Genetics

Dr. Aman Shakya

2080.03.28

Objectives

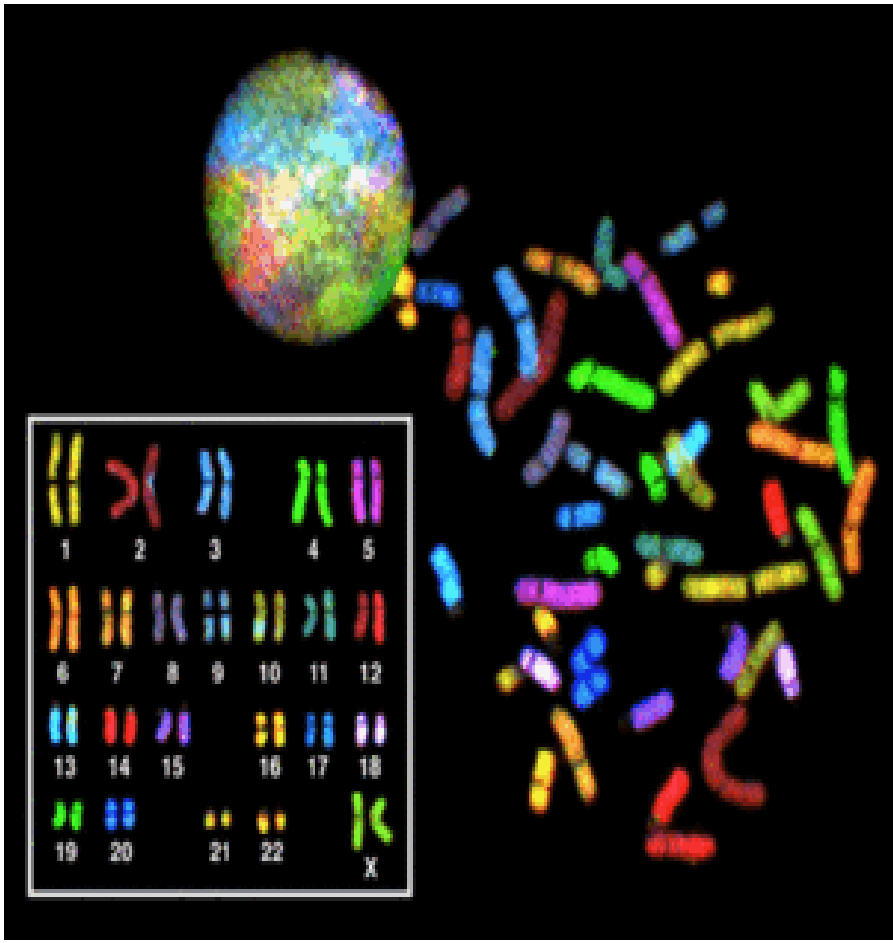
- To discuss about Mendelian Inheritance
- To know about types of Chromosomes
- To describe Chromosomal Disorders
- To discuss Teratogenic Agents

CHROMOSOME

Chromosomes are tiny string like structures present in the nucleus of the cell formed by condensation of chromatin during cell division.

Factors that distinguish one species from another and that enable transmission of genetic information from one generation to the next.

Cytogenetics



- Normal human cell contain 23 pairs of chromosome.
  - 22 pairs called *autosomes*
  - 1 pair called *sex-chromosomes*

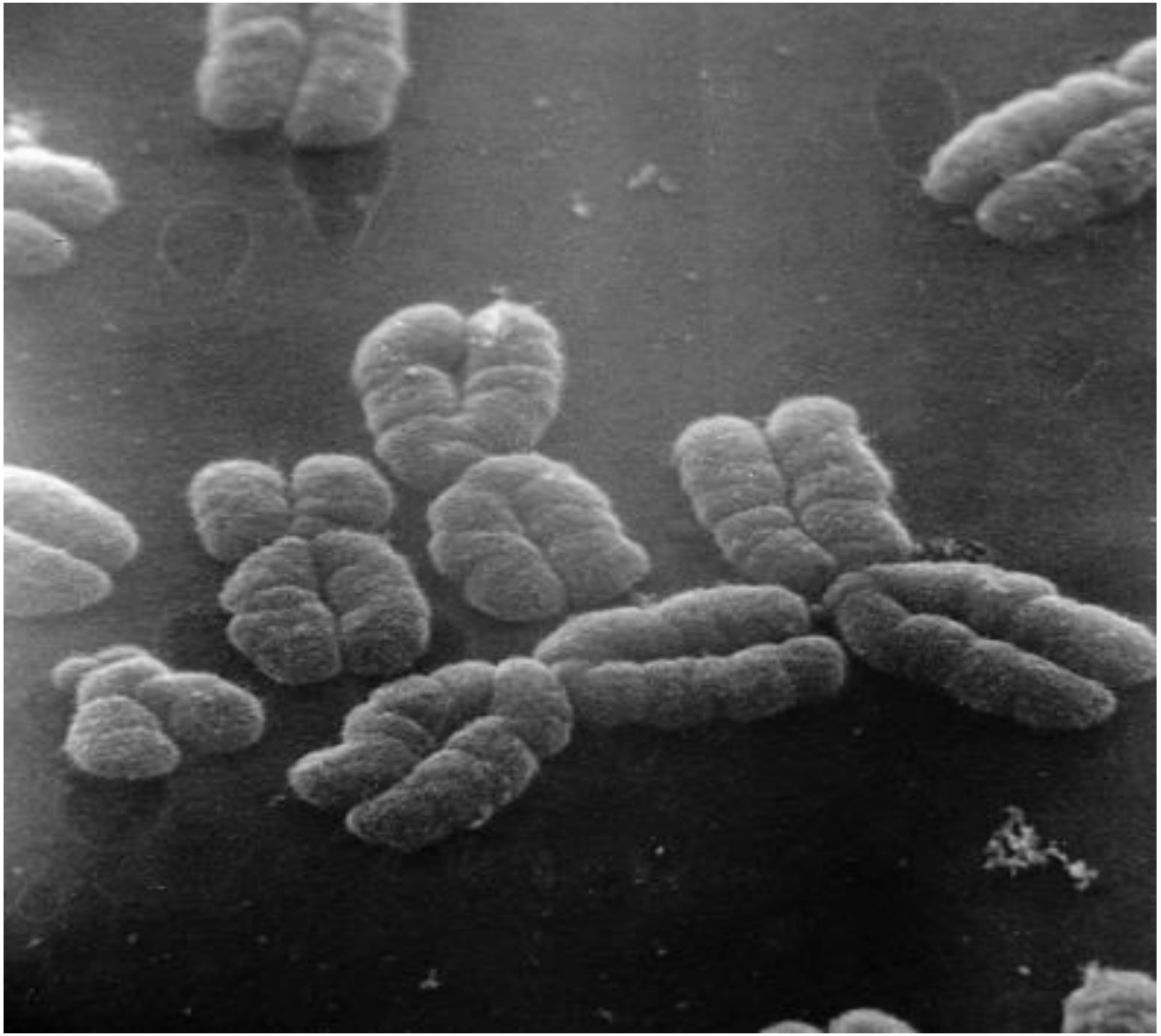
- 46 number of chromosomes present in somatic cell called diploid cell.

- 23 number of chromosomes present in gametes called haploid cell.

Chromosome Morphology

- Two identical strands known as chromatids, or sister chromatids,
- 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.
- Each centromere divides the chromosome into short and long arms, designated “p” and “q” , respectively.

Chromosome Morphology



Chromosomal abnormalities

Definition:

Any deviation either, in number

or

In structure of chromosomes

is referred as chromosomal abnormalities.

Variations in the chromosomes number:

Polyploidy: Presence of multiple of haploid number

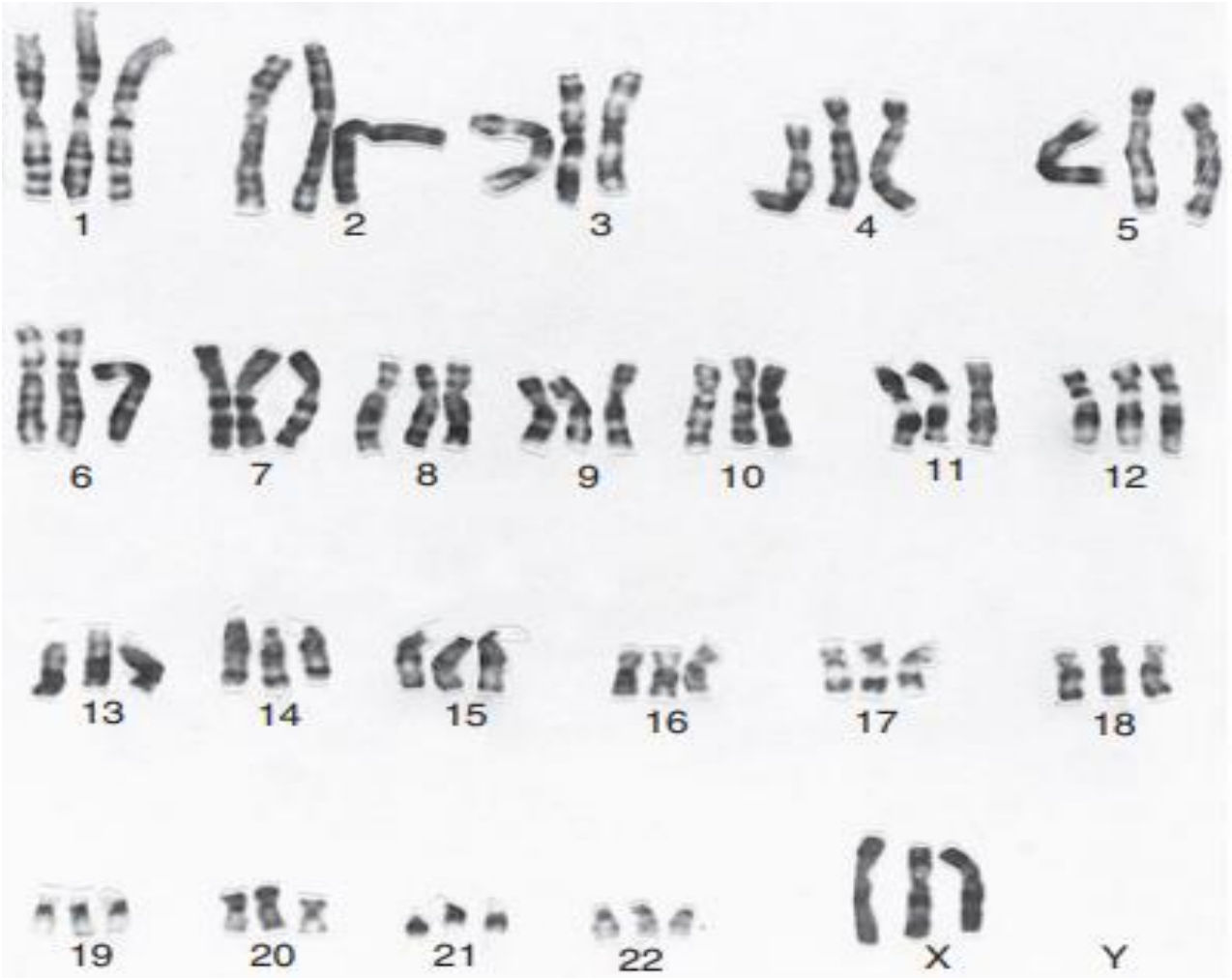
Of chromosomes other than diploid called polyploidy.

Triploidy:

69 chromosomes.

Tetraploidy:

92 chromosomes.



Variations in the chromosomes number:

Aneuploidy / mosaicism : In this condition chromosome number is altered by one chromosome.

