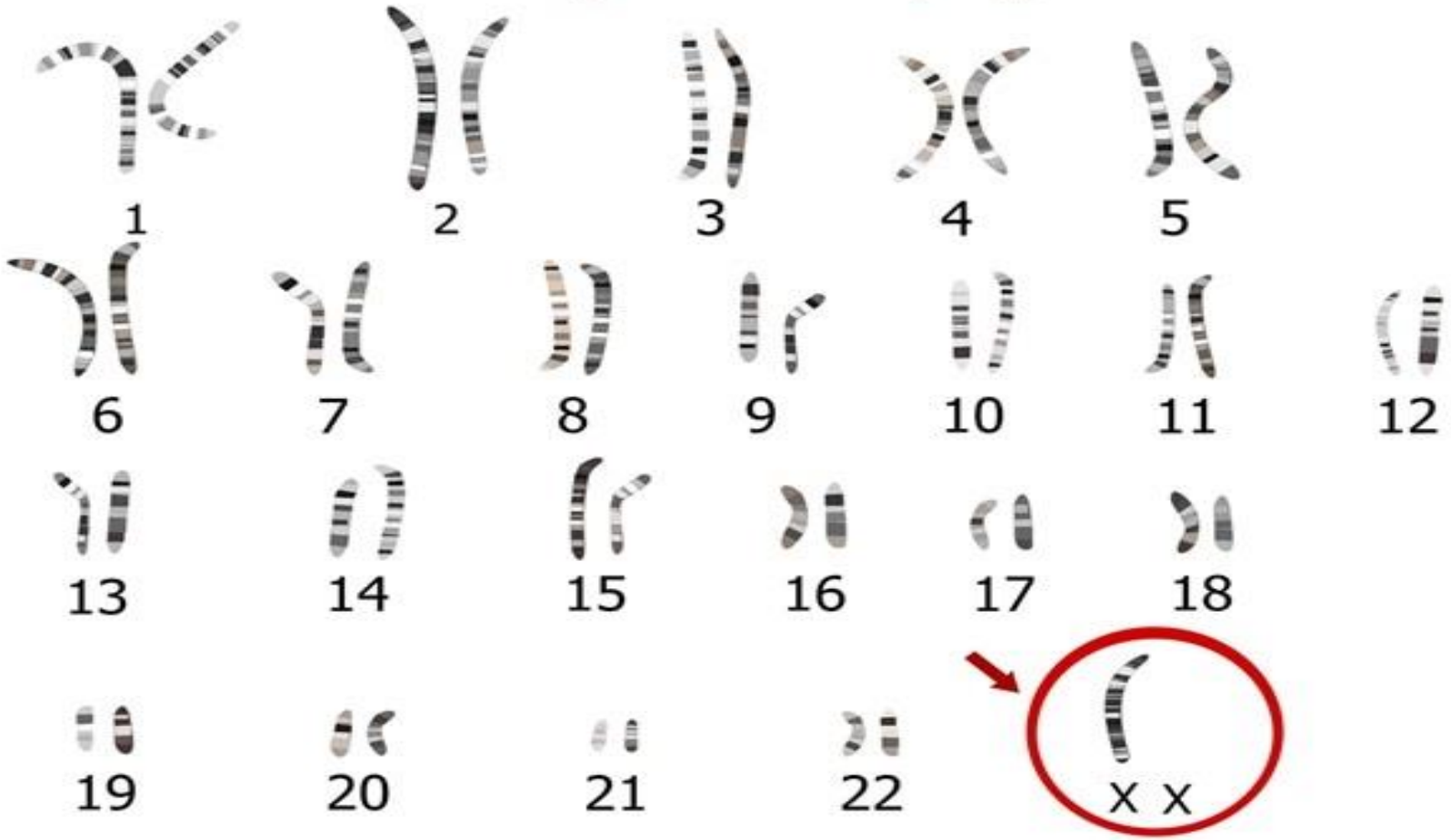
- **B. 47, XYY males:** Individuals are somewhat taller than average and often have below normal intelligence.