Addition of 1 chromosom

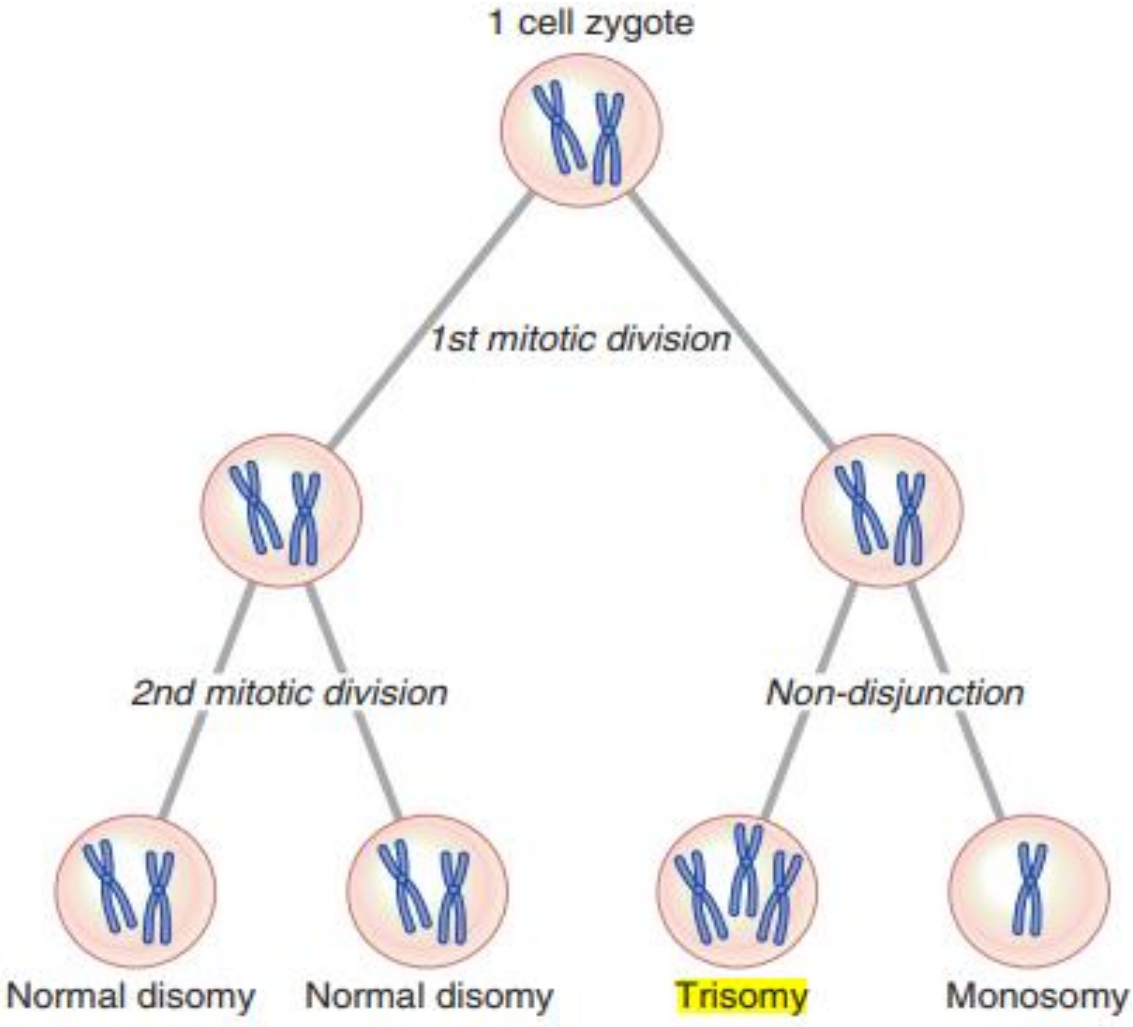
↓

trisomy.

Loss of 1 chromosome

↓

monosomy.



Causes of Non-disjunction:

1. Advancing maternal age
2. Radiation
3. Chemicals
4. Delayed fertilization after ovulation

Structural abnormalities:

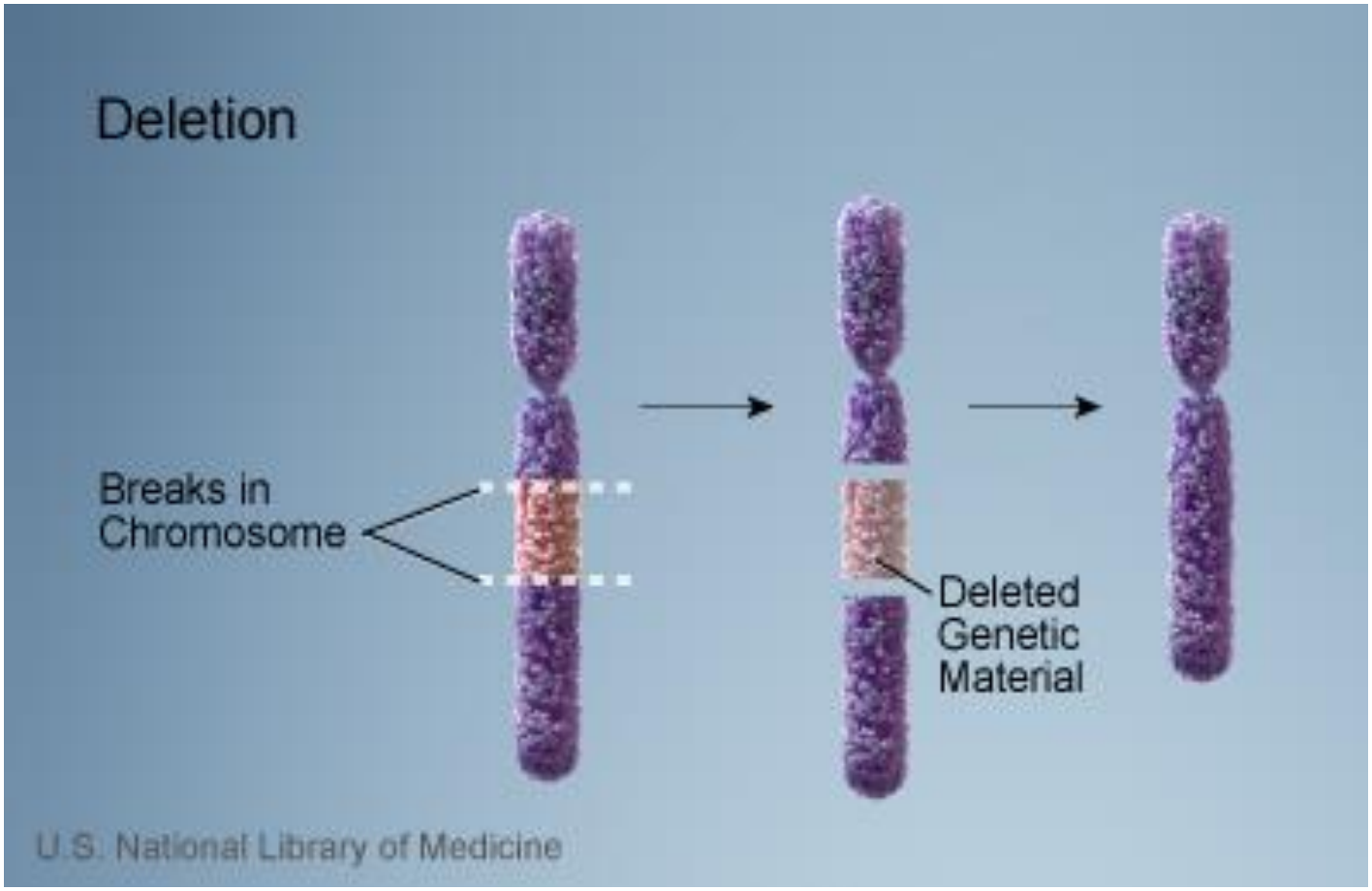
Types of structural abnormities

- Deletion
- Inversion
- Ring chromosome
- Translocation

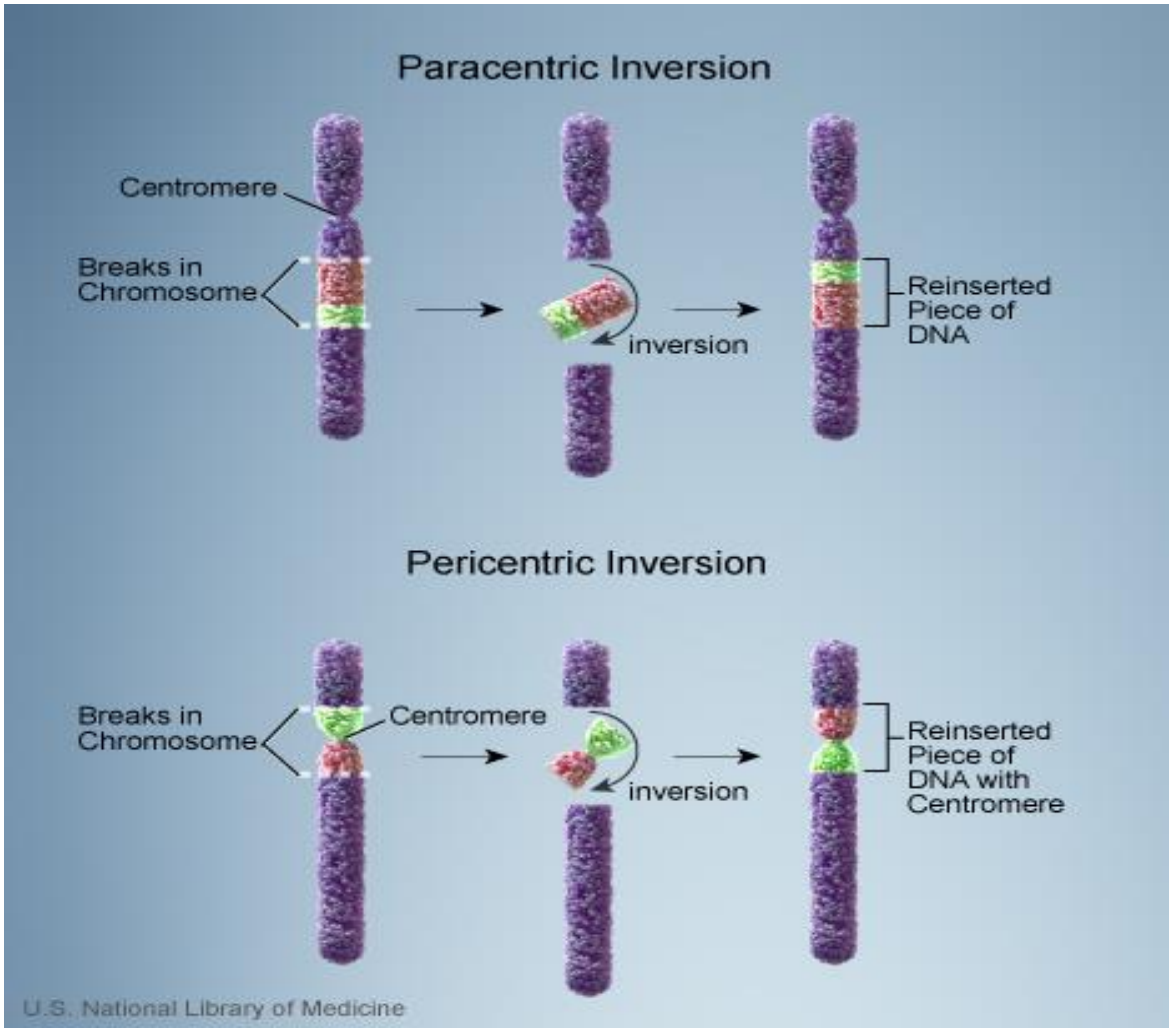
May occur due to:

a) Radiation
b) Chemical agents
c) Viruses

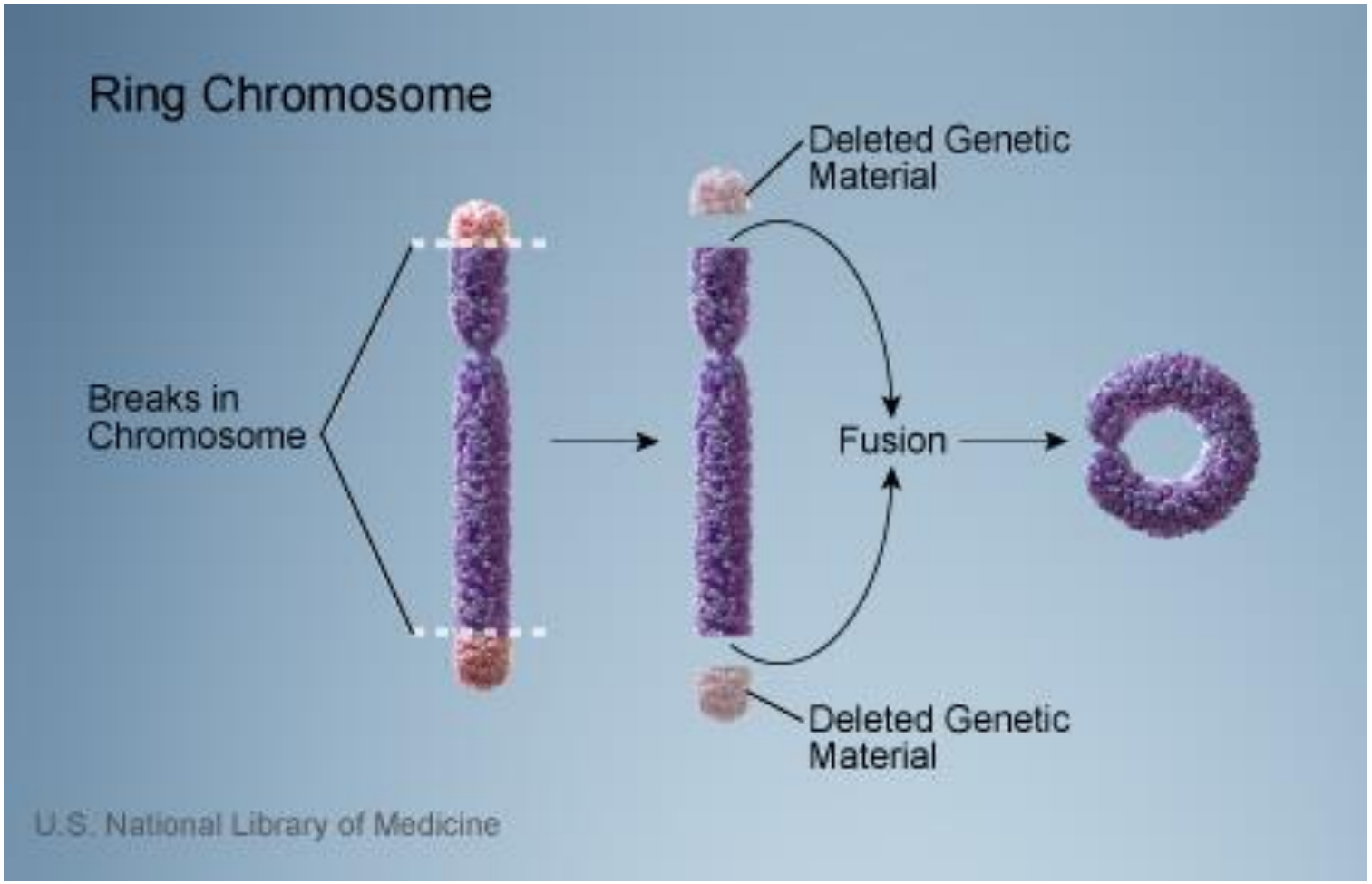
Deletions: loss of a portion of chromosome



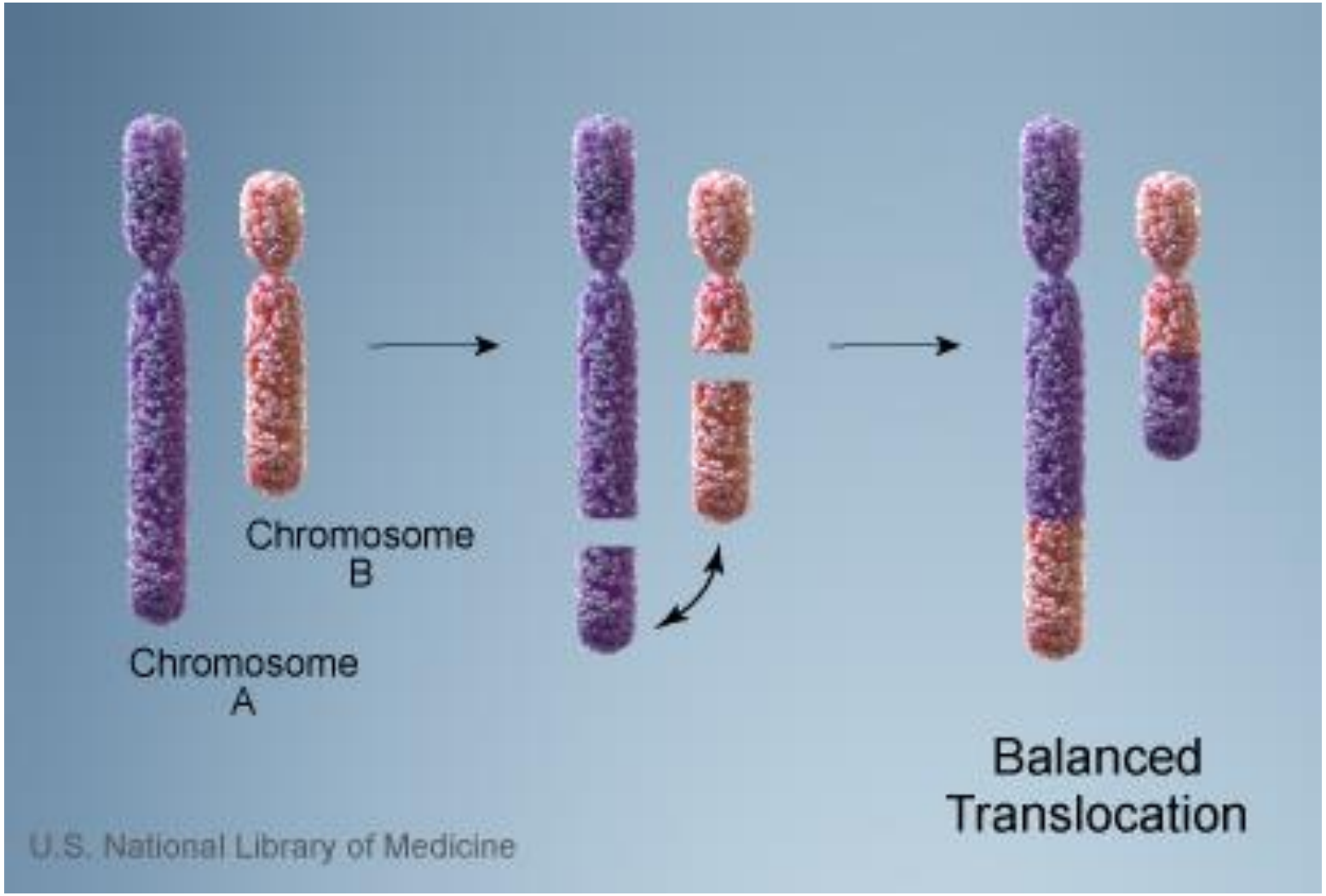
Inversion: 2 breaks, turns upside down and re-attaches



Ring chromosome: 2 break at terminal end and fusion at cut end.



Translocation: One segment transferred to another.



DOWN'S SYNDROME

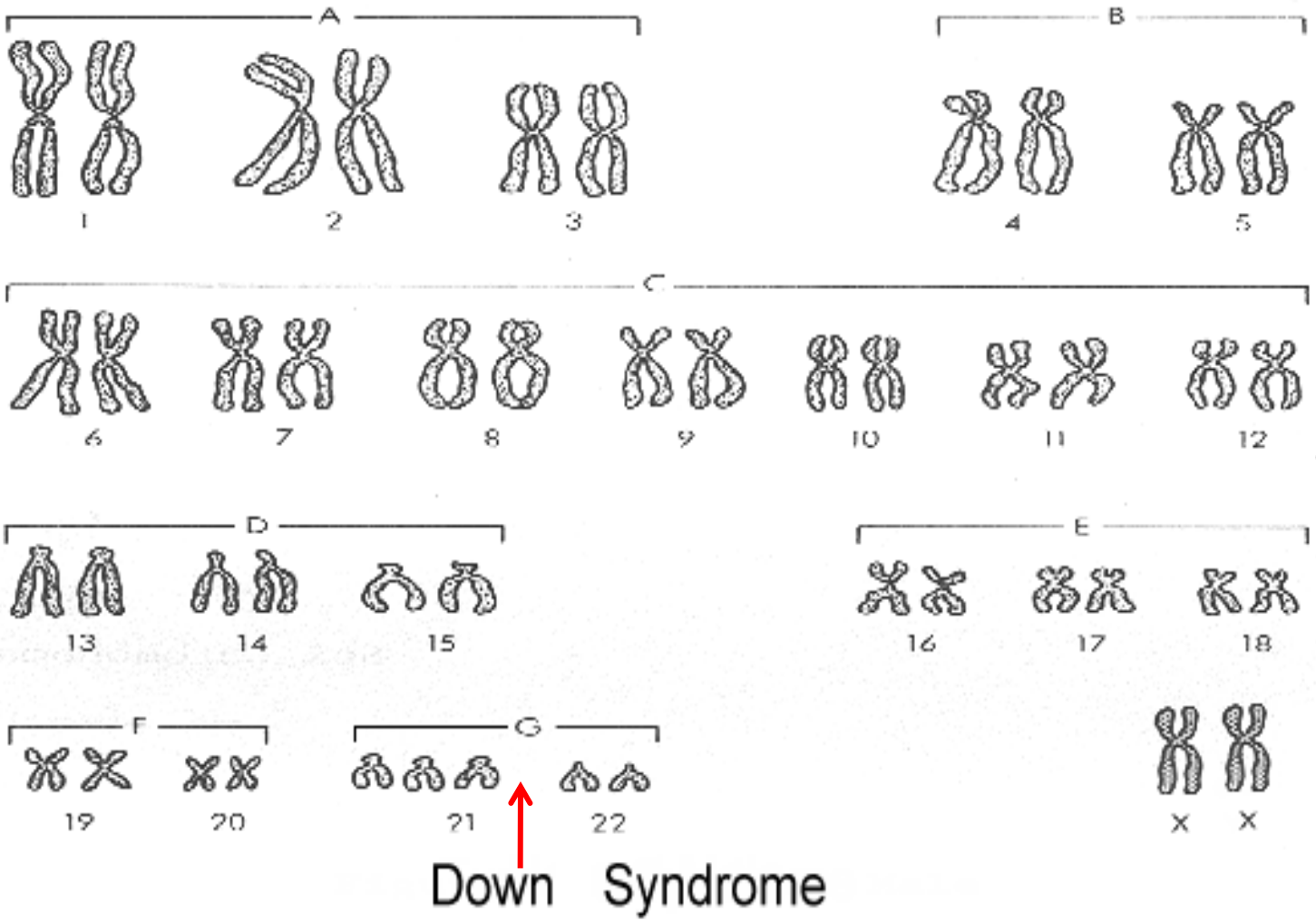
- Trisomy 21 or mongolism
- First identified by Dr Langdon Down in 1866
- Incidence: 1in 700 births
- Male are more affected than female
- Associated with increased maternal age

Karyotype:

47xy + 21

Causes:

- Failure of separation of 21 pair chromosome during meiosis

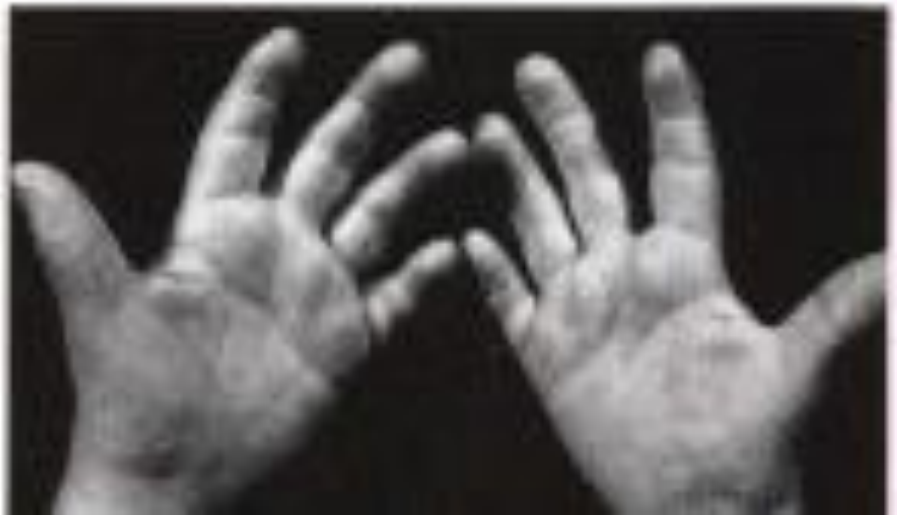

A
B
C
D
E
F
G
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
X
X
Down Syndrome