- **C. 47, XXX females (Trisomy X).** 1:1000 live births - healthy and fertile usually cannot be distinguished from normal female except by karyotype

- **D. XO (Monosomy X)** also called **Turner's syndrome**: 1:5000 live births; **the only viable monosomy in humans** -women with Turner's have only 45 chromosomes!!! XO individuals are genetically female, however, they do not mature sexually during puberty and are sterile. Short stature and normal intelligence.

  Approximately 99% of pregnancies affected with Turner syndrome are miscarried.

Turner syndrome karyotype



Chromosome structural changes

- **Deletions**
- **Duplications**
- **Inversions**
- **Translocations**

Deletions

- In humans, **cri-du-chat syndrome**, also known as chromosome 5p deletion syndrome, is a rare genetic disorder due to a missing part (deletion) of the short arm of chromosome 5. The symptoms of this deletion, include severe mental retardation and an abnormally small head.

Duplications

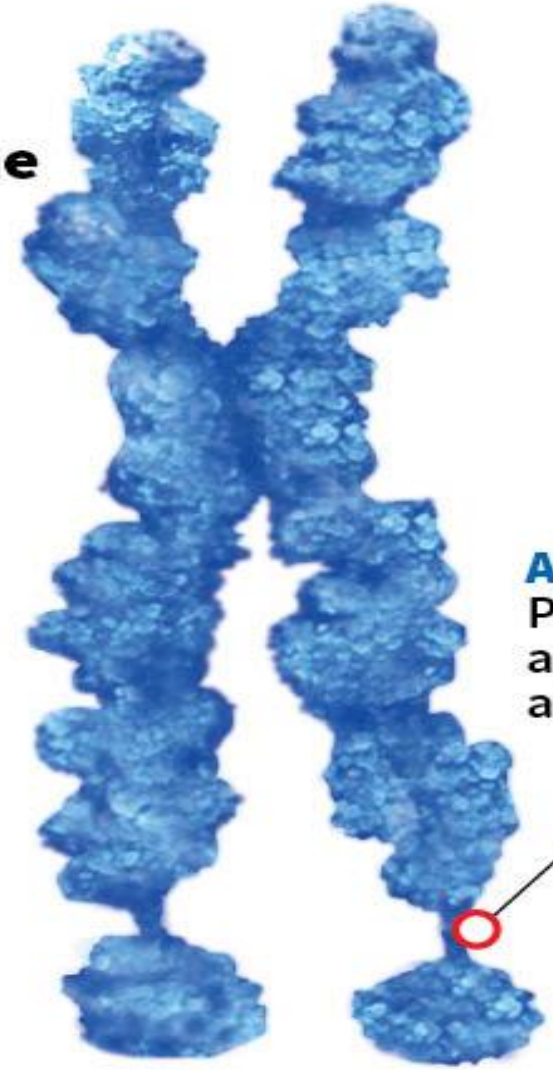
- **Fragile X syndrome** is a genetic disorder which occurs as a result of a **mutation of the fragile x mental retardation 1 (FMR1) gene on the X chromosome**, most commonly an increase in the number of CGG trinucleotide repeats in the 5' untranslated region of FMR1
- In unaffected individuals, the FMR1 gene contains 5–44 repeats of the sequence CGG, most commonly 29 or 30 repeats.
- Individuals with fragile X syndrome have a full mutation of the FMR1 allele, with over 200 CGG repeats.

- In these individuals with a repeat expansion greater than 200, there is methylation of the CGG repeat expansion and FMR1 promoter, leading to the silencing of the FMR1 gene and a lack of its protein product which is most commonly found in the brain and is essential for normal cognitive development and female reproductive function.

- This methylation of FMR1 in chromosome band Xq27.3 is believed to result in constriction of the X chromosome which appears 'fragile' under the microscope at that point, a phenomenon that gave the syndrome its name.