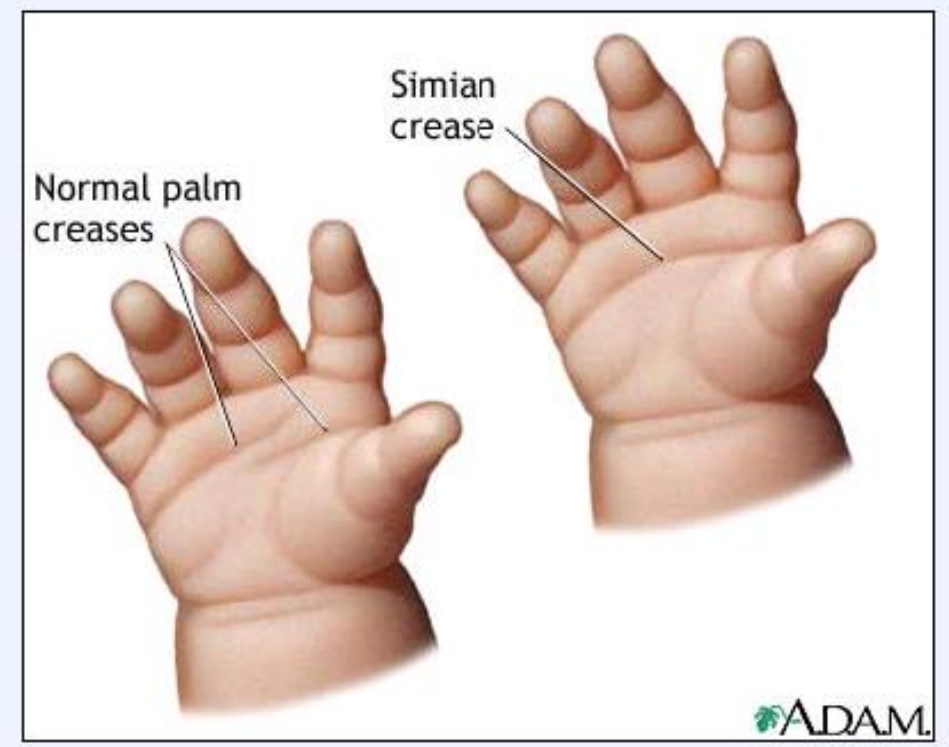
Clinical features

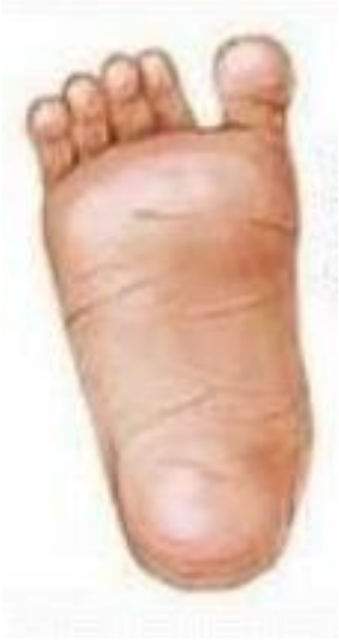
- Mental retardation
- I.Q. range of 25-50
- Short stature
- Hypotonia of muscles
- Approximately 40% of children suffer from heart defect.
- Craniofacial finding:
  - Round face , Oblique palpebral fissure
  - Inner epicanthic fold, open mouth with protruding tongue
  - low set ears , flat nose

Clinical features

- Short and broad hand with single transverse crease (simian crease) in palm.
- Prominent gap between 1st and 2nd toes.
- Umbilical hernia




Simian crease
Normal palm creases
A.D.A.M.



Edward's syndrome

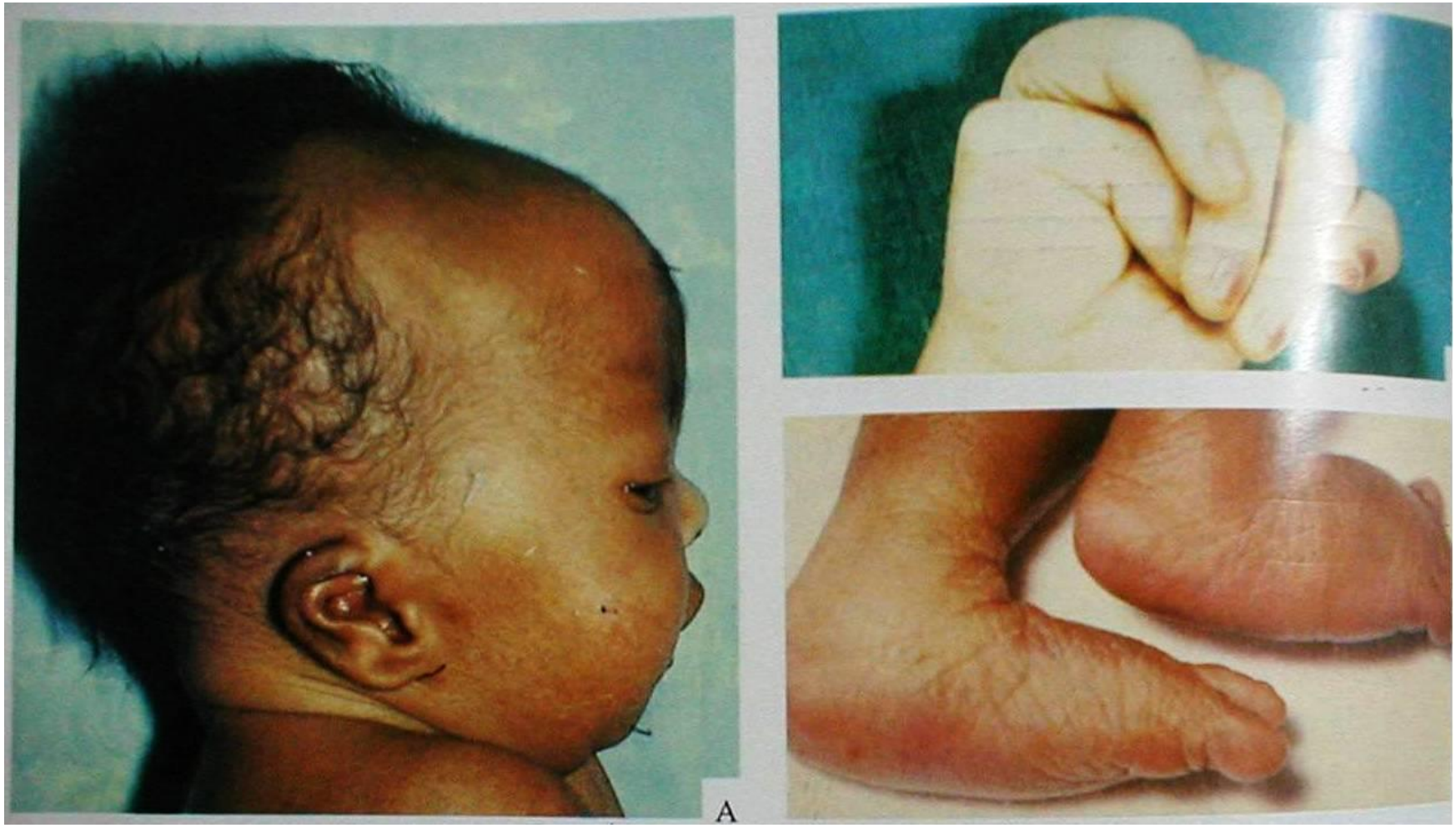
- Trisomy 18
- Described by Edward in 1960
- Incidence1 in 7000 birth
- Rare to find live born
- Do not live beyond few months

Karyotype:

47xy + 18

Clinical features

- Mental retardation
- Failure to thrive
- Hypertonia
- Low set malformed ears
- Short sternum
- Clenched fists
- Rocker bottom feet
- Heart defect


A

PATAU'S SYNDROME

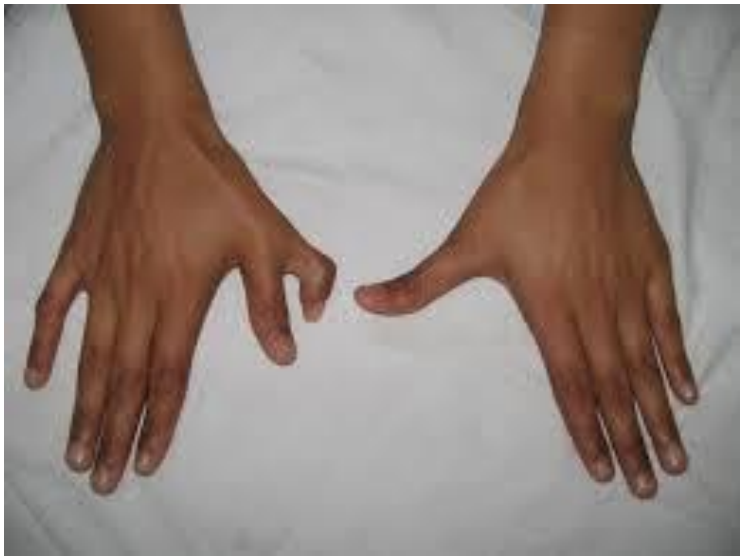
- Trisomy 13
- Incidence 1 in 5000 births
- Die in a month

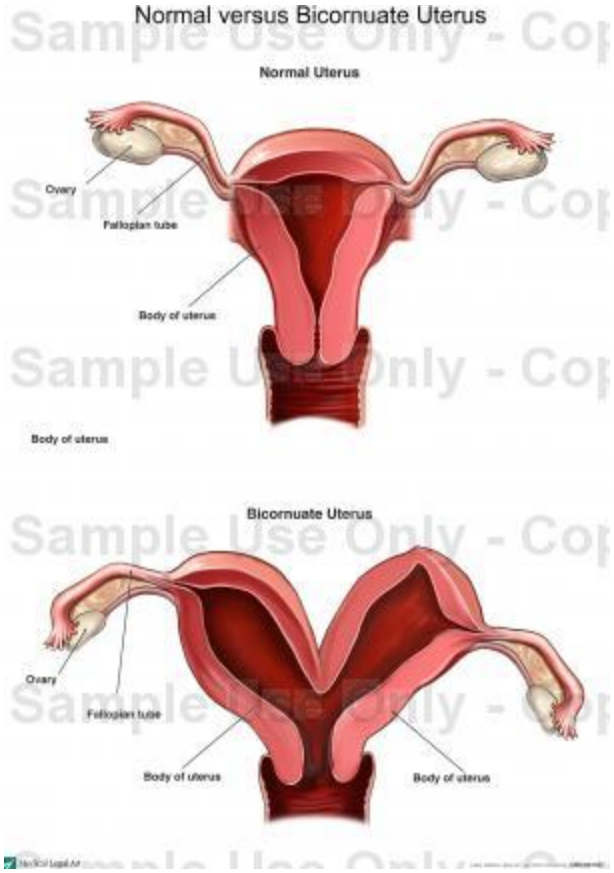
Karyotype

47 XY + 13

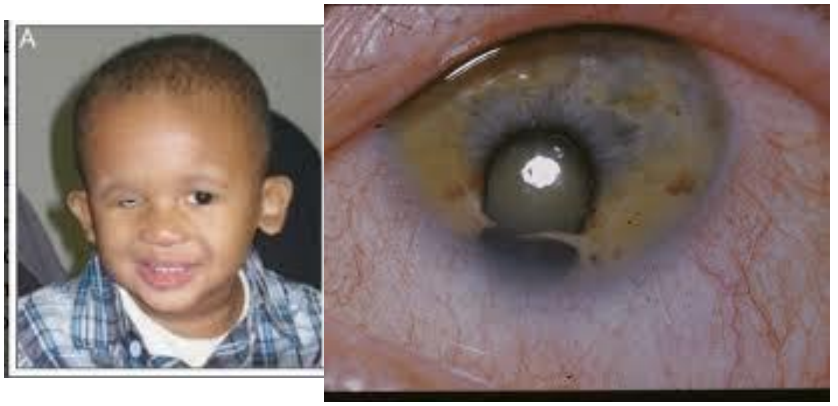
Clinical features

- Growth & mental retardation
- Cleft lip , cleft palate
- Malformed ear
- Microphthalmos
- Polydactyly
- Clenched fists
- Rocker bottom feet
- Bicornuate uterus




Normal versus Bicornuate Uterus
Normal Uterus
Ovary
Fallopian tube
Body of uterus
Body of uterus
Bicornuate Uterus
Ovary
Fallopian tube
Body of uterus
Body of uterus


©Mayo Foundation for Medical Education and Research. All rights reserved.