An X chromosone affected by Fragile X Syndrome

CAUSE
Trinuoleotide repeat in the FMR-1 gene on the X chromosone



APPEARANCE
Portion of chromosone X appears fragile and about to break

Inversions

- An inversion occurs when a chromosome breaks in two places and the region between the break rotates 180° before rejoining with the two end fragments. Inversions do not result in a gain or loss of genetic material, and they have damaging effects only if one of the chromosomal breaks occurs within an essential gene or if the function of a gene is altered by its relocation to a new place in the chromosome.

Translocations

- The balance of genes is still normal (nothing has been gained or lost) but can alter phenotype as it places genes in a new environment.

- Acute promyelocytic leukemia **(APL)** is caused by translocation.

Mitochondrial disorders

- Mitochondria are large organelles present in all aerobic cells to use food and oxygen to make energy.

- The body uses this energy for daily function and growth.

- Cells contain hundreds or thousands of mitochondria molecules; **each mitochondrion contains two to ten copies of a small circular double stranded DNA molecule that makes up approximately 1% of total cellular DNA.**

❖ **The mitochondrial genome differs from the nuclear genome in the following Properties:**

- The mitochondrial genome is circular, whereas the nuclear genome is linear

- The mitochondrial genome is built of 16,569 DNA base pairs, whereas the nuclear genome is made of 3.3 billion DNA base pairs.

- The mitochondrial genome contains 37 genes that encode 13 proteins, 22 tRNAs, and 2 rRNAs.

- ***Mitochondrial ribosome*** *or* ***mitoribosome*** *is a protein complex that is active in mitochondria and functions as a riboprotein for translating mitochondrial mRNAs encoded in mtDNA. Mitoribosomes, like cytoplasmic ribosomes, consist of two subunits — large (mtLSU) and small (mt-SSU).*

- A cell can contain several thousand copies of its mitochondrial genome, but only one copy of its nuclear genome.

- The mitochondrial genome is not enveloped, and is it not packaged into chromatin.

- The mitochondrial genome contains very few noncoding DNA sequences.

- The 13 mitochondrial gene-encoded proteins are mainly involved in electron transport and oxidative phosphorylation. These proteins are inherited from the mother since the sperm has little or no mitochondria and therefore, all zygote mitochondrial DNA are mainly contributed by the ova.

- The small mitochondrial genome is not able independently to produce all of the proteins needed for functionality; thus, mitochondria depend heavily on imported nuclear gene products to facilitate its complete functions.

- A mutation can cause the mitochondria to fail in their function of making energy, allowing both normal and mutated mtDNA to coexist within the patient's tissues, a condition known as **heteroplasmy**. Therefore, clinical phenotype can vary among tissues.

❑ ***Heteroplasmy*** *: the presence of more than one type of organellar genome within a cell or individual. It is an important factor in considering the severity of mitochondrial diseases.*

- Every human organ system can be affected, but tissues with high requirements for oxidative energy metabolism, such as muscle, heart, eye, and brain are particularly vulnerable for mitochondrial mutations.

- Most mitochondrial genetic diseases are associated with myopathies (muscular diseases) and neuropathies disorders.

- Mitochondrial diseases are inherited from 2 types of genetic material:

- Mitochondrial DNA, which are passed on from the mother to all children

- Nuclear DNA, which is passed on from both parents. Therefore ,mitochondrial disease can be inherited as:

- **1. Maternal inheritance**

  A mother with a mitochondrial DNA gene mutation will pass this abnormal gene to all of her children, but these children will be affected with different degrees of severity. The inheritance of the disease does not follow Mendelian pattern .

- **2. Autosomal recessive inheritance**
- The nuclear DNA that make part of the mitochondria is inherited from both parents (half from each parent).

- Autosomal recessive mitochondrial disease can be passed on only if both mother and father are “carriers”.

- The inheritance of the disease trait will follow Mendelian low of distribution between born children.