A

Turner's syndrome

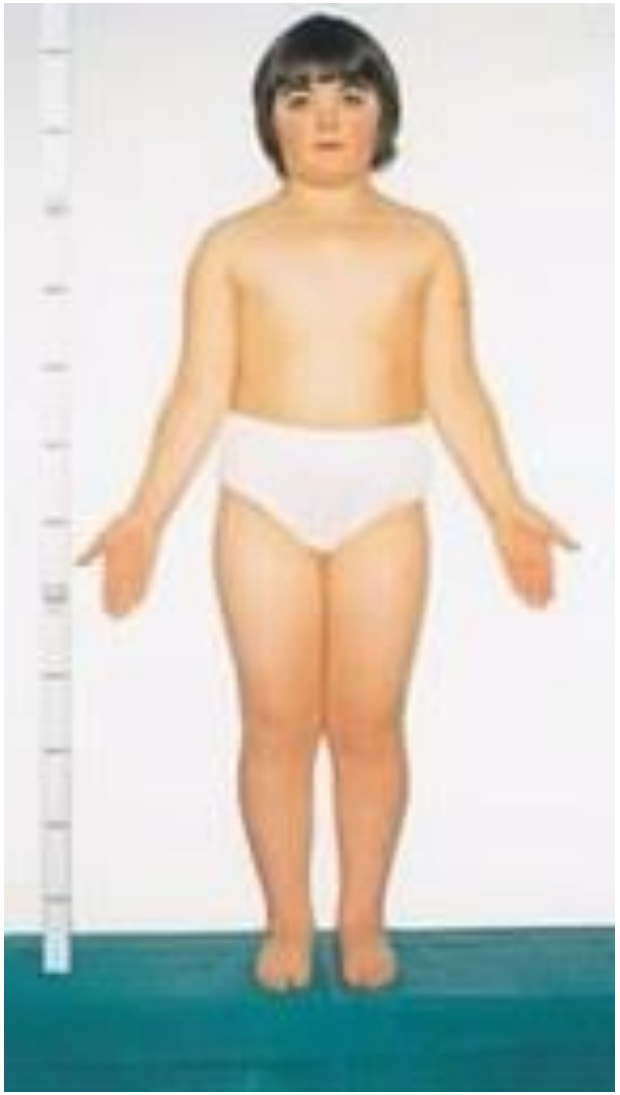
It is a monosomic condition found only in females.

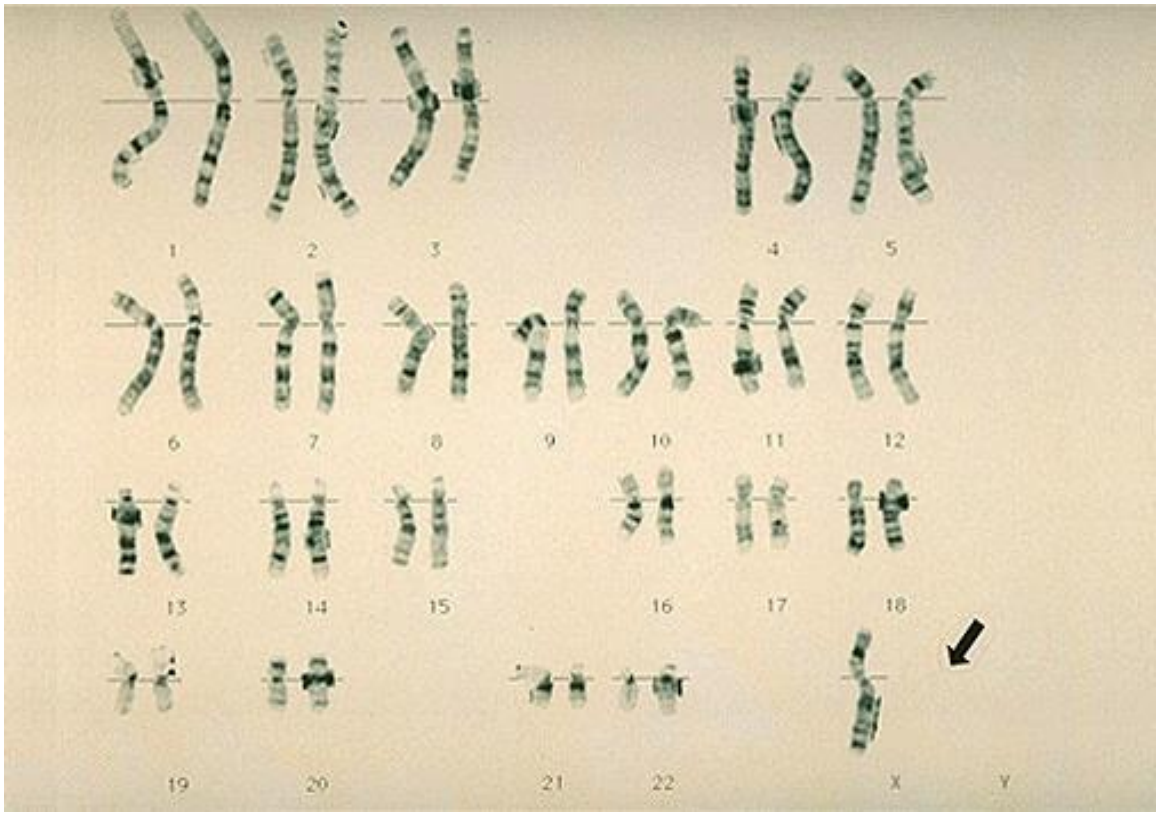
- X monosomy
- Described by Turner in 1938
- Incidence 1 in 5000
- 96-98% do not survive to birth

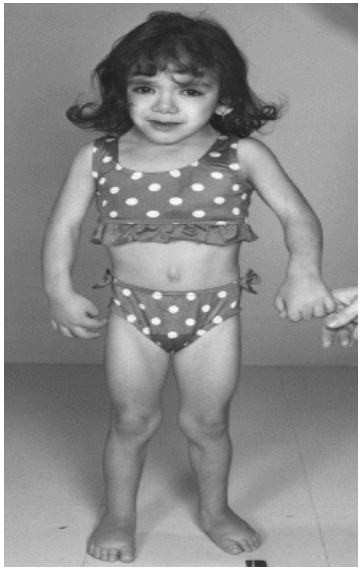
Karyotype:
45 X

Clinical features

- Short stature
- Webbing of neck
- Broad chest with widely spaced nipples
- Low posterior hair line
- Infantile external genitalia
- Gonadal dysgenesis (Amenorrhea, sterility)
- Scanty pubic or axillary hair
- Coarctation of aorta




1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
X
Y



Klinefelter's syndrome

- It is a trisomic condition found only in males.
- Incidence 1 in 1000 birth
- Harry klinefelter in 1942

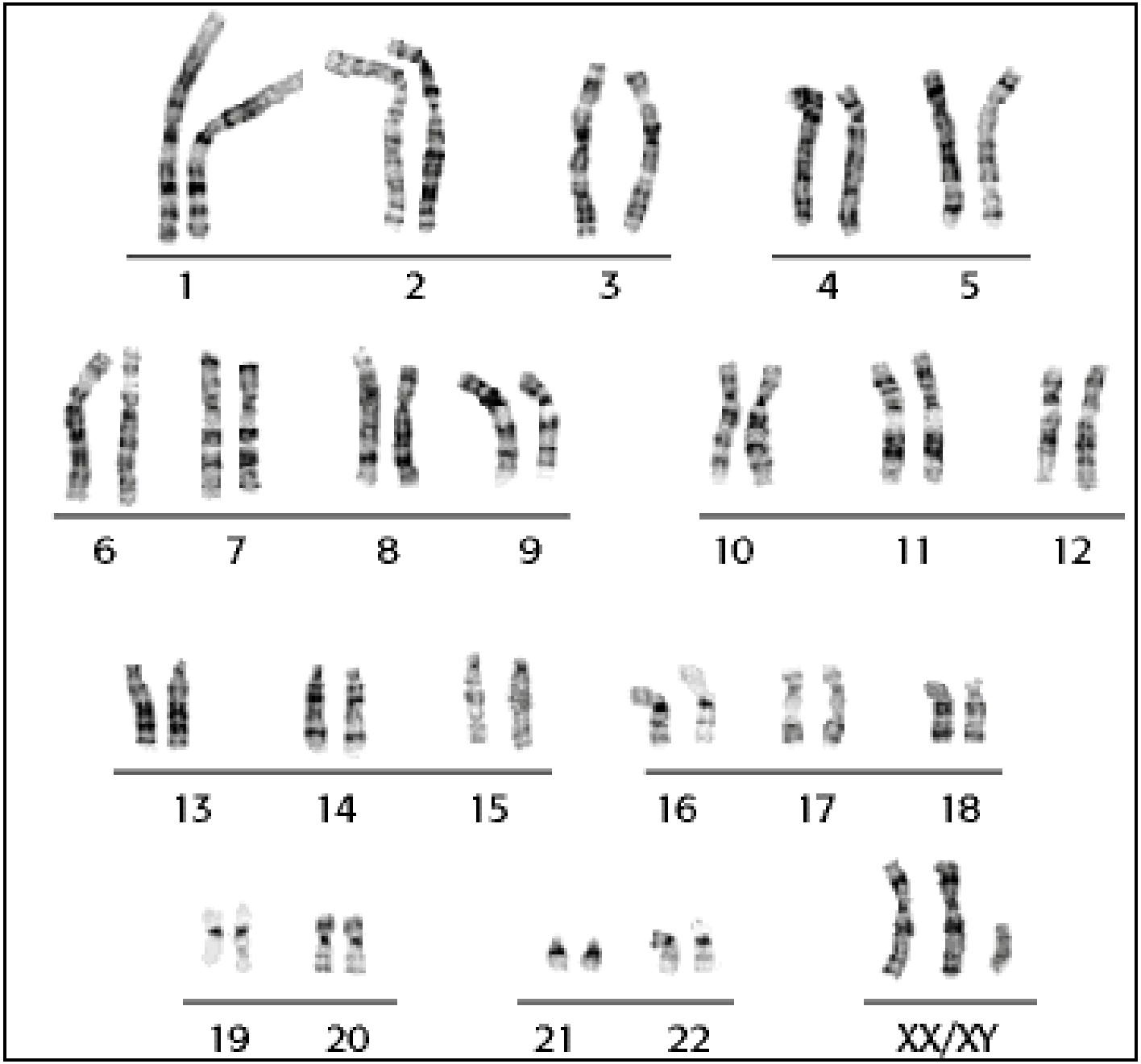
Karyotype:

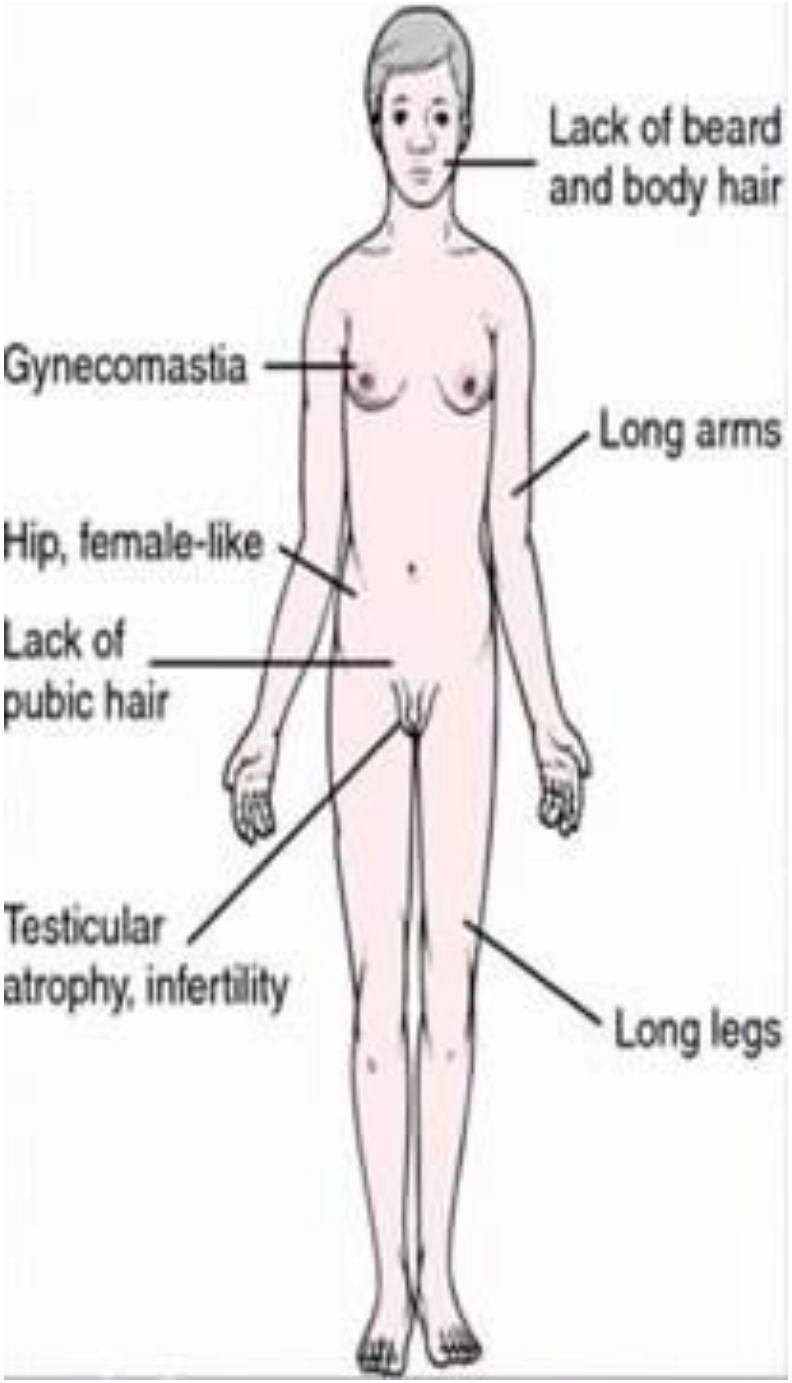
47 XXY

Clinical features

- Patients are tall thin , eunuchoid
- Gynecomastia
- Hypogonadism and associated azospermia and sterility
- Testis are small , scrotum & penis show hypoplasia
- Pubic ,chin & axillary hair reduced
- Length of legs and arms are longer
- Mental retardation