- **3. Autosomal Dominant inheritance**

- **4.X-linked inheritance**

- Some evidence suggests that mutations of mitochondrial DNA might be major contributors to the **aging process** and age-associated pathologies.
- Particularly in the context of disease, the proportion of mutant mtDNA molecules in a cell is termed heteroplasmy. The within-cell and between-cell distributions of heteroplasmy dictate the onset and severity of disease.

Monogenic disorders

- A **single-gene disorder** is the result of a single mutated gene.
- The primary genetic defect is usually a point or frame shift mutations.
- Such genetic changes may affect the synthesis of structural or transport protein or a receptor or coagulation factor or immunoglobulin or peptide hormone or natural inhibitor or an enzyme.
- Also called **In born errors of metabolism** which means inherited defect involving one of the steps in certain metabolic pathway.

- The severity of mutation depends on the function of protein being affected . Some mutations can be harmless like **pentosuria** and fructosuria(Appearance of pentose and fructose sugars in urine due to defect in their metabolisms, respectively).

- Others can be harmful due to decreased formation of an important structural protein like **collagen** or **receptor protein like LDL receptor** or some **enzymatic defect in metabolism** that causes one of the following metabolic changes:

- 1. Decrease in rate of product formation:

❖Deficiency of **glucose 6-phosphatase** liver enzyme in glycogen catabolic pathway leads to reduced formation of glucose from glucose-6-phosphate. The genetic disease is called **Gierke's glycogen storage** disease in which liver abnormally accumulates glycogen without being degraded.

- ## 2.Decrease in rate of substrate removal :

The deficiency of **phenyl alanine hydroxylase** enzyme leads to accumulation of phenyl alanine substrate as well as its chemically deaminated products phenylketones, which appears in urine due to their excessive formation **(Phenylketonuria disease or PKU).**

Normally this enzyme converts the amino acid phenylalanine to the amino acid tyrosine, therefore patients with PKU have low levels of tyrosine. The high levels of phenylalanine metabolites affect neuronal development, which leads to mental retardation. However, the symptoms associated with this disease can be prevented with proper nutrition.

Phenylalanine is an amino acid found in many proteins; therefore, patients affected with PKU can escape the disease by strictly limiting themselves to low phenylalanine protein diets, providing that the disease is detected early.

- 3.Altered feedback control:

  Deficiency of **21-hydroxylase enzyme** causes reduced formation of cortisol which stops the feedback control mechanism and leads to increase secretion of adrenocorticotrophic hormone (ACTH) in a disease called Congenital adrenal hyperplasia.

- *adrenocorticotrophic hormone (ACTH) is produced & secreted by the anterior pituitary gland. Its principal effects are increased production & release of cortisol by the cortex of the adrenal gland.*