Human Karyotype (XXY, 47)



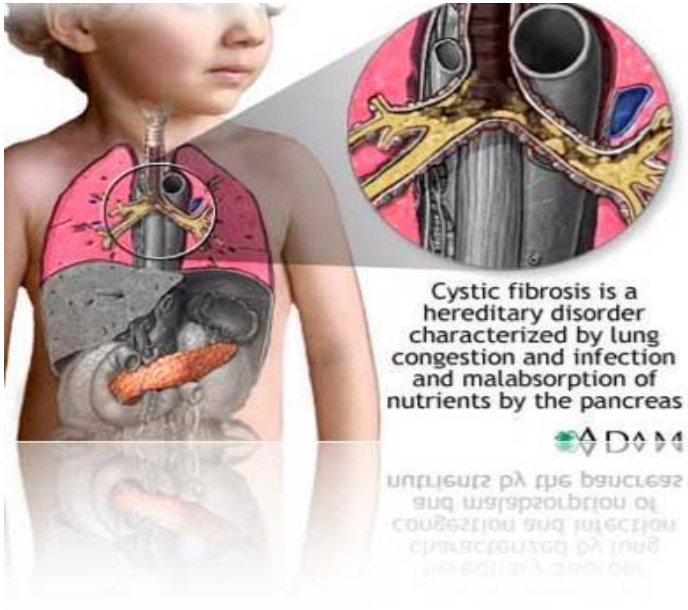

Lack of beard
and body hair
Gynecomastia
Long arms
Hip, female-like
Lack of
pubic hair
Testicular
atrophy, infertility
Long legs

Cystic fibrosis

- It is also known as mucoviscidosis.
- It is autosomal recessive disorder.
- The gene of cystic fibrosis present on the long arm of chromosomes number 7.
- Incidence 1 in 2500 birth

Clinical features

- Recurrent respiratory infection
- Obstruction of respiratory airways
- Obstructive azospermia
- Growth failure

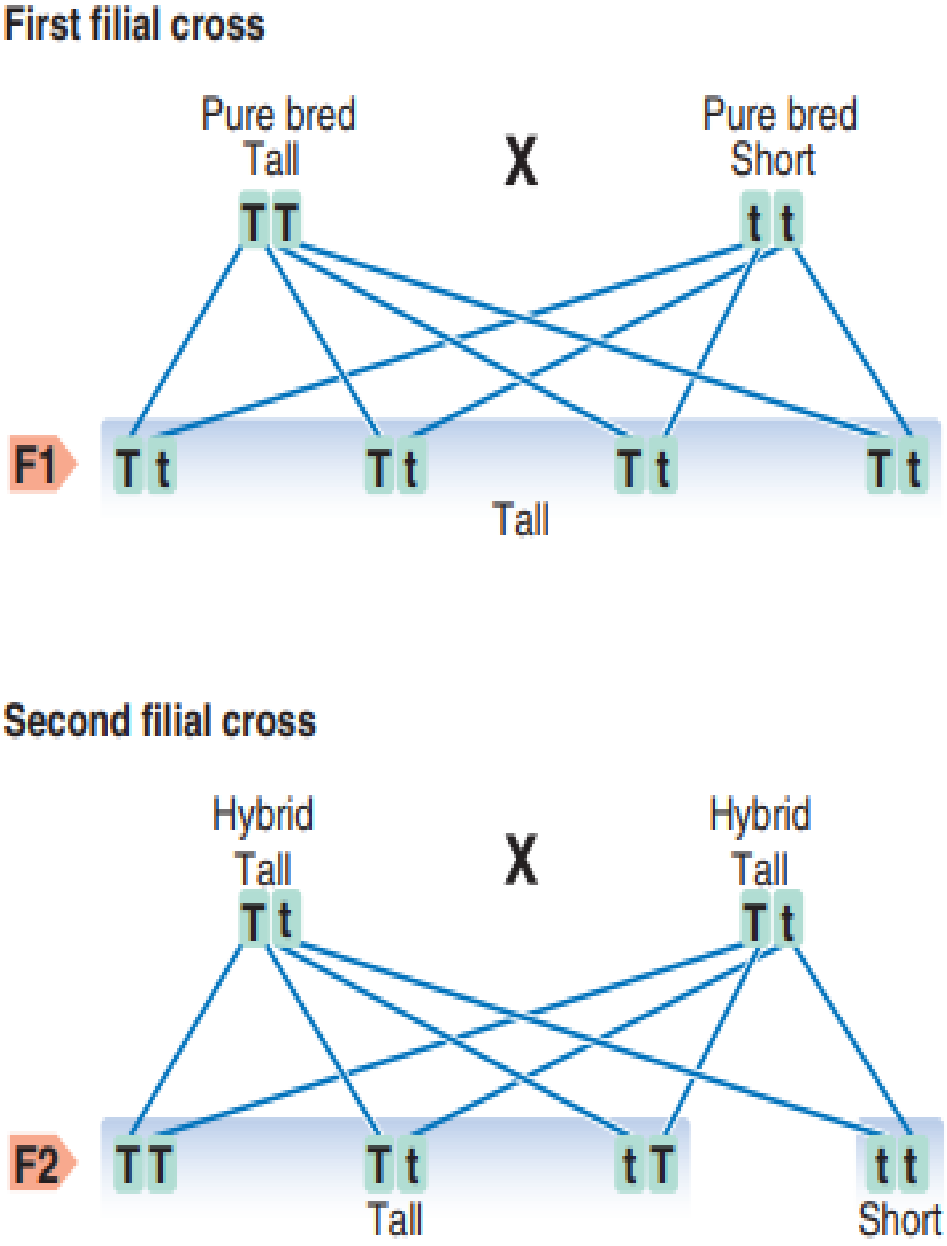


Gregor Mendel (1822-1884)

- Austrian monk
- Results of breeding experiment on garden peas (1865)
- Can be considered as the discovery of gene and how they are inherited
- Danish botanist Johannsen coined the term “ gene”

Breeding experiment

- Dominant characters
- Recessive characters
- Homozygous (TT, tt)
- Heterozygous (Tt)
- Allelomorphs / alleles



Mendel's law

1. The Law of Dominance and Uniformity

- Some alleles are dominant over the other alleles for a given gene. Those traits that are not dominant are termed recessive.

2. The Law of Segregation

- Each person possesses two genes for a particular characteristic, only one of which can be transmitted at any one time.

3. The Law of Independent Assortment

- Alleles of different genes segregate independently of one another during gametogenesis and are distributed independently of one another in the next generation.

Human Genetics

Genetics is the study of gene & the statistical laws that govern the passage of genes from generation to next

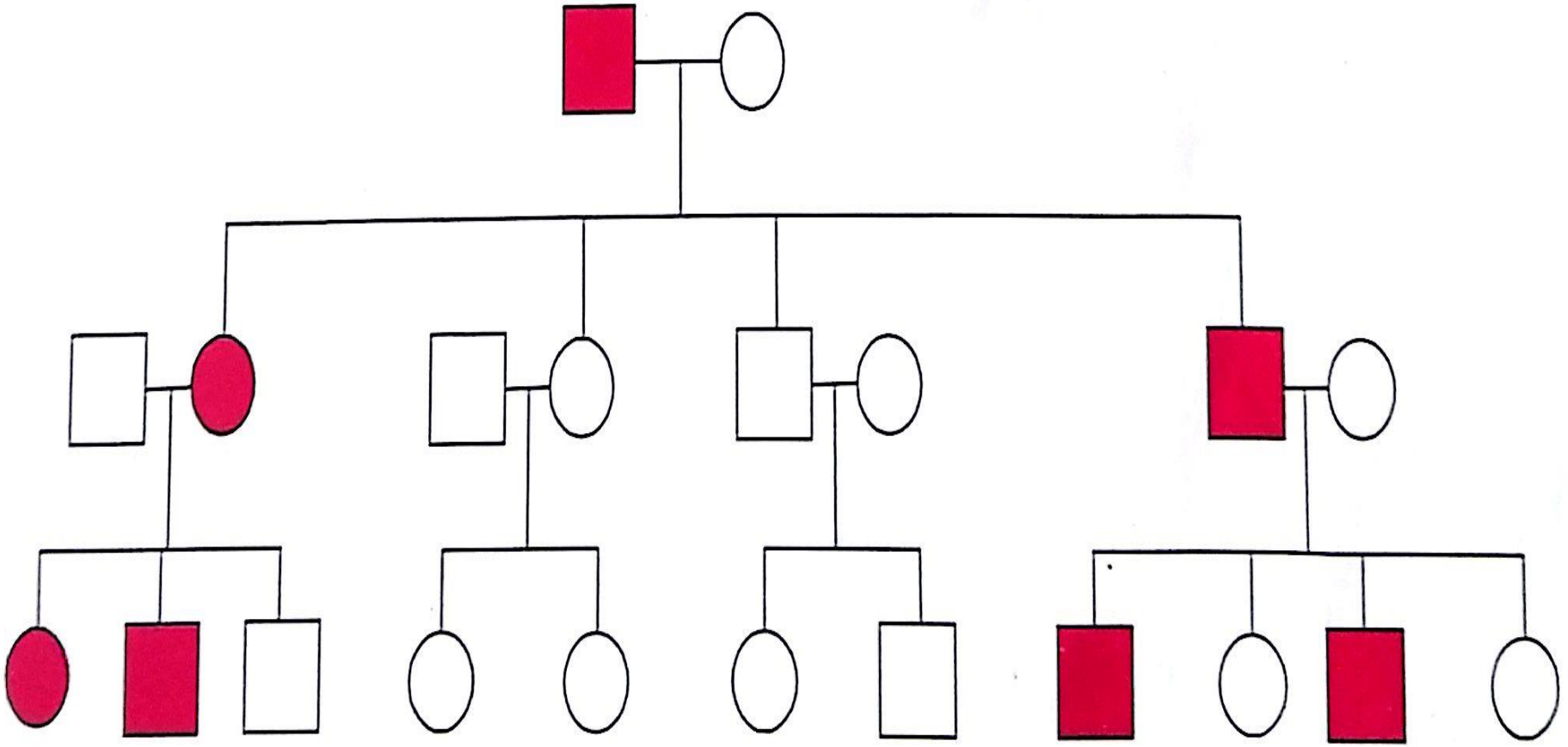
The process of transmission of characters from one generation to next (parents to children) known as **inheritance or heredity**

In general, inheritance patterns for single gene disorders are classified based on whether they are autosomal or X-linked and whether they have a dominant or recessive pattern of inheritance. These disorders are called ***Mendelian disorders***

Autosomal dominant inheritance

- Gene manifest the disorder even in single dose
- Males and females are equally affected with traits
- Disorder is seen in every generation without **skipping**
- **Affected person** will always have an **affected parent**
- Normal offspring of pedigree do not transmit the disorder to next generation as do not have the abnormal gene