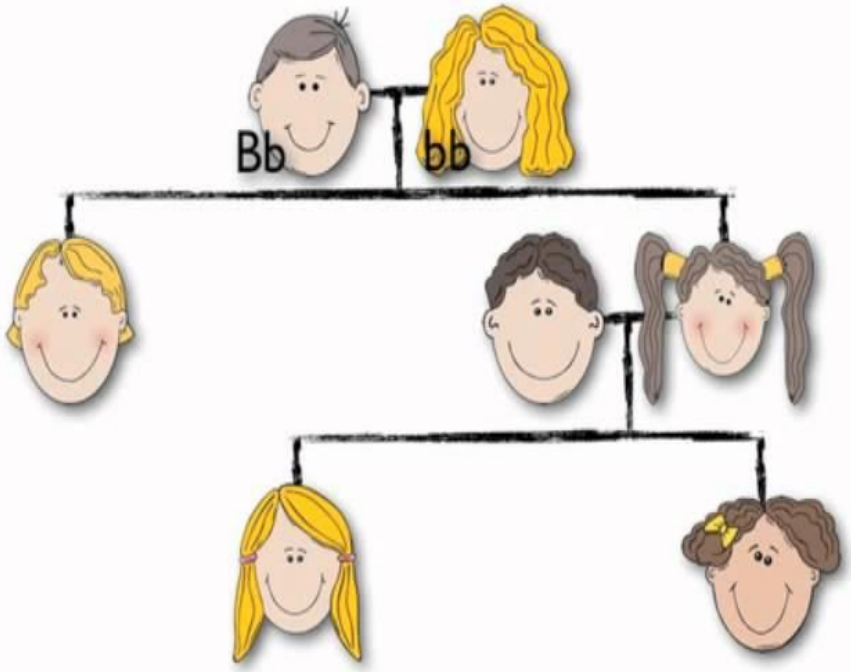
Genetic disease penetrance

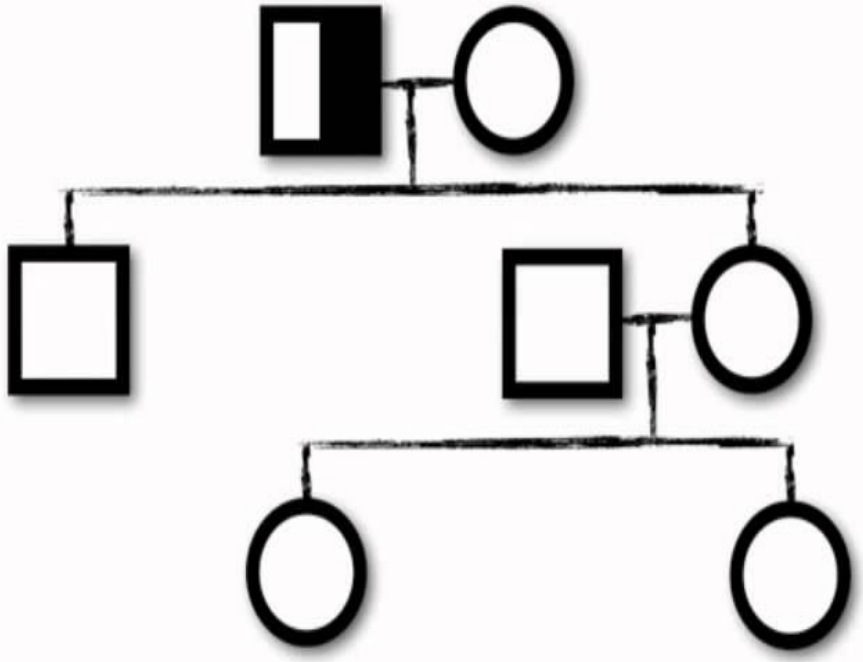
- The penetrance of a disease-causing mutation is **the proportion** of individuals with the mutation **who exhibit clinical symptoms**.
- For example, if a mutation in the gene responsible for a particular genetic disorder has 95% penetrance, then 95% of those with the mutation will develop the disease, while 5% will not.
- **Complete penetrance** if clinical symptoms are present in all individuals who have the disease-causing mutation.
- **Reduced or incomplete penetrance** , means that clinical symptoms are not always present in individuals who have the disease-causing mutation.

Pedigree

- Is a family genetic tree which describes the interrelationship between parents and children for a particular trait.
- The pedigree not only gives genetic information about the history of the family for certain trait, but also can predict to some extent the segregation of this trait in future generations.
- In a pedigree, squares represent males and circles represent females. Horizontal lines connecting a male and female represent mating. Vertical lines extending downward from a couple represent their children. Dark color represents individuals affected by the disease while white color indicates healthy individuals.