Pedigree chart of autosomal dominant inheritance

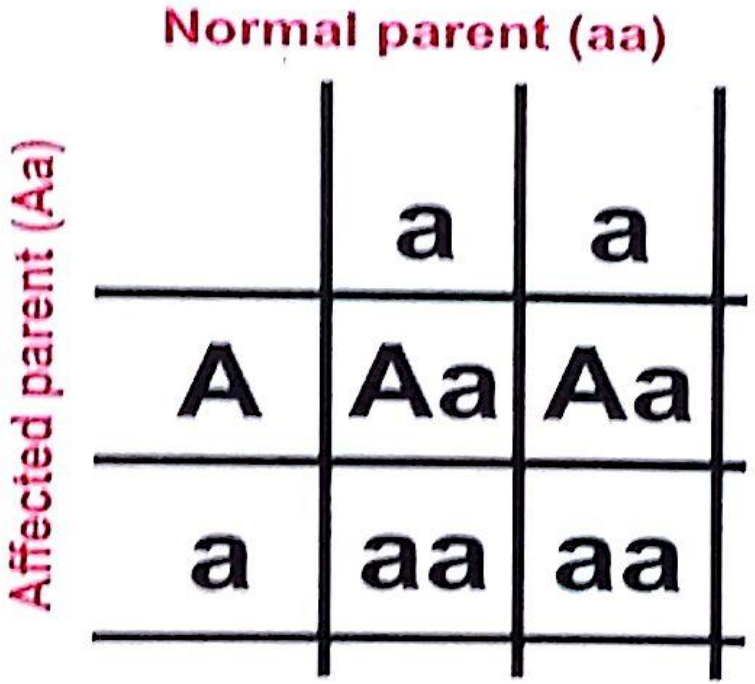


Example of disorders:

- Polycystic kidney
- Neurofibromatosis
- **Achondroplasia –** affected person is a **dwarf** , mutation in fibroblast growth factor gene leading to defective cartilage growth

Matting between normal (aa) & affected (Aa) parents (Aa x aa)

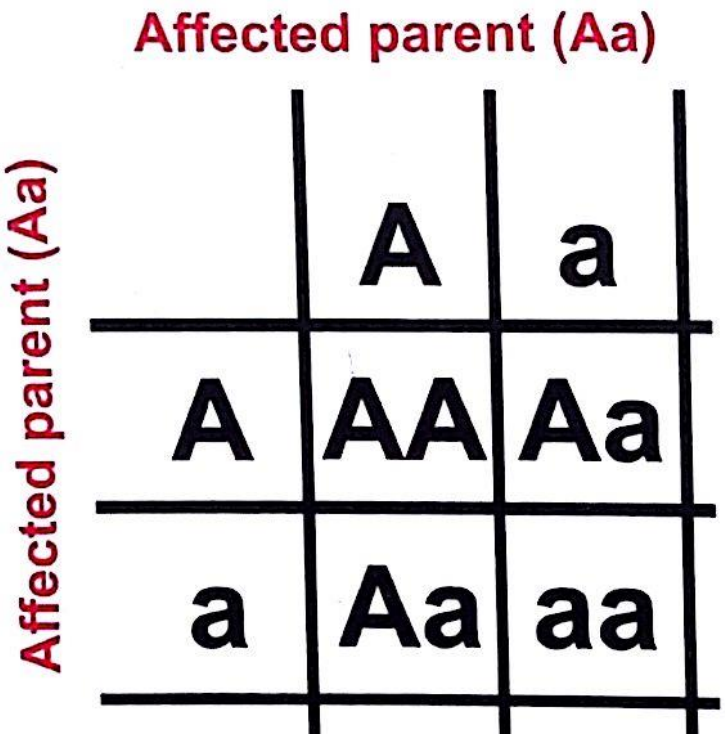
- Normal gene as ‘’a’’ & mutant gene as ‘’A’’
- Genotype normal parent ‘’aa’’
- Affected parent ‘’Aa’’



A = Mutant gene
a = Normal gene
Aa = 50% (Heterozygous affected)
aa = 50% (Homozygous normal)

Mating between both affected parents

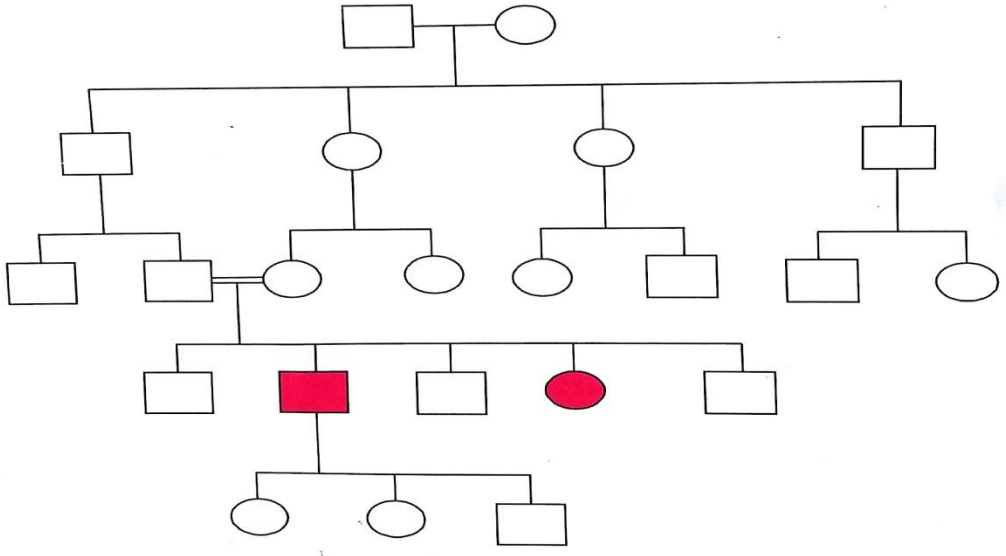
- Homozygous affected offspring (AA) would be severely affected as mutant genes as in double dose



AA = 25% Severely affected
Aa = 50% Affected
aa = 25% Normal

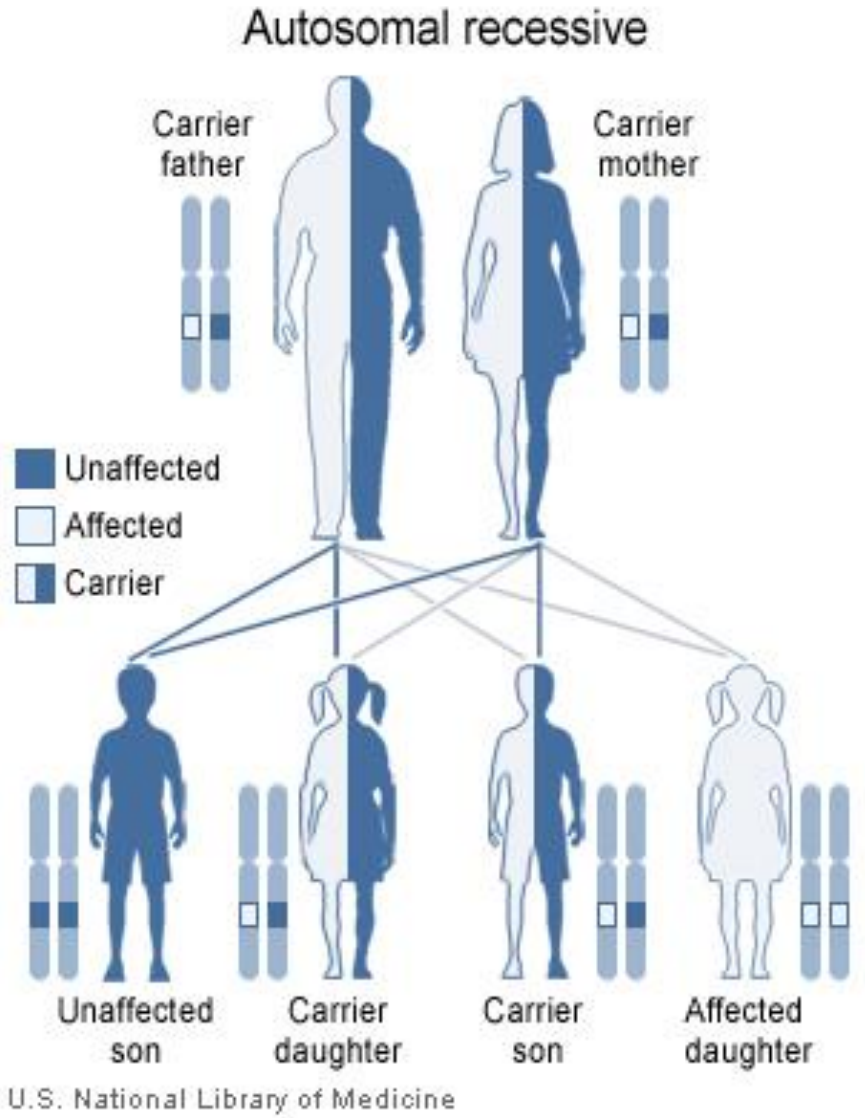
Autosomal recessive inheritance

- Gene manifest only when mutant allele is present in a double dose
- Diseases is transmitted by couple , both of whom are carriers of abnormal gene but couple are not affected
- Only siblings are affected but parents are normal
- Many individuals in a single generation are affected
- Usually affect enzymatic proteins

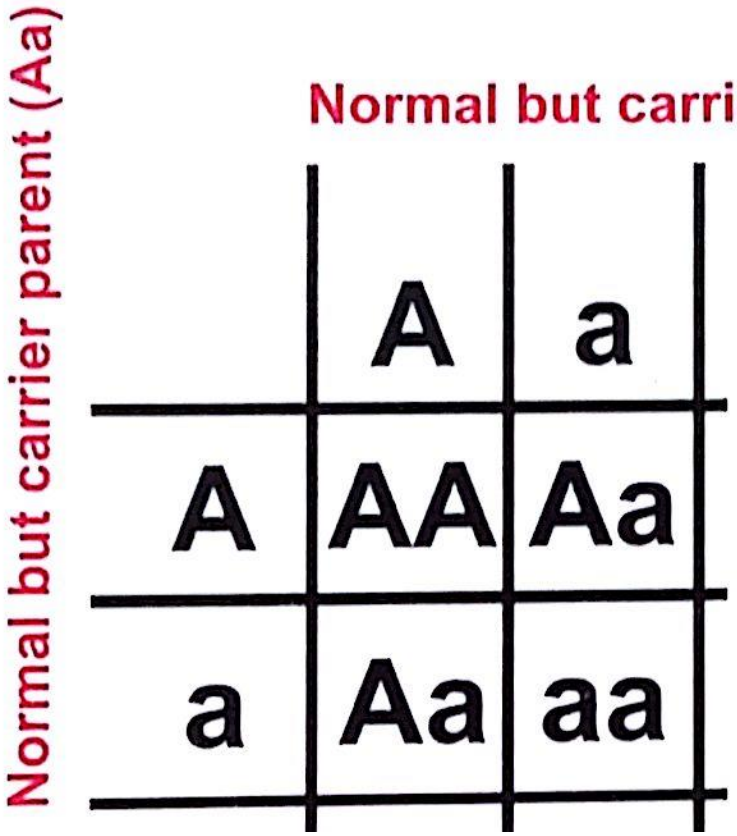


Pattern Of Inheritance:

- Typical pattern is two **heterozygous *unaffected* (carrier) parent**
- The trait does not usually affect the parent, but siblings may show the disease
- Siblings have one chance in four of being affected
- Both sexes affected equally

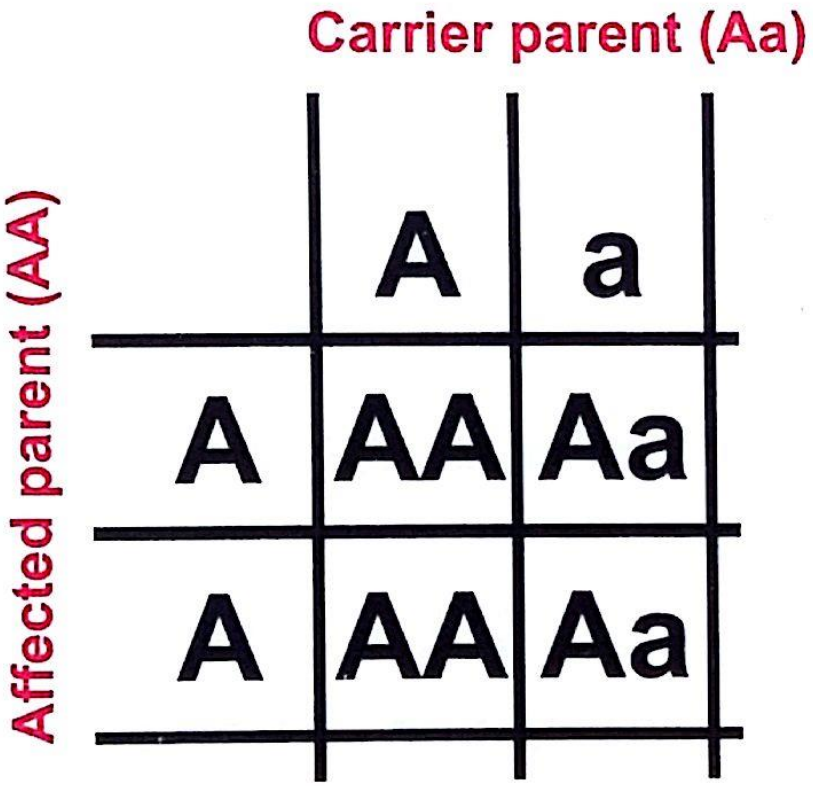


Mating between two carrier parents



A = Mutant gene
a = Normal gene
AA = 25% Affected
Aa = 50% Normal but carrier
aa = 25% Normal

Mating between one carrier and one affected parents

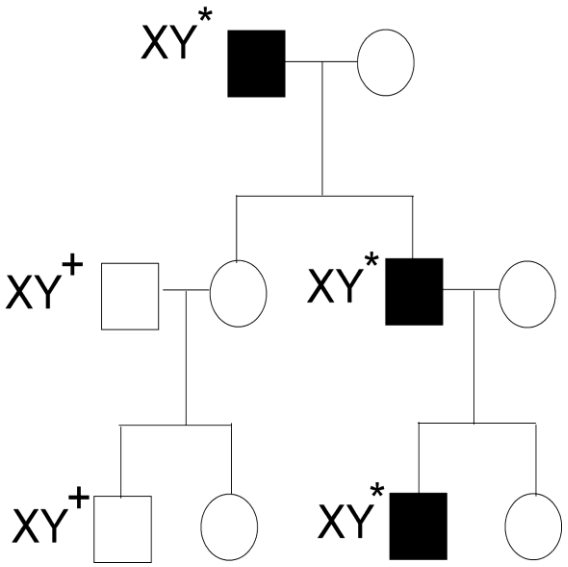


Aa = 50% Normal but carrier
AA = 50% Affected

Example of Autosomal recessive

- Metabolic — Cystic fibrosis
  Phenylketonuria: phenylalanine hydroxylase.
  Glycogen storage diseases
- Hematopoietic — Sickle cell anemia
- Endocrine — Congenital Adrenal hyperplasia

Sex-linked inheritance



- Gene located on X or Y chromosome
- **Y-linked**
- **X-linked**
- **Y-linked inheritance:**
- Very few
- Y- chromosome bears H-Y histocompatibility antigen genes and genes for spermatogenesis

An affected M transmits Y-linked traits to all his sons but daughters remain unaffected (due absence of Y-chr.)

- Only male affected
- All sons of affected males are also affected
- Females never transmits the traits
- i.e growth of **Hair on the pinna of ears**

X-linked inheritance

- May be either recessive or dominant

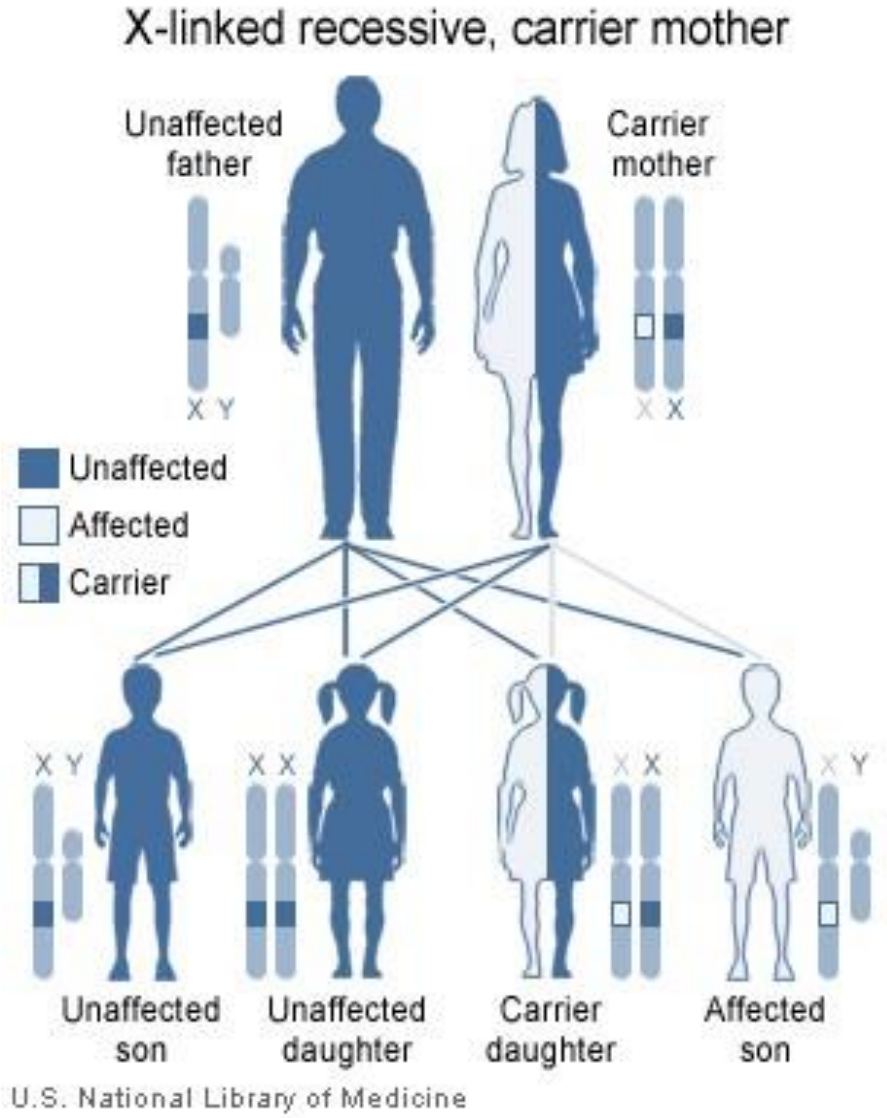
- **X-linked Recessive inheritance:**
- Some of the gene on X-chromosome are functionally similar to genes present on autosomes
- These genes have function other then the determination of sex
  - Gene for colour perception or gene for blood clotting

Disorders-

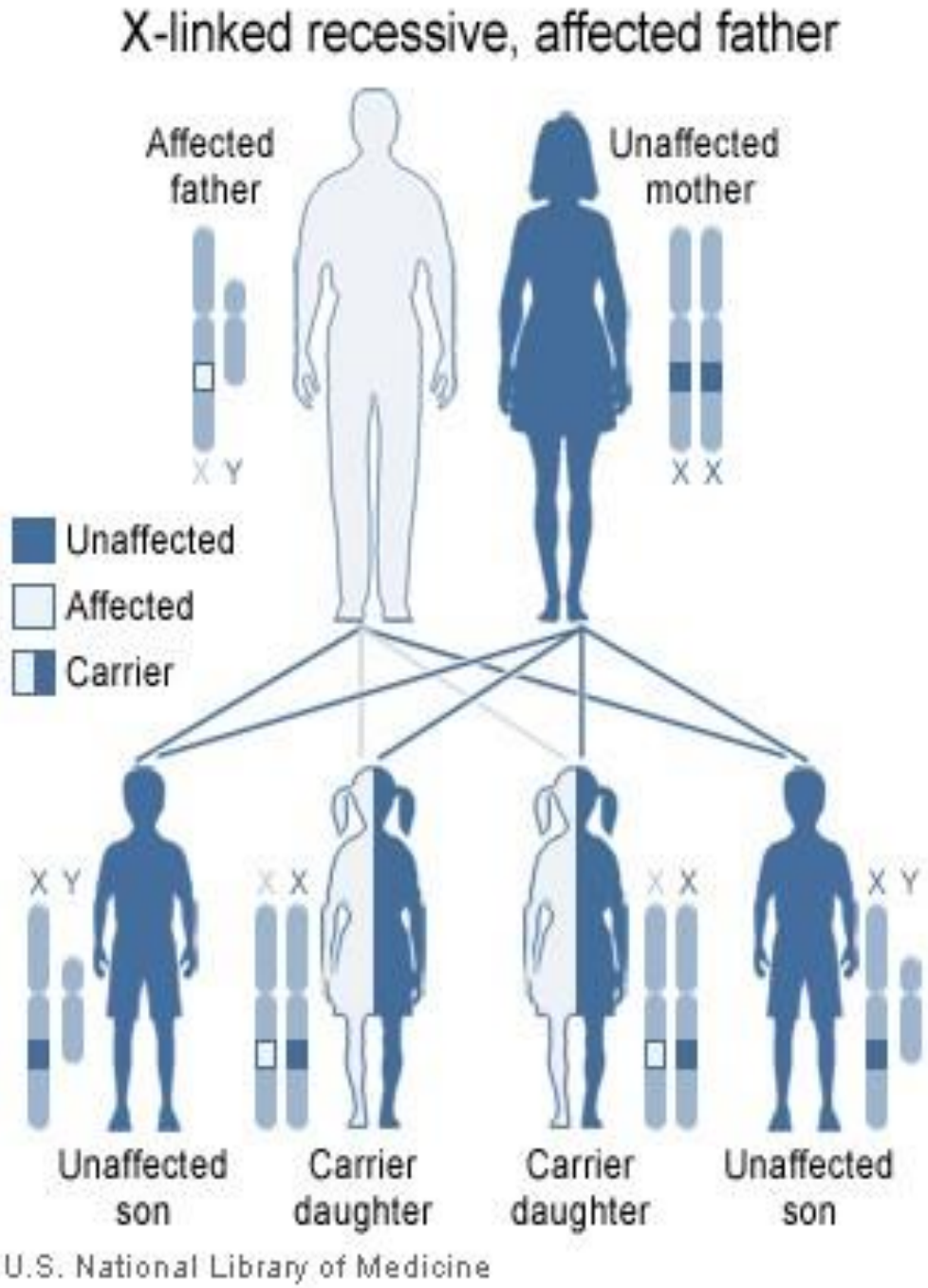
- **Hemophilia**
- **Diabetes mellitus**
- **Colour blindness**

Pattern Of Inheritance:

- Disease usually passed on from carrier mother.
- Expressed in male offspring, females are carriers
- Skipped generations are commonly seen
- In this case, Recurrence risk is half of sons are affected, half of daughters are carriers



- All the daughters are heterozygous carriers and all the sons are homozygous normal



X-linked Dominant Inheritance

- X-linked dominant disorders are seen more commonly in females than in males, or in the case of some diseases, affect only females.
- It is thought that the hemizygous males are so severely affected, they do not survive.
- This may be reflected in the pedigree by multiple miscarriages or male infant deaths.
- Examples: Rett syndrome, the X-linked lissencephaly and double-cortex syndrome, and incontinentia pigmenti type 1, characterized by dermatological, ocular, dental, and neurological abnormalities

- Lissencephaly, which literally means "smooth brain," is a **rare, gene-linked brain malformation** characterized by the absence of normal convolutions (folds) in the cerebral cortex and an abnormally small head (microcephaly). In the usual condition of lissencephaly, children usually have a normal sized head at birth

- Rett syndrome is a **rare genetic neurological and developmental disorder** that affects the way the brain develops, causing a progressive loss of motor skills and speech. This disorder primarily affects girls

Teratogenic Agents

- An agent that can cause a birth defect by interfering with normal embryonic or fetal development is known as a teratogen.
- Many teratogens have been identified and exhaustive tests are now undertaken before any new drug is approved for use by pregnant women.
- The potential effects of any particular teratogen usually depend on the dosage and timing of administration during pregnancy, along with the susceptibility of both the mother and fetus.

Teratogenic Agents

Table 16.6 Drugs With a Proven Teratogenic Effect in Humans

Drug	Effects
ACE inhibitors	Renal dysplasia
Alcohol	Cardiac defects, microcephaly, characteristic facies
Chloroquine	Chorioretinitis, deafness
Diethylstilbestrol	Uterine malformations, vaginal adenocarcinoma
Lithium	Cardiac defects (Ebstein anomaly)
Phenytoin	Cardiac defects, cleft palate, digital hypoplasia
Retinoids	Ear and eye defects, hydrocephalus
Streptomycin	Deafness
Tetracycline	Dental enamel hypoplasia
Thalidomide	Phocomelia, cardiac and ear abnormalities
Valproic acid	Neural tube defects, clefting, limb defects, characteristic facies
Warfarin	Nasal hypoplasia, stippled epiphyses

Teratogenic Agents

Table 16.7 Infectious Teratogenic Agents

Infection	Effects
Viral	
Cytomegalovirus	Chorioretinitis, deafness, microcephaly
Herpes simplex	Microcephaly, microphthalmia
Rubella	Microcephaly, cataracts, retinitis, cardiac defects
Varicella zoster	Microcephaly, chorioretinitis, skin defects
Bacterial	
Syphilis	Hydrocephalus, osteitis, rhinitis
Parasitic	
Toxoplasmosis	Hydrocephalus, microcephaly, cataracts, chorioretinitis, deafness

Thank You