B = Brown Hair b = Blonde Hair





Mode of inheritance for monogenic disorders

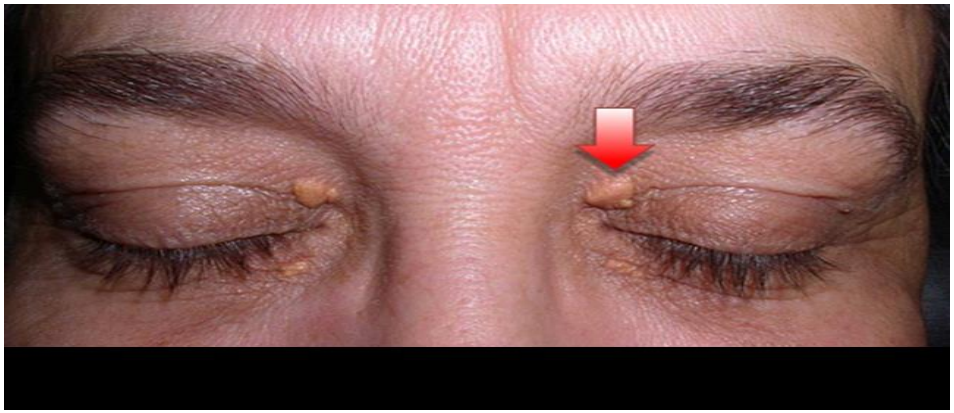
- The mode of inheritance for monogenic disorders can be either **autosomal dominant** or **autosomal recessive** or **sex-linked**

a-Autosomal dominant disorder:

Autosomal (defective gene is present on one of the 22 somatic chromosome pairs) .

The phenotypic properties of the dominant disorder (symptoms) will appear even when the individual has mutation in only one copy of the two gene alleles (heterozygous) .

- **Example**:



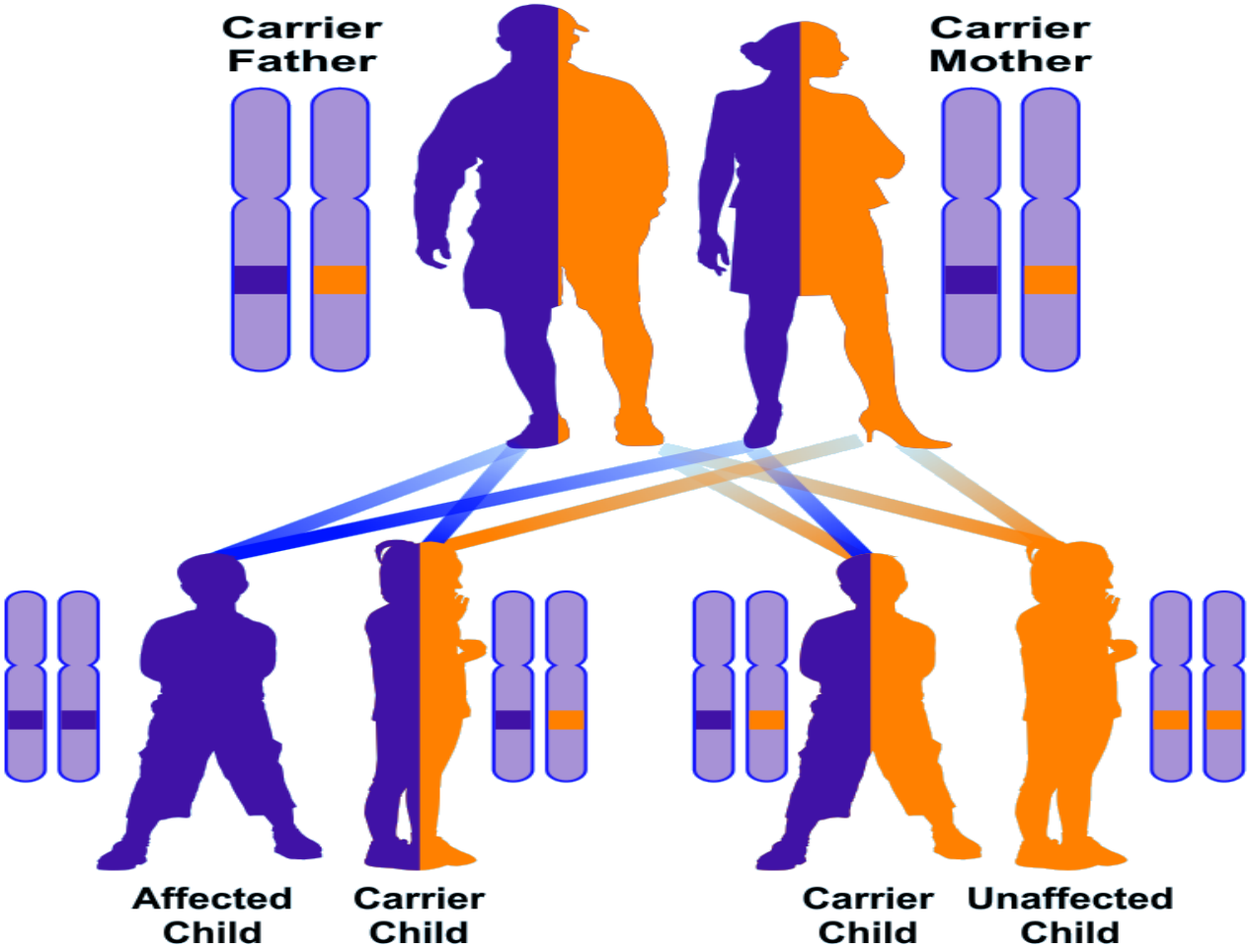
-Familial hypercholesterolemia:

- Monogenic disorder, autosomal dominant.
- LDL receptor gene mutations.
- Very high plasma cholesterol and LDL-C levels.
- Premature CHD (teenage years).
- Lipid deposits at eyelids, tendons, hand, cornea.
- Heterozygotes: also symptomatic, develop CHD at the age of 20s-50s.

b-Autosomal recessive disorders:

- Both parents are heterozygous of this mutation and they are normal carrier or sometimes show mild clinical symptoms. Therefore, autosomal recessive defect has **disease symptoms only in homozygous children** who inherit one recessive allele from each parent.

Autosomal Recessive



c. Sex -linked disorders

- Genes carried either on the y or x sex chromosomes are called sex linked.
- The disorders which are transmitted as y-linked are very rare.
- In contrast the x-linked defective alleles can be inherited either as x-linked recessive or dominant disorders similar to that of the autosomal genetic transmittance.

- As females have two x- chromosomes, they are usually unaffected carriers of x-linked recessive disease trait, unless they are homozygous for the mutated allele (very rare). However males who have only one copy of the x chromosome may develop the clinical symptoms of the disease from the mutated allele (e,g Hemophilia and Duchenne muscular dystrophy).

- The x-linked dominant disorder is rare, which shows the clinical symptoms in the heterozygous female or in a male with single copy of the mutated allele.

❖**X-linked hypophosphatemia (XLH) or X-linked dominant hypophosphatemic rickets or X-linked vitamin D resistant rickets :** a form of rickets, this disease occurs due to an excess excretion of phosphates from the body, which results in bones being unable to properly calcified and having short stature.

- It is associated with a mutation in the PHEX (**Phosphate-regulating neutral endopeptidase, X-linked)** gene sequence. The PHEX protein regulates another protein called fibroblast growth factor 23 (produced from the FGF23 gene).
- Fibroblast growth factor 23 normally inhibits the kidneys' ability to reabsorb phosphate into the bloodstream.
- Gene mutations in PHEX prevent it from correctly regulating fibroblast growth factor 23. The resulting overactivity of FGF-23 reduces phosphate reabsorption by the kidneys, leading to hypophosphatemia and the related features of hereditary hypophosphatemic rickets.

- **Autosomal dominant hypophosphatemic rickets (ADHR)** is a rare hereditary disease in which excessive loss of phosphate in the urine leads to poorly formed bones (rickets).
- ADHR is caused by a mutation in the fibroblast growth factor 23 (FGF23). *FGF23* is located on chromosome 12.

- ADHR may be lumped in with X-linked hypophosphatemia under general terms such as *hypophosphatemic rickets*.

- Mutations in *FGF23* that render the protein resistant to proteolytic cleavage leads to increased activity of FGF23 and the renal phosphate loss found in the human disease autosomal dominant hypophosphatemic rickets.

- **Y-Linked:** These conditions affect only males and carrying a copy of the mutated allele always results in the disease phenotype because men only have one copy of Y.
- It is inherited from father to son affecting all children males.
- Y-linked diseases are generally rare as there are few genes contained on this relatively small chromosome.
- It has been linked to male infertility as a number of genes crucial to spermatogenesis are present on Y chromosome.
- One such condition, **Sertoli syndrome**, results in the complete absence of the germ cells in the testis.

Multifactorial (multigenic) disorders

- These disorders are influenced by the contribution of multiple genes that act together in combination with environmental factors.
- Although these complex disorders often cluster in families, their genetic inheritance usually do not follow simple Mendelian patterns. Therefore, it is difficult to determine a person risk of inheriting the disease or the genetic transfer of these disorders.

- complex disorders are also difficult to study and treat because the specific factors that cause these disorders have not yet been identified.

  Multifactorial genetic diseases represent the single largest class of inherited disorders affecting human population and include **alzheimer**, **cancer**, **coronary heart disease**, **diabetes**, **epilepsy**, **hypertension**, **obesity** and **schizophrenia**.

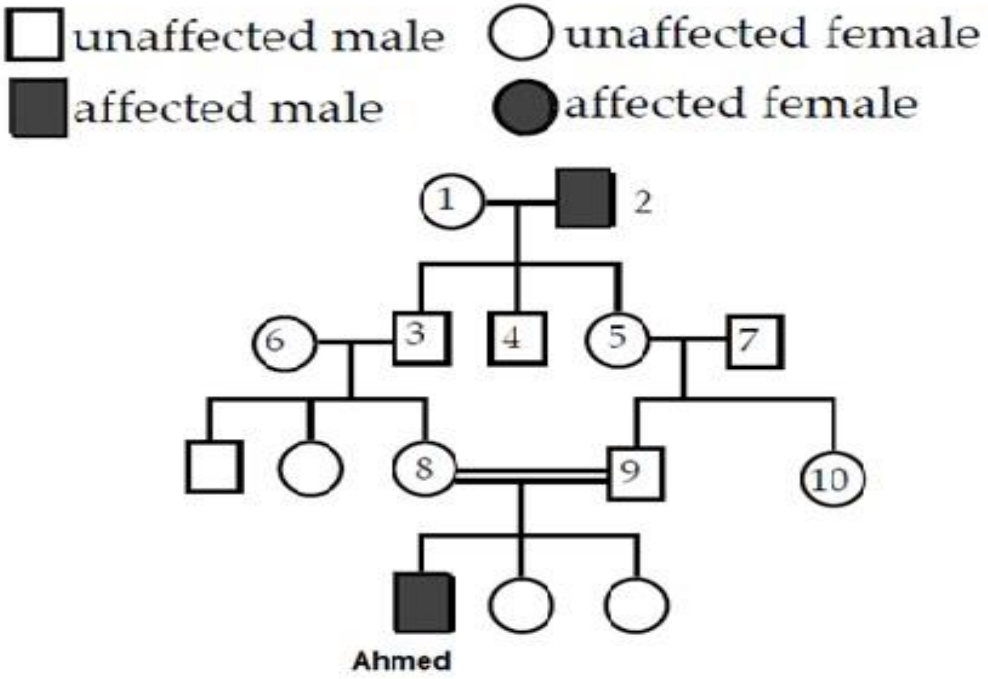
- The role of genetics in these diseases is supported by:

a. Their high frequency in certain ethnic groups.

b. Involvements of family history.

c. Detection of several oncogenes in tumorgenesis.

- Ahmed, a second-year student at the Hashemite university, failed physics. His parents are both physicists, but he remembers that his great grandfather also failed physics. Ahmed constructs the following family pedigree and is convinced that his poor performance in physics is an inherited genetic trait. If Ahmed's hypothesis is true, what is the most likely mode of inheritance?
- Individuals marrying into the family are homozygous for the wild-type (normal) allele. The genotype of individual 10 would be…….(Use G or g to denote the alleles of this gene.)



Autosomal Recessive / GG or Gg